

## Research Article

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# Trajectories of daily antipsychotic use and weight gain in people hospitalized for the first episode of psychosis

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**Abstract**

**Background.** We need to better understand the risk factors and predictors of medication-related weight gain to improve metabolic health of individuals with schizophrenia. This study explores how trajectories of antipsychotic medication (AP) use impact body weight early in the course of schizophrenia.

**Methods.** We recruited 92 participants with first-episode psychosis (FEP,  $n = 92$ ) during their first psychiatric hospitalization. We prospectively collected weight, body mass index (BMI), metabolic markers, and exact daily medication exposure during 6-week hospitalization. We quantified the trajectory of AP medication changes and AP polypharmacy using a novel approach based on meta-analytical ranking of medications and tested it as a predictor of weight gain together with traditional risk factors.

**Results.** Most people started treatment with risperidone ( $n = 57$ ), followed by olanzapine ( $n = 29$ ). Then, 48% of individuals remained on their first prescribed medication, while 33% of people remained on monotherapy. Almost half of the individuals (39/92) experienced escalation of medications, mostly switch to AP polypharmacy (90%). Only baseline BMI was a predictor of BMI change. Individuals in the top tercile of weight gain, compared to those in the bottom tercile, showed lower follow-up symptoms, a trend for longer prehospitalization antipsychotic treatment, and greater exposure to metabolically problematic medications.

**Conclusions.** Early in the course of illness, during inpatient treatment, baseline BMI is the strongest and earliest predictor of weight gain on APs and is a better predictor than type of medication, polypharmacy, or medication switches. Baseline BMI predicted weight change over a period of weeks, when other traditional predictors demonstrated a much smaller effect.

**Introduction**

Obesity is more prevalent among people with schizophrenia than in the general population [1, 2] and contributes to the higher risk of cardiovascular mortality in this group [3]. While there are other causes, antipsychotic medications (AP) are a key contributor to weight gain and one which, unlike most other factors, is completely under the control of the psychiatrist [4, 5]. Therefore, we need to better understand the risk factors for medication-related weight gain.

Traditional risk factors for weight gain include type of medication, duration of treatment, dose, antipsychotic-naïve status, lower age, female gender, nonsmoking status, high parental body mass index (BMI), and baseline BMI [6–12]. We know very little about other clinically highly relevant predictors, such as how medication switches and combinations of medications impact weight. This pertains to the contrast between the strict treatment protocols in randomized controlled trials (RCTs) and the realities of everyday clinical practice, where AP polypharmacy and switches of medications are common [13–15]. Protocols of RCTs usually emphasize one-to-one comparisons or focus on the transition from one monotherapy to another [16–19]. This does not tell us about the polypharmacological scenarios that are dominant in clinical practice. To learn about the impact of combining and switching medications on weight gain, we ultimately need data from everyday clinical practice, which are scarce.

Some real-life studies show limited impact of switches on weight gain [20, 21], while others suggest that both the switch itself and the AP previously administered may contribute to the metabolic outcomes observed in our patients [22–24]. These studies mostly focus on outpatients, where compliance is often an issue. They also frequently lack information on the duration of previous treatment, initial medication, and dosing [20–24]. Also a substantial portion of these studies investigated switches from medications with pronounced metabolic side effects to those

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with smaller impact on metabolism – for example, transitions from olanzapine and clozapine to ziprasidone or aripiprazole [20, 23, 25]. Such switches are rarely seen in clinical practice. In addition, we have very few studies which capture early stages of treatment, where the weight changes may be most pronounced [12, 26]. Only studies in people early in the course of treatment may speak to prevention and identify early predictors of medication-related weight gain.

Thus, we designed this study to fill the abovementioned knowledge gaps, specifically focusing on how sequences, combinations, and switches of medications impact weight gain early in the course of illness. To this goal, we prospectively collected daily medication records and measures of weight in people hospitalized for their first episode of psychotic illness. Inpatient setting allowed us to maximize adherence, precisely measure daily exposure to medication, and gain a snapshot of everyday inpatient psychiatric practice in a large general psychiatric hospital. Using these high-density data, we quantified the trajectory of medication changes taking the sequence, exact duration, dosing, overlaps of medications into account, and tested their effect on weight gain.

