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Long-term treatment of antipsychotics and combined therapy with other psychotropic medications inducing weight gain in patients with non-affective psychotic disorder: Evidence from GROUP, a longitudinal study

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ABSTRACT

Introduction: Antipsychotics (APs) can cause weight gain. Little is known about changes in weight when APs are combined with other psychotropics. This study examines the weight change in patients undergoing long-term treatment with APs or with AP combined with other psychotropics.

Methods: Patients with non-affective psychotic disorder from the GROUP study were divided into three groups: AP medication group (APm) ($n = 100$), AP in combination with other psychotropics (APc) ($n = 73$), and medication-free (Meds-free) ($n = 100$). Weight change was examined at inclusion and after three years using a paired-sample t-test. An Independent-sample t-test was performed to evaluate weight change among patients taking clozapine, olanzapine, and quetiapine and individuals not taking these medications. Linear regression was performed to evaluate the association between covariates and weight.

Results: Patients in the APm group [mean = 1.800 kg, t(99)=2.849, 95% CI(0.546, 3.054), $p = 0.005$] and the APc group [mean = 1.877 kg, t(72)=2.688, 95% CI(0.485, 3.268), $p = 0.009$] showed significant weight gain. Patients taking clozapine, olanzapine or quetiapine showed significant weight gain compared to those not taking these medications [mean difference=1.707 kg, t(271)= 2.061, 95% CI(0.077, 3.337), $p = 0.040$)].

Conclusion: Patients receiving APs and APs with other psychotropics gain weight during long-term treatment. It is possible that weight gain is mainly driven by APs.

Abbreviations: AP, antipsychotic; APs, antipsychotics; APc, antipsychotic in combination with other psychotropic medication; APm, antipsychotic medication group; BMI, body mass index; IQ, intelligence quotient; Meds-free, medication-free; NOS, not otherwise specified; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition.

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1. Introduction

Causes of overweight and obesity in schizophrenia and related disorders are multifactorial (Cooper et al., 2016; De Hert et al., 2009; McEvoy et al., 2005). However, antipsychotic (AP) treatment seems to influence this outcome significantly (Allison et al., 1999; Bak et al., 2014; Musil et al., 2015). Overweight and obesity often have a huge impact on health, increasing the risk of comorbidities such as type 2 diabetes, cardiovascular disease, hypertension, and certain cancers (Newcomer, 2005). In addition, AP-induced weight gain can be a predictor of treatment discontinuation and therefore predispose patients to relapse (Garcia et al., 2016; Higashi et al., 2013; Mustafa et al., 2018). The CATIE study, for example, demonstrated that more patients discontinued olanzapine owing to weight gain or metabolic effects (9% vs. 1 to 4% with the other four drugs studied, $p < 0.001$) (Lieberman et al., 2005).

A meta-analysis (Allison et al., 1999) including 81 studies reported that most APs were associated with weight gain. Among the five APs studied (clozapine, olanzapine, risperidone, sertindole, and ziprasidone), ziprasidone had the lowest weight gain (0.04 kg), and clozapine had the highest (4.45 kg), within 10-weeks treatment. Since this meta-analysis, several authors have shown the association between the use of APs and increased risk of weight gain and, also, metabolic syndrome (Allison et al., 2009; American Diabetes Association, 2004; Bak, 2020; Bak et al., 2014; Burghardt et al., 2018; Lieberman et al., 2005; Musil et al., 2015). A recent review indicated that none of the second-generation APs studied are fully devoid of metabolic disorders (Bernardo et al., 2021). Other findings concerning AP-associated weight gain show that patients most at risk are younger, have lower body mass index (BMI), and are female (Castellani et al., 2019; Musil et al., 2015). Furthermore, AP naïve status has also been reported to be associated with more pronounced weight gain, independent of agent AP class (Correll et al., 2009; Zipursky et al., 2003).

Most of the weight gain is reported to occur in the first weeks of treatment. However, existing studies also demonstrate that patients continue to gain weight even during long-term AP use (Musil et al., 2015). A recent meta-analysis reported that clinically relevant weight gain, even for first-generation APs, occurs with an increased duration of AP use (Bak et al., 2014). A study by Bai et al. (2009) evaluated 349 patients undergoing long-term treatment with clozapine reported long-term weight gain reaching a plateau after 42 months. Similarly, it has been demonstrated that when drug-naive first-episode patients are followed over the long-term, the differences between individual antipsychotic agents disappear at the 12-month mark (Perez-Iglesias et al., 2008).

