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Brief communication

A 12-month follow-up study of treating overweight schizophrenic patients with aripiprazole

Schorr SG, Slooff CJ, Postema R, Van Oven W, Schilthuis M, Bruggeman R, Taxis K. A 12-month follow-up study of treating overweight schizophrenic patients with aripiprazole.

Objective: To investigate the feasibility of switching overweight schizophrenic patients to aripiprazole and to assess the impact of 12 months of aripiprazole treatment on weight in routine practice.

Method: This was a non-controlled cohort study in overweight schizophrenic patients. Data were collected before treatment with aripiprazole was started and at 12-month follow-up.

Results: A total of 53 patients were included; of these 55% continued using aripiprazole for 12 months. Aripiprazole treatment for 12 months ($P = 0.027$) and stopping clozapine or olanzapine treatment ($P = 0.038$) predicted weight loss (≥ 3 kg). Patients receiving aripiprazole monotherapy ($n = 16$, mean -3.0 kg) had similar weight loss than patients receiving aripiprazole in addition to another antipsychotic drug ($n = 13$, mean -4.4 kg).

Conclusion: In routine practice once aripiprazole treatment was started, more than half of the patients remained on aripiprazole and most of them lost weight. Adding aripiprazole to clozapine gave similar weight loss as monotherapy with aripiprazole.

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Key words: aripiprazole; schizophrenia; antipsychotic agents; overweight; body weight changes

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Significant outcomes

- Aripiprazole treatment over 12 months was a significant predictor for weight loss.
- Adding aripiprazole to clozapine is an option for overweight patients on clozapine.
- Patients and psychiatrists are reluctant to change antipsychotic treatment for overweight patients.

Limitations

- Only 53 patients could be included in the study.
- There was no control group to compare treatment of aripiprazole.
- Other factors such as changes in lifestyle could also have an effect in patients treated with aripiprazole, but were not included in the analysis.

Introduction

The absolute risk of developing coronary heart disease is around twice as high in schizophrenic patients compared with the general population (1). One of the reasons for this is the high (1.5–2-fold) prevalence of overweight in this population (2). Antipsychotic drugs can have a considerable impact on weight. Of the second-generation anti-

psychotic drugs, clozapine and olanzapine cause the largest weight gain followed by risperidone and quetiapine. Less weight gain appears to be associated with aripiprazole and ziprasidone (3). Treatment for overweight consists mostly of lifestyle interventions. Another option is a switch to an antipsychotic drug with lower weight gain capacity, such as aripiprazole (4). After switching patients to aripiprazole weight changes between

+0.04 kg after 52 weeks (5) and -5.5 kg after 12 weeks (6) were found. Six studies were conducted over a relatively short period of time (4–18 weeks) (6–11). Four studies followed patients for 26 weeks or longer (5, 12–14). Three of the studies with longer follow-up were randomized controlled clinical trials (RCTs) or extension of RCTs. Patients who received aripiprazole were compared with patients on olanzapine (5, 13, 14), quetiapine (14) or risperidone (14). Patients receiving aripiprazole gained less or lost weight (between +0.04 and -1.4 kg) compared with patients in the other treatment arm, who gained on average weight in all three studies (between +1.4 and +4.23 kg). However, these studies used strict inclusion and exclusion criteria, such as excluding patients on clozapine (13, 14), or including only a small number of patients on clozapine (5, 15). There was only one study conducted in routine practice; patients lost on average 2.7 kg (12). Unfortunately overweight was not an inclusion criterion for this study and baseline antipsychotic drugs were not recorded. Therefore, it remains unknown whether the effects of aripiprazole on overweight patients shown in RCTs will also be found in long-term treatment in routine practice.

Aims of the study

To investigate the feasibility of switching overweight schizophrenic patients to aripiprazole and to assess the impact of 12 months aripiprazole treatment on weight in routine practice.