## Methods

### Materials and methods

Between 2016 and 2021, the Early-Stage Schizophrenia Outcome (ESO) study recruited participants from 10 psychiatric hospitals in the Czech Republic. Most of our patients (83%) came from one large psychiatric hospital with 1135 beds serving the Prague and Central Bohemian regions. We focused on individuals with first-episode psychosis (FEP), who met the following inclusion criteria: (a) were undergoing their first psychiatric hospitalization; (b) had the ICD-10 diagnosis of SZ (F20), or acute and transient psychotic disorders (F23) made by a psychiatrist according to Mini-International Neuropsychiatric Interview; (c) had <24 months of untreated psychosis; and (d) were 18–35 years old. We wanted to recruit participants at the early stages of illness to minimize the effects of illness and medications. Thus, participants who were hospitalized before meeting the duration criteria for schizophrenia were included in the study and received the working diagnosis of acute and transient psychotic disorders, which is congruent with the DSMIV brief psychotic disorder. All participants provided written informed consent for the study protocol approved by the Ethics Committee at the National Institute of Mental Health in Klecany. The treating psychiatrist evaluated the patients' capacity to provide informed consent before they were approached by the study team.

### Study procedures

Participants were assessed using the Positive and Negative Symptom Scale (PANSS). Weight and height were measured at the time of assessment by trained clinicians. BMI was calculated using the standard formula:  $BMI = \text{weight (kg)} / \text{height (meters)}^2$ . Concurrent somatic illness as well as history of substance use, including smoking, alcohol, and other recreational drugs, were assessed in a structured interview with the study psychiatrist. Subsequently, using the inpatient charts, we collected data from the time of admission, including BMI, and calculated the duration of inpatient treatment, that is, the interval between admission and research visit in days. Using the daily chart notes, we recorded daily medication exposure, calculated the precise doses for every administered

antipsychotics, and ranked AP medications based on the strength of their association with body weight using whole numbers from 1 to 12 according to recent network meta-analyses [11, 27, 28] (see [Supplementary Material](#) for details).

### Quantifying polypharmacy

We calculated the trajectory of AP polypharmacy by plotting the rank of medication (*y*-axis) over time in days (*x*-axis) with points at the time of prescription and termination of each medication (see [Figure 1](#)). The rank of subsequent medications in plotting was summed with the rank of any medications that were active at the time of their prescription or discontinuation. Termination of medications was noted with an additional point at the summed rank of all remaining medications. A regression line was fitted through these points, and the intercept and slope were extracted as a measure of the metabolic impact of the initial prescription, and the change in metabolic impact throughout treatment, respectively. In order to separately account for the dose of medications, we repeated the above-described procedure using the average standardized daily dose, instead of rank, for each medication. Even if medications were used short time or as needed, we accounted for them when quantifying the medication-related slopes and intercepts. The result was an intercept and slope for each medication rank and dose. These four measures were used as predictors of change in weight or BMI, described below.