In addition to a large body of literature substantiating the association between APs and weight gain, other studies have also shown weight gain with the use of other classes of psychotropic drugs (Dent et al., 2012; Fava, 2000; Nihalani et al., 2011; Pijl and Meinders, 1996; Schwartz et al., 2004). Data from the AMSP project reported cases of severe weight gain with various drugs from different classes of psychotropics (Schneider et al., 2020). Valproate and lithium have been associated with significant weight gain (Abosi et al., 2018; Chengappa et al., 2002). Some types of antidepressants have also been associated with weight gain (Abosi et al., 2018; Bet et al., 2013).

Despite the evidence showing that weight gain is associated with several classes of medications, very few studies have evaluated weight gain in patients using APs combined with other psychotropic medications. A cross-sectional study with 626 patients from 4 psychiatric hospitals evaluated the metabolic effects resulting from combined therapy of APs and valproic acid compared to AP monotherapy. This study reported no differences in weight gain or other metabolic outcomes between the two groups. However, the authors argued some limitations that could have led to these results, including a cross-sectional design, and insufficient power, highlighting the need for future studies (Zuo et al., 2015). Conversely, two studies in pediatric populations have shown that metabolic adverse events caused by APs tend to be worse when multiple APs or other classes of psychotropic medications are co-prescribed (Mcintyre and Jerrell, 2008; Rubin et al., 2015).

Given the high prevalence of combination treatment in patients with psychosis spectrum disorders (Gaudiano et al., 2018; Yang et al., 2018) this present study aims to examine weight change during long-term treatment of patients with non-affective psychotic disorders and the effects of antipsychotic medication with and without other psychotropic medication. Our hypothesis is that patients in the combined drug therapy would gain more weight than patients using only AP drug therapy.

2. Methods

2.1. Study Design

This cohort study used the GROUP database. The GROUP study is a multi-center longitudinal cohort study designed to evaluate the onset and course of non-affective psychotic disorders influenced by genetic and environmental factors. It included 1120 patients, 1057 siblings, 919 parents, and 590 healthy controls. Patients were followed during a period of 6 years with three measurements (baseline, 3-year, and 6-year follow-up). Four university medical centers (Amsterdam, Groningen, Maastricht, and Utrecht) and their affiliated mental health care institutions were involved in the assessment. For further details on GROUP design and characteristics, refer to Korver et al. (2012).

2.2. Participants

The inclusion criteria for patients in GROUP were the following: (1) age range of 16-50 years (extremes included); (2) a diagnosis of non-affective psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 2000), (3) good command of the Dutch language; and (4) able and willing to give written informed consent. The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. After full verbal and written information about the study, written informed consent was obtained from all participants. Confidentiality of data is maintained by using a unique research identification (ID) for each respondent. The ID number does not include any data related to the name of the participant or information that could lead to the identification of the person. Before the start of the study, all interviewers met for training workshops to practice the assessments of all measures used in the GROUP project (Korver et al., 2012).

Sociodemographic data were collected from the GROUP database: age, gender, ethnicity, marital status, and tobacco use. Furthermore, the study scores from Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), in order to estimate the intelligence quotient (IQ), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al.,1987) were included. The PANSS is used to assess a variety of symptoms in patients with schizophrenia. It consists of three subscales: positive syndrome scale (7 items), negative syndrome scale (7 items), and general psychopathology scale (16 items). From the 1120 patients included in the GROUP, 615 patients completed the 6-year follow-up. Only patients receiving long-term treatment were included. Those who received treatment equal to or longer than 38 consecutive weeks ($n = 520$) were included in the present study. This threshold was based on previous studies (Bak et al., 2014). Moreover, patients had to have two weight measurements ($n = 351$). Patients taking any other class of psychotropic medication, except antipsychotics, mood stabilizers, antidepressants, or benzodiazepines ($n = 281$), were excluded. Finally, outliers, gaining or losing an extreme amount of weight, using as reference the Hoaglin et al. study (Hoaglin and Iglewicz, 1987), were taken out. Two hundred and seventy-three patients remained, as shown in Fig. 1.