Material and methods

This was a non-controlled cohort study. It was carried out in a mental health care centre in the North of the Netherlands, covering about 175 000 inhabitants. Between September 2004 and February 2006 patients were included if they had a diagnosis of schizophrenia or other psychotic disorder (DSM criteria 295-298), if their body mass index (BMI) was >25 and/or their waist circumference was >88 cm for females and >102 cm for males [threshold values for metabolic syndrome NCEP/ATP III (16)] and if patient and psychiatrist agreed on starting treatment with aripiprazole. All patients gave informed consent. Aripiprazole was started additionally to baseline antipsychotic drug and after 2–4 weeks the dose of baseline antipsychotic drug was reduced stepwise aiming at stopping the baseline antipsychotic drug. Data were collected at baseline and at 12-month follow-up assessment. A trained nurse assessed patient's somatic and mental health using a

standardized patient interview, including questions about medication and psychiatric symptoms, and a short physical examination, including waist circumference and blood pressure. At the same time, laboratory values, including fasting glucose and triglycerides, were measured. The patient's psychiatrist discussed the findings with the patient and decided on further treatment options, including starting treatment with aripiprazole. Our study was part of a disease management programme, which aimed at evaluating standard of care, patient's needs and effectiveness of interventions. Other interventions offered to overweight patients included consultation by a dietician, exercise programmes and/or referral to general practitioner for further medical treatment.

Data were analysed to find predictive variables for weight loss (≥ 3 kg). In the logistic regression model we included the variables aripiprazole use for 12 months, age (>35 years), sex (male) and stopping clozapine/olanzapine, defined as receiving clozapine/olanzapine at baseline, but not at 12-month follow-up. Patients were excluded from this analysis if data were missing for any of the predictive variables.

Patient characteristics were compared between patients who discontinued and who continued treatment with aripiprazole using the *t*-test, Mann-Whitney test and chi-squared test. Weight changes and changes in antipsychotic drug treatment were analysed descriptively on a patient level for patients who continued and discontinued using aripiprazole. The number of patients losing or gaining 7% or more of their baseline weight was calculated for better comparison with other published studies (5, 10, 13, 14). In a subanalysis weight change was calculated for patients receiving aripiprazole in addition to their baseline antipsychotic drug. For patients receiving clozapine in combination with aripiprazole, dosage at 12 month assessment and change in dosage of clozapine were calculated.

Results

During the inclusion period, in total, 405 patients were screened in the disease management programme and 298 (74%) of these patients were overweight (BMI >25 and/or waist circumference >88 cm for females and >102 cm for males). A total of 53 (21 female, 32 male) patients were included in the study. In addition, 11 patients received aripiprazole during the inclusion period of the study but could not be included in the study (nine patients did not have a baseline screening and two patients were not overweight at baseline