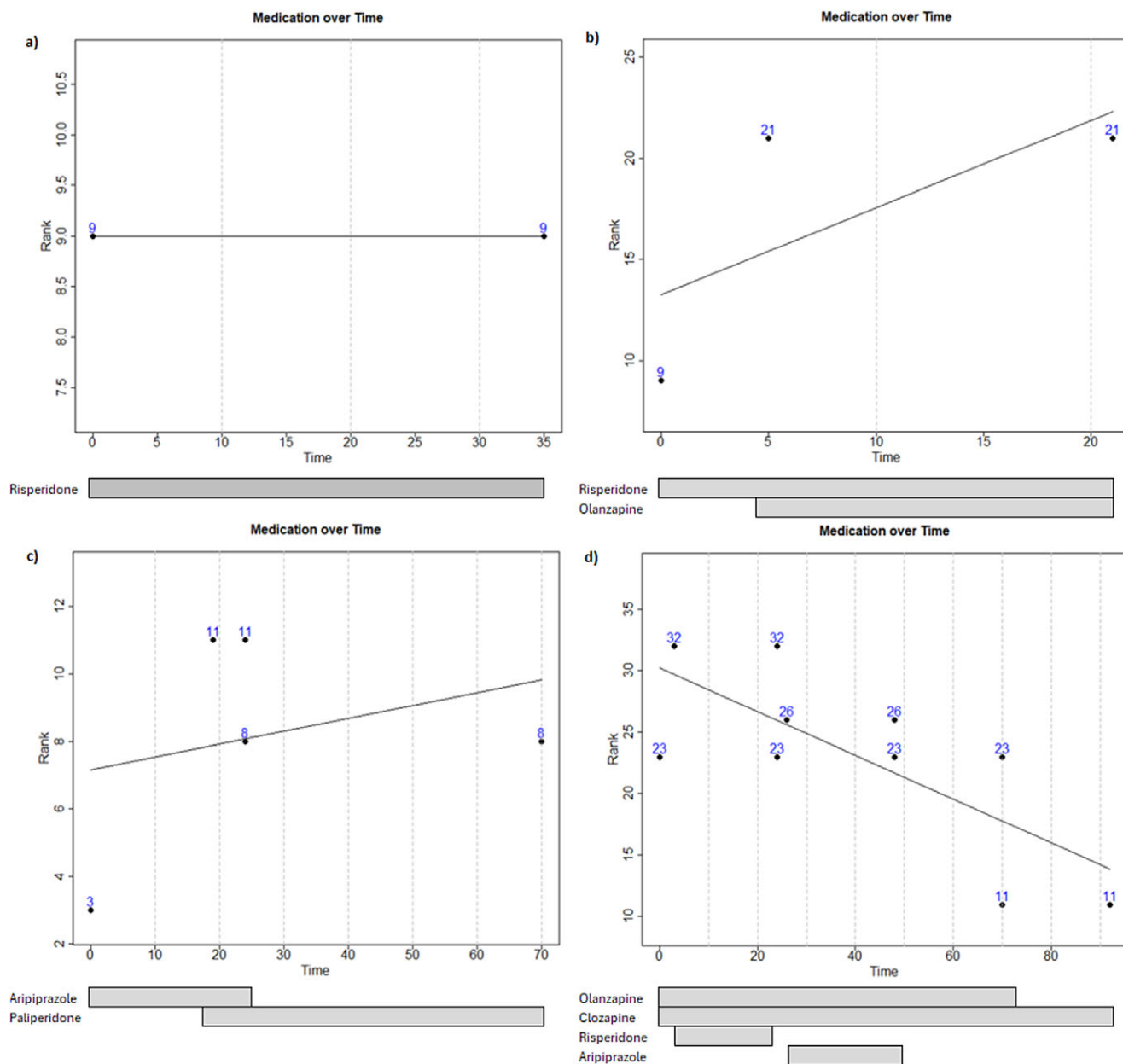
We also performed alternative analyses, where we included average weight gain per medication as estimated in meta-analyses [11, 27, 28]. However, this was not consistently done for the first generation of antipsychotics – consequently, we assigned the same number to all these medications. Also, the duration of studies used to calculate this markedly differed. We then recalculated polypharmacy trajectories using average weight gain associated with each medication instead of medication ranking. As this analysis is based on more assumptions and more heterogeneous set of studies, we only include this information in the supplement, as a sensitivity check (see [Supplementary Table S1](#)). Among the individuals who were on more than one medication during the hospitalization, 93.5% were on polypharmacy. Consequently, we could not compare metabolic switches versus polypharmacy.

### Statistical analyses

We used linear multiple regression modeling to test whether baseline BMI or change in BMI over time, were associated with a number of predictors. Baseline BMI was tested for association with the intercept of medication rank and dose. Change in BMI was tested for associations with the slope and the intercept of both the medication rank and dose, as well as baseline BMI, and treatment duration. We controlled for age and sex in all of the models. We used linear regression modeling to test for associations between changes in BMI with PANSS scores (positive, negative, and global) while controlling for age, sex, duration of treatment, and medication dose intercept.

Residuals were confirmed as normally distributed using the Kolmogorov–Smirnov test for normality, as well as visually using QQ plots. Multicollinearity was tested by calculating the variance inflation factor among all predictors in a model and was negligible.

Finally, participants were split into those whose change in BMI was in the top or bottom 33%, and the two groups were compared in demographic and clinical variables using either pairwise two-tailed *t* tests for continuous variables or Chi-square testing for categorical



**Figure 1.** Examples of polypharmacy plots for four participants: (A) shows a 35 day follow-up of an individual with FEP on risperidone monotherapy (rank 9); (B) shows a 20 day follow-up of an individual with FEP on risperidone during the initial 5 days of hospitalization, olanzapine (rank 12) was added on the 5th day; (C) shows a 70 day follow-up of an individual with FEP initially prescribed aripiprazole (rank 3) from days 1 to 24, on day 19, paliperidone (rank 8) was added until day 70, the cumulative rank (11) is the sum of ranks 3 and 8; (D) 92 day follow-up of an individual with FEP, olanzapine was administered between days 1 and 70, clozapine between days 1 and 92, risperidone between days 3 and 24, and aripiprazole between days 26 and 48.

variables. This same procedure was completed to compare participants with a positive medication rank slope relative to those with a negative slope. In addition, to check for regression to the mean, we performed a median split based on the baseline BMI and compared the BMI change in each subgroup.