2.3. Procedures

Patients were divided into three groups: group 1: only AP medication (APm group), which included patients in AP monotherapy or AP in combination with other AP treatment ($n = 100$); group 2, AP in combination with other psychotropic medication (APc group) ($n = 73$); and group 3, receiving no psychotropic medication (Meds-free group) ($n = 100$). Since patients did not have an objective weight measurement at baseline (T0), measurements at 3-year (T1) and at 6-year (T2) follow-up were used. The weight difference was calculated by subtracting weight at T1 from weight at T2.

The duration of each treatment for APm and APc was taken as the difference between the date of T2 and the last date the medication was added to the patient's prescription. Furthermore, the variable "status of medication" in T2 should be registered as "currently using". If the patient was using more than one medication, we used the duration of the last medication added to patient's prescription to calculate the duration of all psychotropic medication. Patients who were not taking medication in T1 and in T2 were included in Meds-free group.

As clozapine, olanzapine and quetiapine showed the highest increase in weight in previous studies (De Hert et al., 2012; Zhang et al., 2016), secondary analyses were performed, dividing the sample in two groups: (a) using clozapine, olanzapine or quetiapine (combined with other psychotropic or not) ($n = 99$), and (b) not using clozapine, olanzapine or quetiapine ($n = 174$).

2.4. Statistical analysis

All statistical analyses were performed with IBM SPSS version 25.0. Sample characteristics were compiled using mean and standard deviation for continuous variables, and percentages for categorical variables.

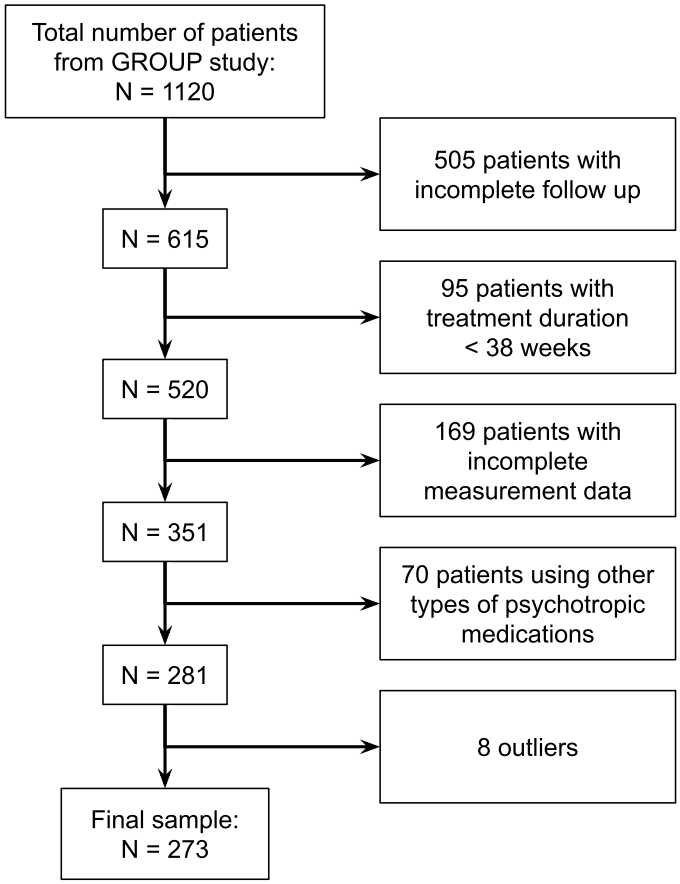

Fig. 1. Sample selection.

Analysis of variance (ANOVA) and Chi-square tests were applied to investigate the group differences in all groups, and independent or paired sample t-test to investigate between group differences. The Bonferroni method was used to adjust for multiple comparisons in the post-hoc analysis. Weight change between T1 and T2 for each group was calculated. In the APc group, psychotropic medication other than antipsychotics (mood stabilizers, antidepressants, benzodiazepines) and the effect of combination treatment on weight change was assessed. Since the groups were not homogeneous with respect to age, duration of treatment, duration of illness, number of psychotropic medications in use, IQ, diagnosis, and PANSS scores, we performed linear regression with each of these confounders to analyze if there was any association with the weight change. In order to analyze other possible confounders, we evaluated the association between each of these covariates and weight change: gender, weight in T1, height, ethnicity, and tobacco use. General Linear Model (Repeated Measure) was performed using as covariates gender and weight in T1. Normality was assumed through histogram layout. We assumed a statistical significance when the two-sided p-value was equal to or lower than 0.05.