Table 1. Baseline data

Variable	Total population (<i>n</i> = 53)	Patients, who were lost to follow-up (<i>n</i> = 6)	Patients, who continued (<i>n</i> = 29)	Patients, who discontinued (<i>n</i> = 18)	<i>P</i> -values†
Female	21 (40)	4 (67)	14 (48)	3 (17)	<i>P</i> = 0.028‡
Male	32 (60)	2 (33)	15 (52)	15 (83)	
Age in years	35 (SD=10.1)	33 (SD=9.4)	34 (SD=10.7)	38 (SD=9.3)	<i>P</i> = 0.144§
Schizophrenia	35 (66)	3 (50)	19 (66)	13 (72)	<i>P</i> = 0.837‡
Schizoaffective disorder	9 (17)	1 (17)	5 (17)	3 (17)	
Other psychotic disorder	9 (17)	2 (33)	5 (17)	2 (11)	
Duration of disease in years	10.4 (SD=8.9; <i>n</i> = 48)	10.7 (SD=9.4; <i>n</i> = 6)	10.9 (SD=9.8; <i>n</i> = 25)	9.6 (SD=7.8; <i>n</i> = 17)	<i>P</i> = 0.888§
Olanzapine	18 (34)	1 (17)	9 (31)	8 (44)	<i>P</i> = 0.141‡
Clozapine	15 (28)	0	9 (31)	6 (33)	
Risperidone	10 (19)	1 (17)	8 (28)	1 (6)	
Other antipsychotics	4 (8)	2 (33)	2 (7)	0	
Combinations of antipsychotics	5 (9)	1 (17)	1 (3)	3 (17)	
No antipsychotic	1 (2)	1 (17)	0	0	
Antidepressants	22 (42)	3 (50)	13 (45)	6 (33)	<i>P</i> = 0.435‡
Antimuscarinic drugs	4 (8)	0	2 (7)	2 (11)	<i>P</i> = 0.615‡
Hypnotics	9 (17)	2 (33)	5 (17)	2 (11)	<i>P</i> = 0.566‡
Anxiolytics	5 (9)	1 (17)	2 (7)	2 (11)	<i>P</i> = 0.615‡
Mood stabilizer	8 (15)	1 (17)	2 (7)	5 (28)	<i>P</i> = 0.051‡
Weight in kg	97 (SD = 15.1)	88 (SD = 12.3)	95 (SD = 14.3)	105 (SD = 14.7)	<i>P</i> = 0.024¶
BMI	31.0 (SD = 4.1)	31.6 (SD = 5.3)	30.6 (SD = 3.9)	31.5 (SD = 4.3)	<i>P</i> = 0.444§
Waist circumference in cm	108 (SD = 12.0)	108 (SD = 13.0)	106 (SD = 12.1)	112 (SD = 11.3)	<i>P</i> = 0.064§
Male	108 (SD = 10.0)	110 (SD = 3.5)	104 (SD = 9.3)	111 (SD = 10.3)	
Female	109 (SD = 14.9)	107 (SD = 16.6)	107 (SD = 14.7)	115 (SD = 17.9)	
Metabolic syndrome*	24 (45)	4 (67)	13 (45)	7 (39)	<i>P</i> = 0.638§

Values within parenthesis are expressed in percentage, unless otherwise stated.

*Based on the definition of ATP/NCEP (16). For missing glucose values, HbA1c values were used ($\geq 6.2\%$).

†*P*-values comparing patients who continued and who discontinued using aripiprazole.

‡*P*-values calculated using the chi-squared test.

§*P*-values calculated using the Mann–Whitney test.

¶*P*-values calculated using the *t*-test.

screening). At baseline patients were on average 35.0 years old with an average disease duration of 10 years (Table 1). Olanzapine (*n* = 18, 34%) and clozapine (*n* = 15, 28%) were the most frequently prescribed monotherapy of antipsychotic drugs. The average weight of patients was 97 kg (range: 69–135 kg) and average BMI was 31. Of the 53 patients who started with aripiprazole, after 12 months, six patients (11%) were lost to follow-up, 18 patients (34%) had discontinued using aripiprazole and 29 patients (55%) had taken aripiprazole during the entire study period. Of the patients who continued using aripiprazole, 16 (55%) patients received aripiprazole as monotherapy, nine (31%) patients in combination with clozapine and four (14%) patients in combination with another antipsychotic drug. Reasons for discontinuation were ineffectiveness (*n* = 13), side-effects (*n* = 1), non-compliance (*n* = 2) or patient's request (*n* = 2).

There were 46 patients with complete data for performing a logistic regression for identifying variables predicting weight loss (≥ 3 kg) after 12 months (Table 2). Receiving aripiprazole for 12 months and stopping clozapine or olanzapine

were statistically significant predictors for weight loss. Ten patients stopped olanzapine and one patient clozapine treatment between both assessments. Table 1 shows the comparison of patients who discontinued and who continued using aripiprazole for 12 months; patients who discontinued aripiprazole had significant higher weight (*P* = 0.024) and were more often male (*P* = 0.028).