We performed a retrospective power analysis for each effect shown in Table 2, using an effect size as calculated from the *t*-statistic for the respective effects, a confidence level of 0.95, and a power level of 0.80. In each case, we determined the number of observations required to achieve this power and confidence level given the present effect size.

## Results

### Sample

The sample included 92 participants (70.7% male) with a mean age of 25.2 years (SD = 4.9). More than half (59.8%) of the participants were medication naive, and the onset of symptoms was on average 4.58 months prior to the study date (SD = 4.60). In participants with prior medication, the average duration of prehospitalization treatment with antipsychotics was 4.27 months (SD = 6.12). Participants had a mean baseline BMI at hospitalization of 22.84 (SD = 4.40), and a mean BMI at follow-up of 23.70 (SD = 4.25). Those with BMI

**Table 1.** Demographic and clinical characteristics of participants with either a positive or a negative medication rank slope (\*,  $p < 0.05$ )

	Medication rank slope		
	Negative or zero	Positive	Significance
Sample size	53	39	
Age – Mean (SD)	25.84 (5.02)	24.42 (4.71)	$t(90) = -1.38, p = 0.172$
Sex, male – No. (%)	37 (69.8)	28 (71.8)	$\chi^2 = 0.01, p = 1.000$
Drug-naïve – No. (%)	32 (60.4)	23 (59.0)	$\chi^2 = 0.01, p = 1.000$
Baseline BMI – Mean (SD)	23.48 (4.88)	22.00 (3.58)	$t(77) = -1.49, p = 0.139$
Follow-up BMI – Mean (SD)	24.23 (4.84)	22.98 (3.16)	$t(89) = -1.39, p = 0.167$
Change in BMI – Mean (SD)	0.67 (1.97)	0.83 (1.67)	$t(76) = 0.37, p = 0.709$
PANSS Global – Mean(SD)	28.48 (7.38)	31.24 (8.29)	$t(88) = 1.66, p = 0.100$
PANSS Positive – Mean (SD)	10.25 (3.33)	12.03 (3.24)	$t(88) = 2.53, p = 0.013^*$
PANSS Negative – Mean (SD)	15.50 (5.40)	18.71 (6.04)	$t(88) = 2.65, p = 0.010^*$
Weighted medication rank sum – Mean (SD)	434.17(326.19)	668.21 (457.37)	$t(90) = 2.87, p = 0.005^*$
Weighted medication gain sum – Mean (SD)	108.73 (96.20)	186.02 (137.34)	$t(90) = 3.18, p = 0.002^*$
Proportion AP problematic – Mean (SD)	0.70 (0.33)	0.60 (0.22)	$t(66) = -1.40, p = 0.167$
Treatment prior to hospitalization – Mean (SD)	2.10 (4.13)	1.48 (0.87)	$t(88) = -0.90, p = 0.368$

recorded at both times experienced a statistically significant average increase of 0.74 (SD = 1.84) between admission and the research visit ( $t(77) = 3.56, p < 0.001$ ) and we observed clinically significant weight gain ( $\geq 7\%$ ) in 30.4% of participants. Within our sample, none of the participants had a personal history of type 2 diabetes mellitus or hypertension; one participant was diagnosed with and treated for hypothyroidism, two were chronically treated for allergies, and one was treated for gastroesophageal reflux disease. Additionally, none of the participants exhibited signs of hypertension or diabetes in their blood work and blood pressure measurements. Among the participants, 51.2% reported nicotine use, and none had a prior diagnosis or treatment for substance use disorder at the time of admission.