After performing the analysis, the power to detect results was calculated. Our sample size consists of 100 subjects in the APm group and 73 subjects in the APc group. We found 8% power to detect a -0.077 kg (SD 0.95) difference in weight change between the two groups (APm compared to APc), assuming a two-tailed test with an alpha level of 0.05. We found 81% power to detect a 1.8 kg (SD 6.318) difference in weight change between T1 and T2 in APm group, assuming a two-tailed test with an alpha level of 0.05. We found 76% power to detect a 1.877 kg (SD 5.965) difference in weight change between T1 and T2 in APc group, assuming a two-tailed test with an alpha level of 0.05.

3. Results

3.1. Characteristics of patients

Table 1 shows the characteristics of the patients (i.e., data collected at T1). Patients in the APc group had a higher mean age compared to patients in the Meds-free group. Regarding diagnosis, there was a higher prevalence of schizophrenia in the APm group, compared to the Meds-free group. In contrast, the percentage of patients with schizoaffective disorder was higher in the APc group, compared to the APm group and Meds-free group. The percentage of psychotic disorder NOS (Not Otherwise Specified) and schizophreniform disorder were higher in the Meds-free group, compared with the APm group and the APc group.

Regarding the duration of current treatment, only patients taking medications for at least 38 weeks were included. Patients in the APm group had a significantly higher mean duration of treatment compared to the APc group [mean difference=62.7 weeks, t(171)=3.46, 95% CI (26.9, 98.5), $p = 0.001$]. The APc group (9.9 ± 4.3 years) had a longer duration of illness compared to the Meds-free group (7.4 ± 3.9 years), [mean difference=2.4 years, $p = 0.002$].

The APc group showed higher scores on the positive scale of the PANSS compared to the Meds-free group, [mean difference=0.24, $p = 0.017$]. The APm group showed higher scores on the negative scale of the PANSS than the Meds-free group, [mean difference=0.25, $p = 0.031$]. There were no significant differences in general psychopathology scale scores among the three groups.

Patients in the Meds-free group showed significantly higher IQ scores compared to patients in the APm group, [mean difference=6.95, $p = 0.01$]. The Meds-free group also showed higher IQ scores compared to the APc group, however, it was not significant, [mean difference=5.81, $p = 0.078$].

No statistical differences were found among the three groups regarding gender, ethnicity, marital status, tobacco use, weight at T1, and height.

Table 2 (supplementary material) and Table 3 (supplementary material) show the types of medications used by patients in each group.

Table 1
Characteristics from the sample at T1, divided by the three different medication groups.