Patients who continued aripiprazole for 12 months lost on average 3.6 kg (between −27 and +10 kg); this was 4% of baseline weight. Twelve (23%) patients lost 7% or more and three (6%) patients gained 7% or more of baseline weight. Weight changes for patients who discontinued aripiprazole ranged between −5.6 and

Table 2. Logistic regression (*n* = 46) predicting weight loss ≥ 3 kg

Variable	Odds ratio	95% Confidence interval	<i>P</i> -value
Age > 35 years	0.660	0.13–3.37	0.617
Male sex	0.492	0.10–2.41	0.381
Aripiprazole treatment for 12 months	14.011	1.34–146	0.027
Stopping clozapine/olanzapine	6.969	1.12–43.6	0.038

+21.7 kg, average weight gain was 4 kg (4% of baseline weight). No patient lost 7% or more while four patients (22%) gained 7% or more of their baseline weight.

Patients with aripiprazole monotherapy ($n = 16$) lost on average 3.0 kg (−3.2% of baseline weight) and patients with combination therapy ($n = 13$) lost on average 4.4 kg (−4.4% of baseline weight). Two of the patients on combination therapy received a combination of olanzapine and aripiprazole and nine a combination of clozapine and aripiprazole. In these patients, average dosage at 12 month follow-up was 19 mg (SD = 8.5) aripiprazole and 328 mg (SD = 177.0) clozapine. On average, baseline clozapine dosage was reduced by 28% (between −92% and +50%).

Discussion

In our study it was feasible to switch 55% of the patients successfully to aripiprazole mono- or combination therapy. However, in relation to the 298 patients who fulfilled the inclusion criteria (overweight and diagnosis) during the study period, only in 21% ($n = 64$) aripiprazole treatment was started. Eighteen per cent ($n = 53$) of the patients were included in the study and 11% ($n = 29$) were treated with aripiprazole over 12 months. This low percentage shows that switching patients to aripiprazole was not considered as one of the main treatment options in overweight patients. Probably the main reason for this low percentage is the relatively high risk for relapse when switching medication in chronic psychiatric patients. Consequently, psychiatrists and patients are hesitant to change antipsychotic medication, especially in treatment-resistant patients receiving clozapine, which was one-third of our population. In our study the main reason for discontinuing aripiprazole was worsening of psychiatric symptoms ($n = 13$, 72% of patients who discontinued).

Patients who eventually chose to receive aripiprazole and continued treatment had a high chance of losing weight. Patients who were treated for 12 months with aripiprazole lost on average weight, while patients who discontinued using aripiprazole gained on average weight. The average weight loss for patients who were treated for 12 months with aripiprazole was 3.6 kg, which is within the range of published literature values [between −5.6 kg (6) and +0.04 kg (5)], and was higher than in other published long-term studies [between −2.7 kg (14) and +0.04 kg (5)]. However, patients who were motivated to continue using aripiprazole throughout the study may also have been motivated to lose weight. Comparing charac-

teristics of patients who continued with those who discontinued using aripiprazole, we found that patients who discontinued were more often male and had a higher baseline weight. The high percentage of men in the discontinuation group may be at least partly due to the lower compliance rate seen in male schizophrenic patients (17). The higher baseline weight of patients can be explained by the significantly higher number of male patients. This would suggest that male patients may not benefit from aripiprazole treatment the same way as female patients and may therefore stop aripiprazole.

The other significant predicting factor for weight loss was stopping clozapine or olanzapine. There was one patient who stopped clozapine, and 10 patients who stopped olanzapine. Patients who received clozapine at baseline were more likely to receive aripiprazole in addition to clozapine than to stop clozapine treatment. Surprisingly we found that patients receiving a combination of aripiprazole and clozapine showed similar weight loss as patients receiving aripiprazole monotherapy. Similar to data from Henderson et al. (7), our study would therefore suggest that adding aripiprazole is an option in overweight patients on clozapine. This needs to be further investigated in a larger number of patients including a control group.