### Prescription patterns

The numbers of people prescribed each of the following medications as their first medication after admission were: risperidone ( $n = 57$ ), olanzapine ( $n = 29$ ), quetiapine ( $n = 3$ ), aripiprazole ( $n = 2$ ), and clozapine ( $n = 1$ ). The total number of different medications used was 15 (mean = 2.52 medications per individual, SD = 1.68) in our sample. More than half of the individuals (57%) who received risperidone or olanzapine were additionally treated with another AP medication during hospitalization. Less than half of the individuals (44/92) remained on their first prescribed medication for the whole duration of follow-up (for 33.1 days [SD = 17.1], with a median of 31 days). The average duration before the first change of medications (switch or addition of a new medication), was 17.6 (SD = 17.9, median = 10) days.

One third of individuals (32.6%) remained on a monotherapy for the entire duration of follow-up (33.1 [SD = 17.1] days, median 31 days). Almost half of the individuals (42.4%) had a positive slope for ranking of meds based on metabolic side effects. This was related to switch to a combination treatment:  $N = 12$ , switch to a metabolically more problematic medication:  $N = 4$ , and a switch to a combination treatment with a more metabolically problematic medication:  $N = 23$ . Therefore, 35/39 individuals in

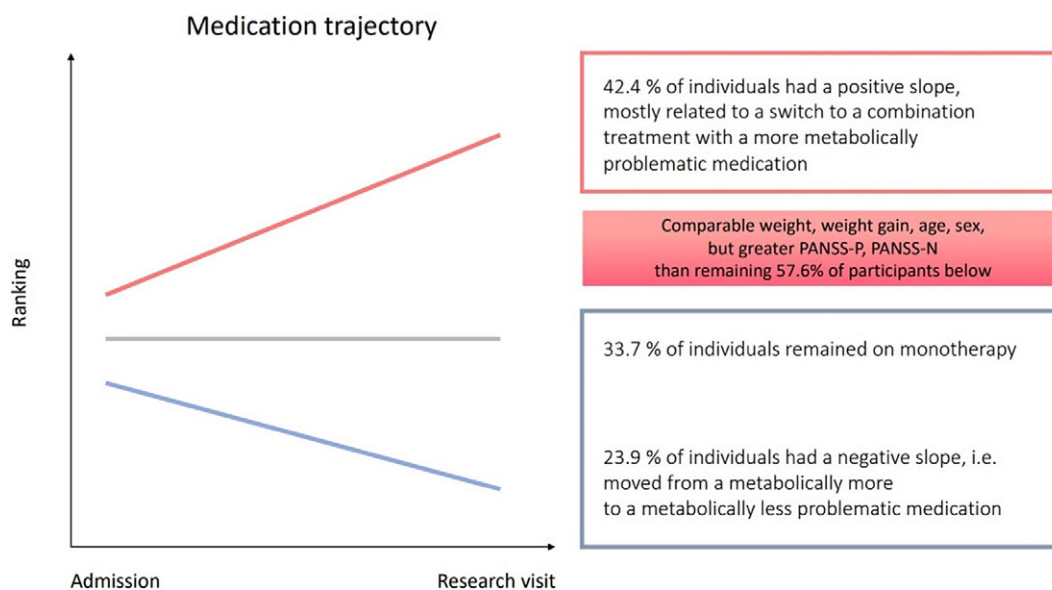
this group (~90%) moved to treatment with polypharmacy. Only 23.9% of individuals ( $n = 22$ ) had a negative slope, that is, moved from a metabolically more to a metabolically less problematic medication. Relative to those with negative slope, individuals with positive slope had greater PANSS scores for positive and negative symptoms at follow-up (see Table 1), indicating possibly that people with more symptoms/worse response needed escalation of medication (see Figure 2). Twenty-six of 92 participants (28.2%) were treated with antidepressants, 5 individuals took valproic acid, 1 lithium, and 1 modafinil.

### Impact of prescription patterns on baseline weight or weight gain

Baseline BMI was not associated with the slope or intercept of medication ranking or dose (see Table 2) or with the initial dose ( $t(74) = -1.21, p = 0.231$ ) or the initial medication's rank ( $t(74) = -0.13, p = 0.897$ ), suggesting that weight was not a factor in selecting the initial medication. When we jointly analyzed the main predictors of weight gain, age, sex, duration of treatment, and baseline BMI with the new measures, including slope and intercept for dose, rank, only low baseline BMI was a predictor of greater BMI increase (see Table 2). Sex did not influence the effects of rank slope ( $F(1,65) = 2.39, p = 0.127$ ), rank intercept ( $F(1,65) = 0.01, p = 0.939$ ), dose slope ( $F(1,65) = 0.49, p = 0.485$ ), or dose intercept ( $F(1,65) = 0.53, p = 0.471$ ), on weight gain. Taking a median split on baseline BMI, the lower 50% of participants gained on average 1.53 points (SD = 2.28). The higher 50% of participants also gained weight, on average gaining 0.40 points (SD = 2.12). Notably, the slope or intercept of medication ranking, or dose were not significantly associated with change in BMI (see Table 2). Retrospective power analysis shows that effects of medication rank would not be significantly associated with change in BMI, even at a much higher sample size, that is, thousands of participants, thus suggesting this to be a true negative finding (see Table 2).