		Medication Groups						
		AP group(APm)		Combination group(APc)		Medication-free group(Med-f)		
		Mean (SD)	*N* (%)	Mean (SD)	*N* (%)	Mean (SD)	*N* (%)	*p* value
Number of subjects			100		73		100	
Age (years)		30.4 (7.2)		32.1 (6.5)		29.2 (7.1)		**.033**[1]
Gender	Male		82 (82)		57 (78.1)		78 (78)	.737[2]
	Female		18 (18)		16 (21.9)		22 (22)	
Ethnicity	Caucasian		88 (88)		63 (86.3)		88 (88)	.932[2]
	Other		12 (12)		10 (13.7)		12 (12)	
Marital status	Not married		90 (90)		59 (80.8)		82 (82)	.286[2]
	Married		9 (9)		10 (13.7)		15 (15)	
	Divorced		1 (1)		4 (5.5)		3 (3)	
Tobacco use*	No		44 (44)		32 (44.4)		41 (41.4)	.905[2]
	Yes		56 (56)		40 (55.6)		58 (58.6)	
Weight at T1 (kg)		83.1 (16.3)		84.6 (13.9)		81.5 (18.4)		.473[1]
Weight at T2 (kg)		84.9 (15.8)		86.5 (14.4)		81.7 (17.9)		.144[1]
Height at T1 (m)		1.80 (0.09)		1.79 (0.09)		1.80 (0.09)		.407[1]
BMI at T1 (kg/m^2)		25.5 (4.9)		26.5 (4.3)		24.9 (5)		.109[1]
Duration of current medication treatment (weeks)		201.8 (145.9)		139.1 (60.5)				**.000**[3]
Duration of illness (years)		8.4 (4.8)		9.9 (4.3)		7.4 (3.9)		**.002**[1]
Number of psychotropic medications in use		1.2 (0.5)		2.5 (0.7)		0 (0)		**.000**[1]
WAIS-III Estimated IQ		98.6 (15.4)		99.7 (14.6)		105.5 (17)		**.006**[1]
Diagnosis	Schizophrenia		71 (71)		42 (57.5)		45 (45)	**.000**[2]
	Schizoaffective disorder		15 (15)		21 (28.8)		10 (10)	
	Psychotic disorder NOS		5 (5)		4 (5.5)		18 (18)	
	Schizophreniform disorder		2 (2)		1 (1.4)		10 (10)	
	Brief psychotic disorder		3 (3)		2 (2.7)		6 (6)	
	Other		4 (4)		3 (4.1)		11 (11)	
PANSS	Positive scale	1.49 (0.63)		1.60 (0.63)		1.36 (0.46)		**.024**[1]
	Negative scale	1.73 (0.78)		1.54 (0.58)		1.48 (0.59)		**.025**[1]
	General scale	1.46 (0.44)		1.48 (0.43)		1.37 (0.38)		.197[1]

SD: standard deviation, BMI = body mass index, WAIS-III = Wechsler Adult Intelligence Scale-Third Edition, PANSS = Positive and Negative Syndrome Scale, NOS = not otherwise specified *Daily use of cigarettes in the last 12 months

[1] ANOVA
[2] Chi-square
[3] Independent-sample t-test

There were no statistical differences among the types of AP used between the APm group and the APc group. In the APm group, 85 patients were taking only one AP, 10 patients were taking two APs, and 5 patients were taking three APs. In the APc group, 56 patients were taking only one AP, 15 were taking two APs, and 2 were taking three APs. Regarding other psychotropics in the APc group, 61 patients were taking one other medication, 10 patients were taking two other medications, and 2 were taking three other medications. The most frequent class of other psychotropic medication prescribed in combined therapy was antidepressants (n = 40), followed by mood stabilizers (n = 27), and