This study was limited by the low number of patients included in the study. Therefore, only a limited number of variables could be included in the logistic regression. Many other factors including lifestyle changes or changes in co-medication could also have an effect on weight.

In conclusion, in routine practice, only a small percentage of the total number of overweight psychiatric patients were switched to aripiprazole. Once aripiprazole treatment was started, more than half of the patients remained on aripiprazole and most of them lost weight. Adding aripiprazole to clozapine gave similar weight loss as monotherapy with aripiprazole.

Declaration of interest

C.J. Slooff received an unconditional grant from Bristol Myer Squibb for initiating the disease management programme. Part of the data collected within the disease management programme were also used in this study. Bristol Myer Squibb had no role in study design, data analysis and writing of the manuscript. All other authors declare that they do not have any relation with Bristol Myer Squibb. R. Bruggeman received speaker fees from Janssen Cilag, AstraZeneca and Eli Lilly. S.G. Schorr, R. Postema, M. Schilthuis, W. van Oven and K. Taxis do not have a conflict of interest. Data analysis was conducted at the University of Groningen, in the Department of Pharmacy, Division of Pharmacotherapy and Pharmaceutical Care by S.G. Schorr, K. Taxis and R. Postema. The study

protocol can be obtained from the corresponding author K. Taxis (k.taxis@rug.nl).

References

1. HENNEKENS CH, HENNEKENS AR, HOLLAR D et al. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005;**150**:1115–1121.
2. NEWCOMER JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry* 2007;**68**(suppl. 4):8–13.
3. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;**27**:596–601.
4. WEIDEN PJ. Switching antipsychotics as a treatment strategy for antipsychotic-induced weight gain and dyslipidemia. *J Clin Psychiatry* 2007;**68**(suppl. 4):34–39.
5. CHRZANOWSKI WK, MARCUS RN, TORBEYNS A et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology* 2006;**189**:259–266.
6. DE HERT M, HANSSENS L, VAN WINKEL R et al. A case series: evaluation of the metabolic safety of aripiprazole. *Schizophr Bull* 2007;**33**:823–830.
7. HENDERSON DC, KUNKEL L, NGUYEN DD et al. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. *Acta Psychiatr Scand* 2006;**113**:142–147.
8. KIM SH, IVANOVA O, ABBASI FA et al. Metabolic impact of switching antipsychotic therapy to aripiprazole after weight gain: a pilot study. *J Clin Psychopharmacol* 2007;**27**:365–368.
9. SPURLING RD, LAMBERTI JS, OLSEN D et al. Changes in metabolic parameters with switching to aripiprazole from another second-generation antipsychotic: a retrospective chart review. *J Clin Psychiatry* 2007;**68**:406–409.
10. CASEY DE, CARSON WH, SAHA AR et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology* 2003;**166**:391–399.
11. MARDER SR, McQUADE RD, STOCK E et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* 2003;**61**: 123–136.
12. CHRISTENSEN AF, POULSEN J, NIELSEN CT et al. Patients with schizophrenia treated with aripiprazole, a multicentre naturalistic study. *Acta Psychiatr Scand* 2006;**113**:148–153.
13. McQUADE RD, STOCK E, MARCUS R et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004;**65**(suppl. 18):47–56.
14. KERWIN R, MILLET B, HERMAN E et al. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR) study. *Eur Psychiatry* 2007;**22**:433–443.
15. PIGOTT TA, CARSON WH, SAHA AR et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry* 2003;**64**:1048–1056.
16. NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP). Executive summary of the Third Report of The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–2497.
17. MORKEN G, GRAWE RW, WIDEN JH. Effects of integrated treatment on antipsychotic medication adherence in a randomized trial in recent-onset schizophrenia. *J Clin Psychiatry* 2007;**68**:566–571.