There was a positive association between dose intercept versus rank intercept ( $t(90) = 3.18, p = 0.002$ ). That is, when treating





**Figure 2.** Comparison of AP medication trajectories from admission to the research visit and their characteristics.

**Table 2.** Predictors of baseline BMI, change in BMI, and change in weight (\*,  $p < 0.05$ )

Outcome	Predictor	Estimate (SE)	Standardized coefficient (SE)	Significance	Sample required for power 0.80
Baseline BMI	Rank intercept	0.080 (0.142)	0.068 (0.119)	$F(1,74) = 0.32, p = 0.573$	1838
	Dose intercept	0.001 (0.001)	-0.211 (0.118)	$F(1,74) = 3.18, p = 0.079$	187
	Age	0.232 (0.103)	0.246 (0.109)	$F(1,74) = 5.11, p = 0.027^*$	117
	Sex (M)	2.961 (1.046)	0.340 (0.120)	$F(1,74) = 8.01, p = 0.006^*$	75
BMI change	Medication rank slope	-0.469 (1.569)	-0.079 (0.263)	$F(1,69) = 0.09, p = 0.766$	6052
	Medication rank intercept	-0.029 (0.065)	-0.105 (0.237)	$F(1,69) = 0.02, p = 0.658$	2748
	Dose slope	-0.001 (0.001)	-0.150 (0.219)	$F(1,69) = 0.47, p = 0.495$	1151
	Dose intercept	0.001 (0.001)	0.280 (0.307)	$F(1,69) = 0.83, p = 0.364$	651
	Baseline BMI	-0.115 (0.052)	-0.497 (0.225)	$F(1,69) = 4.89, p = 0.030^*$	113
	Treatment duration	0.007 (0.013)	0.164 (0.297)	$F(1,69) = 0.31, p = 0.582$	1770
	Age	-0.027 (0.047)	-0.123 (0.218)	$F(1,69) = 0.32, p = 0.574$	1697
	Sex (M)	0.623 (0.488)	0.310 (0.243)	$F(1,69) = 1.63, p = 0.206$	334

Note: The sample size required to achieve a power of 0.80, given the size of each effect, is shown.

clinicians used a high dose, they also used a more metabolically problematic medication.

Medication-naïve participants gained on average 0.98 BMI points (SD = 2.27), while those with treatment history gained 0.94 (SD = 2.27). Being medication-naïve had no significant influence on weight gain when controlling for baseline BMI, age, sex, and duration of treatment ( $F(1,72) = 0.21, p = 0.652$ ). Being prescribed an antidepressant was not significantly associated with change in BMI ( $t(75) = 0.78$ ),  $p = 0.438$ ). The use of other medications was so low to prevent any systematic analyses of their associations with weight gain.

### Comparison of extremes

Relative to the third of individuals who gained the least amount of weight (mean BMI change of -1.02, SD = 0.87), the third of individuals who gained the most weight (mean BMI change of 3.24, SD = 2.25) had significantly lower global, positive and negative

symptom scores at the end of the follow-up, a trend for longer prehospitalization antipsychotic treatment and a trend for greater exposure to medications with the highest potential for weight gain (expressed as weighted medication gain sum; see Table 3). However, when constrained to the same medications, change in BMI was not significantly associated with positive ( $t(66) = 1.28, p = 0.205$ ); negative ( $t(66) = 1.80, p = 0.077$ ); or global ( $t(66) = 0.04, p = 0.968$ ) PANSS scores.