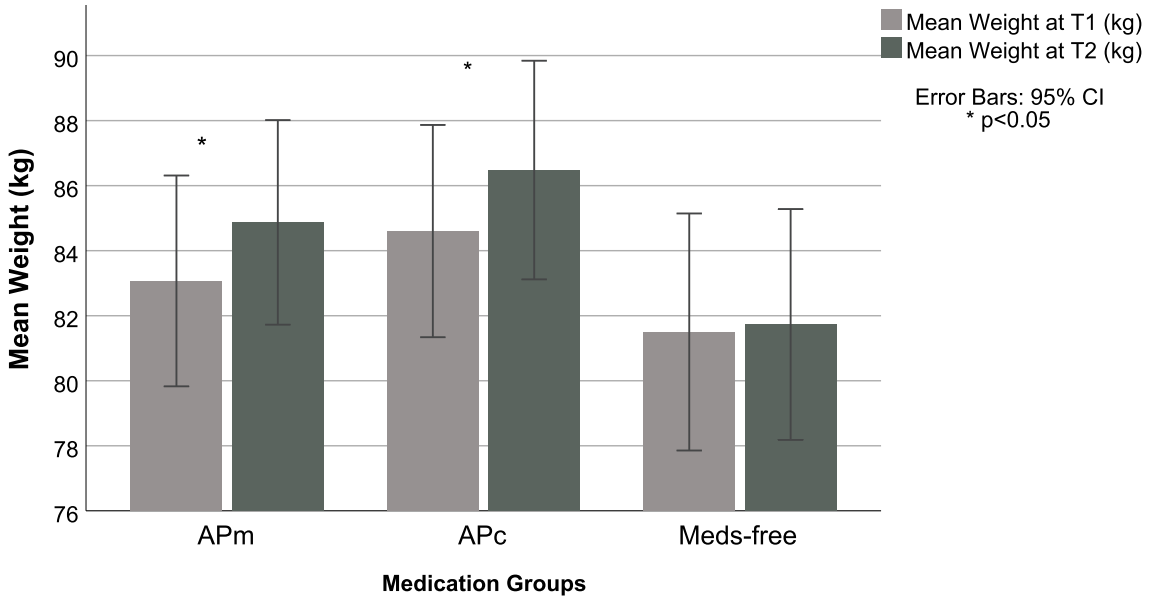

Fig. 2. Mean weight (kg) between T1 and T2 in each medication group. APm: antipsychotics only; APc: antipsychotics in combination with other psychotropic medication; Meds-free: medication free.

benzodiazepines ($n = 24$).

3.2. Outcomes

3.2.1. Weight change between T1 and T2

The mean duration of follow-up (T1-T2) was 2.7 (± 0.54) years. Both the APm group [mean difference=1.800 kg, t(99)=2.849, 95% CI (0.546, 3.054), $p = 0.005$] and the APc group [mean difference=1.877 kg, t(72)=2.688, 95% CI(0.485, 3.268), $p = 0.009$] had a statistically significant weight gain between T1 and T2. In contrast, the Meds-free group did not show statistically significant weight gain [mean = 0.230 kg, t(99)=0.316, 95% CI(-1.212, 1.672), $p = 0.752$], as shown in Fig. 2.

Comparing weight change between APm group and APc group, no statistically significant difference was found [mean difference = -0.077 kg, t(171)= -0.081, 95% CI (-1.952, 1.799), $p = 0.936$].

Patients taking clozapine, olanzapine, or quetiapine gained statistically significant more weight than those who were not taking these three drugs [mean difference=1.707 kg, t(271)= 2.061, 95% CI(0.077, 3.337), $p = 0.040$)], as shown in Fig. 3.

In the APc group, no statistically significant weight change was found comparing the three classes of combined psychotropic medication (antidepressants, mood stabilizers, or benzodiazepines), (Fig. 4, supplementary material). Comparing each class separately, there was no statistically significant weight gain for any of the combined classes of psychotropic medications between T1 and T2.

3.2.2. Covariates

Since the groups were not homogeneous with respect to age, duration of treatment, duration of illness, number of psychotropic medications in use, IQ, diagnosis, and PANSS scores, linear regression was performed with each of these confounders to analyze if there was any correlation with the weight change. No association was found between any of these variables and weight change.

Regarding possible other confounders, an association between gender and weight was found, with women gaining significantly more weight than men [mean difference=2.207 kg, t(271)=2.242, 95% CI (0.269, 4.146), $p = 0.026$] (Fig. 5, supplementary material). Also, weight at T1 and weight change were inversely associated [$R^2 = 0.053$, B=-0.092, 95% CI (-0.139, -0.045), $p \leq 0.001$]. The lower the weight at T1, the higher the amount of weight gain was observed (Fig. 6, supplementary material).

In the general linear model, only weight at T1 showed a significant effect on weight gain [F(1, 268) = 12.214, $p = 0.001$]. Gender [F(1, 268)= 1.334, $p = 0.249$] and medication group [F(2, 268)=2.561, $p = 0.079$] did not show an effect on weight gain in the multivariate tests.

There were no significant differences in gender and weight at T1 between the group taking clozapine, olanzapine, or quetiapine, and the group not taking any of these three medications.

4. Discussion

Our main hypothesis was that patients in the combined drug therapy (AP and other psychotropic medication) would gain more weight than patients using only AP drug therapy. Our results showed that patients in the APc group (combined therapy) indeed gained weight between the two measurements; however, they gained almost the same amount of weight as the APm (AP only) group. Patients in the Meds-free group (no medication) did not show statistically significant weight change between the two measurements. These results show that the use of psychotropic medication is associated with weight change even in long-term treatment.

In contrast to our hypothesis, patients in the APc group did not show a higher weight increase compared to patients taking AP only. Thus, continuous long-term weight gain could be primarily driven by APs that are known to cause severe weight gain (i.e., clozapine, olanzapine, and quetiapine) and not by the use of antidepressants, mood stabilizers, and/or benzodiazepines. To the best of our knowledge, the present study is the first to evaluate the weight change in patients with psychosis spectrum disorders using AP medications alone vs AP medications combined with other psychotropic drug classes during a 6-year follow-up.