### Discussion

This study provides ecological insights into inpatient treatment of FEP and its impact on weight. Most individuals admitted to the hospital for the first episode of psychosis started treatment with either risperidone or olanzapine. Less than half of the individuals remained on the same medication throughout their first hospitalization, and only a third of people with FEP remained on monotherapy. The first switch or addition of new medication happened

**Table 3.** Demographic and clinical characteristics of participants whose change in BMI during treatment was among the lowest and highest 33% (\*,  $p < 0.05$ )

	Change in BMI		Significance
	Bottom 33%	Top 33%	
Sample size	26	28	
Age – Mean (SD)	25.10 (4.72)	23.66 (4.09)	$t(52) = -1.19, p = 0.238$
Sex, male – No. (%)	17 (65.4)	24 (85.7)	$\chi^2 = 2.04, p = 0.153$
Drug-naïve – No. (%)	15 (57.7)	18 (64.3)	$\chi^2 = 0.05, p = 0.828$
Baseline BMI – Mean (SD)	23.86 (4.14)	22.01 (4.65)	$t(52) = -1.54, p = 0.130$
Follow-up BMI – Mean (SD)	22.84 (3.82)	25.25 (4.78)	$t(52) = 2.04, p = 0.047^*$
Change in BMI – Mean (SD)	-1.02 (0.87)	3.24 (2.25)	$t(52) = 9.03, p < 0.001^*$
PANSS Global – Mean (SD)	33.40 (6.92)	26.50 (7.09)	$t(51) = -3.58, p = 0.001^*$
PANSS Positive – Mean (SD)	12.40 (4.13)	10.04 (3.11)	$t(51) = -2.37, p = 0.022^*$
PANSS Negative – Mean (SD)	18.08 (5.26)	14.79 (4.63)	$t(51) = -2.43, p = 0.019^*$
Problematic AP, average daily dose – Mean (SD)	400 (218)	360 (221)	$t(40) = -0.58, p = 0.567$
Nonproblematic AP, average daily dose – Mean (SD)	465 (503)	308 (284)	$t(40) = -1.27, p = 0.211$
Problematic AP, cumulative exposure – Mean (SD)	12821 (9615)	16134 (13034)	$t(40) = 0.92, p = 0.363$
Nonproblematic AP, cumulative exposure – Mean (SD)	11381 (11514)	9322 (7751)	$t(40) = -0.69, p = 0.494$
Medication rank intercept – Mean (SD)	13.49 (3.98)	14.65 (4.10)	$t(48) = 1.02, p = 0.315$
Medication rank slope – Mean (SD)	0.04 (0.16)	0.04 (0.18)	$t(48) = -0.04, p = 0.969$
Medication dose intercept – Mean (SD)	13142 (8306)	16515 (13022)	$t(48) = 1.09, p = 0.280$
Medication dose slope – Mean (SD)	122 (191)	70 (222)	$t(48) = -0.89, p = 0.380$
Weighted medication rank sum – Mean (SD)	480.84 (260.64)	603.44 (440.11)	$t(48) = 1.20, p = 0.237$
Weighted medication gain sum – Mean (SD)	118.12 (65.32)	170.22 (137.43)	$t(48) = 1.71, p = 0.093$
Proportion AP problematic – Mean (SD)	0.60 (0.29)	0.62 (0.30)	$t(40) = 0.21, p = 0.834$
Treatment prior to hospitalization – Mean (SD)	1.39 (1.73)	3.36 (4.93)	$t(51) = 1.92, p = 0.060$

within a median of 10 days. Almost half of the individuals (42.4%) experienced an escalation of medications, mostly a switch to a medication with a worse metabolic profile than their initial treatment. De-escalation of medications, that is, switch to a medication with less propensity for metabolic changes was rare, happened only in 23.9% of individuals. The medication choices and changes appeared to be primarily related to symptoms and were unrelated to baseline BMI. Among the potential predictors, only lower baseline BMI was associated with greater weight gain. Slope or intercept for medication rank or dose, which reflect the patterns of medication changes were not related to weight gain and would not be even with thousands of individuals. Even when we expressed the metabolic burden of medications as average weight gain reported in previous meta-analyses, the results remained the same.

The observation that baseline BMI might serve as a predictor for subsequent weight gain during antipsychotic treatment is an extensively replicated finding. Baseline BMI is a predictor of weight gain over long (3–5 years [8, 9]) intermediate (39–52 weeks, [7, 10]) or even relatively short term of 3 months [29, 30] in people with schizophrenia spectrum disorders. Importantly, our study is the first to demonstrate that baseline BMI predicts weight gain in naturalistic setting, over a very short period of 6.3 weeks in a population experiencing their first episode of psychosis. This did not appear to be a simple regression to the mean, as individuals in both the higher and lower median gained weight.