Several explanations could be considered for not finding a greater weight increase in patients using combined drug therapy. First, APs, especially clozapine, olanzapine, and quetiapine, appear to cause such a degree of weight gain that when other medications are added to the prescription, they do not contribute much beyond that. In other words, a "ceiling" effect may exist. Second, the study population is characterized by individuals that have already been diagnosed with schizophrenia spectrum disorder for more than three years. To this last point, it is well established that individuals in their first episode with minimal previous exposure to psychotropic medications are most sensitive to AP-induced weight gain. As such, it is possible that in a first episode psychosis population, one would be able to see the effect of polypharmacy more

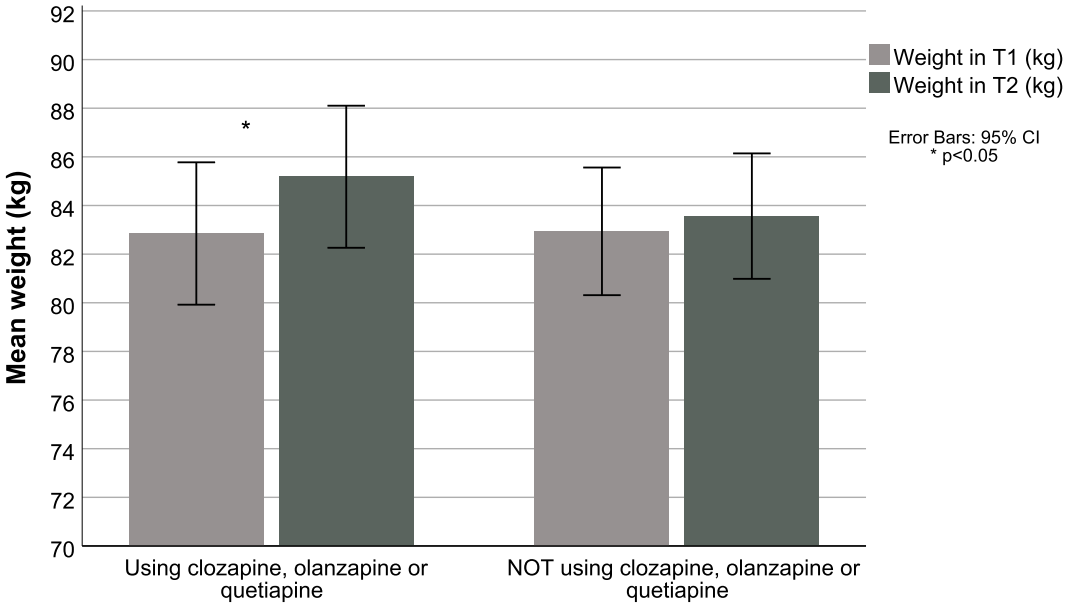

Fig. 3. Mean weight between T1 and T2 in patients using clozapine, olanzapine or quetiapine and patients not taking any of these three medications.

clearly. Third, in this present study, we grouped additional psychotropic medications together, which could have been a confounder since some of these drugs can be potentially weight neutral or can even cause weight loss (i.e., bupropion, lamotrigine).

In the APc group, there was no association between weight gain and a specific class of psychotropic medication (antidepressants, mood stabilizers, or benzodiazepines). We had no information available regarding which specific medications in these classes patients were using. This could be one of the reasons why we did not find statistically significant weight gain for a specific class. It is known that only certain antidepressants induce weight gain. In a recent review article, Abosi et al. (2018) reported early weight gain (within a 4–12-week period) for specific agents, including amitriptyline, mirtazapine, and nortriptyline. With medium- and long-term treatment, other antidepressants were also associated with weight gain: paroxetine, mirtazapine, amitriptyline, citalopram, and nortriptyline. In contrast, antidepressants such as bupropion can induce weight loss (Abosi et al., 2018; Gadde and Xiong, 2007). Likewise, mood stabilizers such as divalproex and lithium are known to induce weight gain, while lamotrigine is considered to be weight-neutral agent (Schwartz et al., 2004), and topiramate induces weight loss, and has been studied to mitigate AP-related weight gain (Hahn et al., 2013; Khera, 2016). Only a small number of patients could be divided into each medication category. Therefore, further analysis was not possible.

Sample differences were found among the three groups. Patients in the Meds-free group, had a higher prevalence of schizophreniform disorder and psychotic disorder NOS compared to the patients using APs, which is in keeping with briefer course and/or less certain indication for long-term treatment with an AP. In contrast, the APm group and the APc group showed higher prevalence of schizophrenia and schizoaffective disorder, respectively. According to the literature, there is no consensus if patients with schizoaffective disorder should be treated with APs, mood stabilizers or combinations of these drugs (Jager et al., 2010). However, some studies point out that the majority of the patients with schizoaffective disorder are treated with more than one class of psychotropic drugs (Murru et al., 2011). This could have contributed to the higher prevalence of this diagnosis in the APc group.

Our data showed that weight at T1 had a negative influence on weight gain. Heavier patients at T1 tended to gain less weight during follow-up. Possibly this is caused by a ceiling effect. This finding is in accordance with the Worldwide Schizophrenia Outpatient Health Outcomes studies. These studies included 4626 patients with long-term AP treatment and showed that the proportion of patients gaining more weight was smaller with higher BMI (Bushe et al., 2013). It is also documented in the literature that the greatest amount of weight gain occurs in the first few months of the treatment (Manu et al., 2015). While previous studies have shown that younger age is a risk factor for AP-weight gain (Musil et al., 2015), we did not find any correlation between age and weight in our study. Conversely, in keeping with previous studies that have reported a higher risk of weight gain for female patients than male patients (Aichhorn et al., 2006; Castellani et al., 2019; Musil et al., 2015), we found a similar association between gender and weight change.

Further prospective studies with long-term follow-up, focusing on populations with first-episode psychosis patients, are necessary to evaluate the effect of polypharmacy on weight and on other metabolic factors. Furthermore, strategies to prevent weight gain caused by psychotropics are necessary. Several approaches have been explored to prevent weight gain caused by APs, for example, switching APs to agents with lower weight gain potential (Siskind et al., 2021), adjunctive metformin, adjunctive topiramate, and the new combined olanzapine/samidorphan treatment (Marteene et al., 2019; Wharton et al., 2020). However, there are currently a few treatments approved by the U.S. Food and Drug Administration (Correll et al., 2020; Dayabandara et al., 2017), highlighting the importance of further studies.

4.1. Limitations

This study had several limitations. The GROUP study was not designed for the assessment of treatment's side effects. Thereby, some measures were missing for a large portion of the dataset (only 351 out of 520 patients had the two weight measures required for the analysis). Also, the weight measures at the baseline interview were not recorded. Thus, we were not able to evaluate the weight variation over the six-year follow-up and observe the weight gain in the first weeks of treatment. It was not possible to accurately ascertain the extent of weight gain associated with a particular medication or combination. This means that individuals who had been receiving the same medication for many years may have already gained all of the weight they ever would. We knew the last date each medication was added to the prescription and if the patient was currently using it in T2. We assumed that patients were taking the medications according to their prescription, but since it was a retrospective analysis, we do not have the guarantee of treatment adherence, which may confound the course of weight change. Besides, we were not able to consider the dose of each medication used.

We had no information about variables such as exercise and nutritional habits. Thus, it was not possible to control for other variables that may have had an influence on weight over time. We included in our study the maximum number of patients in each group. However, since we used pre-existing data, we did not have adequate power to detect the differences between the two groups to support our hypothesis. Since we worked with pre-existing data, we were not able to increase the sample size. Hence, there might be a type II error in the analysis that no statistically significant differences were found between the groups.

Another limitation was that the different classes of other psychotropic medications were not considered individually. Since we did not have a large sample, we were not able to evaluate the influence of each class of medication on weight separately.

5. Conclusion

The current study showed that patients with non-affective psychotic disorder progressively continue to gain weight even after long-term treatment with AP or with combined therapy. Our findings indicate that long-term weight gain may be mainly driven by APs medications (mainly clozapine, olanzapine, and quetiapine) and that polypharmacy may not further influence the weight change. Women gained more weight than men. Since our study had several limitations, more research is necessary to evaluate the implications of combined therapy not only on weight gain but also on other key metabolic parameters.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

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