Our study provides support for two other predictors of weight gain, type of medication, and duration of medication treatment.

After on average weeks of treatment, the effect of these factors was evident, but only as trend and when comparing extremes of weight change. People who gained the most weight had a trend for greater exposure to metabolically more problematic meds or a longer duration of prehospitalization treatment than people who lost weight. This is in line with many previous studies [4, 27, 31, 32]. It is likely that over time the effect of the type of medication and duration of treatment would become more pronounced and would not be evident only when comparing extremes of weight change. This further suggests that baseline BMI is a faster and more general predictor than type of medication or duration of treatment. In addition, there is little we can do about the duration of treatment or the selection of medication, which are mostly dictated by the severity/type of illness. However, we can screen for people with baseline low BMI and be particularly cautious in treating those, by prescribing them medications with the lowest potential for weight gain.

In our study, the starting point or trajectory of medication changes was not related to weight gain after an average of 6.3 weeks of treatment. This is in contrast to studies, where transitioning to olanzapine for 3 months to 1 year was associated with significant weight gain [33, 34]. In a before-to-after switch meta-analysis, there was no statistically significant change evident when switching to amisulpride, quetiapine, paliperidone, risperidone, or lurasidone [17]. This is similar to our findings. In contrast, a significant increase in weight was noted when switching to olanzapine (+2.7 kg) and clozapine (+2.8 kg) [17], but the mean study duration

was 26.3 weeks compared to 6.3 weeks in our study. With these longer intervals, we are essentially seeing the effect of the prolonged use of the new medication. This is in keeping with our findings, where individuals who experienced the most pronounced weight gain had greater exposure to metabolically more problematic meds than people with the lowest weight gain. We can conclude from this that the switch itself even to a more metabolically problematic medication is not causing weight gain over a relatively short period of time (weeks to months). In the short term, baseline BMI was a more sensitive predictor of weight gain than medication changes.

We observed an association between weight change and symptoms, such that individuals who gained the most weight showed fewer symptoms at follow-up than individuals who lost weight. This association was documented in other studies [35–38]. However, when constrained to the same medications, BMI change was not associated with any symptoms in any model. We only saw this effect in a strict comparison of the top and bottom 33% (i.e., Table 3) based on weight gain. However, people in these two groups were not treated with the same medications. So in our study, treatment response to a medication was not associated with weight gain. What we effectively observed was that individuals who gained weight had a trend for greater exposure to metabolically more problematic medications and fewer symptoms at follow-up; that is, a more aggressive treatment led to both a greater weight gain and fewer symptoms. This seems in keeping with the presumably greater efficacy of metabolically more (-ines) versus metabolically less problematic (-oles) medications [27].

Our study provides an interesting snapshot of how closely the treatment in a large psychiatric hospital conforms with guidelines. In certain instances, the observed patterns were in line with guidelines. The majority of individuals with FEP in our study initiated treatment with risperidone ( $n = 57$ ), followed by olanzapine ( $n = 29$ ), which is in keeping with the Czech guidelines [39]. Other international guidelines, such as National Institute for Health and Care Excellence [40], Guidelines for the Pharmacotherapy of Schizophrenia in Adults, Canada [41], and APA guidelines [42] do not recommend specific medications in individuals with FEP, but only advocate for consideration of side effects. In contrast, Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for early psychosis [43] and Swiss guidelines for early psychosis [44] treatment caution against olanzapine as the first-choice medication, recommending it only as a second-line option. Guidelines, to some extent, do seem to determine treatment in a given country. It is thus concerning that there are such vast differences between guidelines when all should be based on the same evidence. Greater attempts should be made to synchronize the guidelines and make them more closely reflect the most up to date evidence.

Our study also reveals a notable discrepancy between clinical practices and guideline recommendations. Approximately two-thirds of individuals in our sample were treated with AP polypharmacy. This is in keeping with some other studies from Europe, Canada, and the United States, which have reported polypharmacy rates ranging widely from 19% to 67% [13, 45–49]. While there is evidence supporting the potential superiority of antipsychotic cotreatment over monotherapy in certain clinical situations, such as combining aripiprazole with clozapine associated with the lowest risk of rehospitalization [49, 50], the current recommendations for first-line treatment in early psychosis continue to emphasize antipsychotic monotherapy. Despite limited research on polypharmacy in FEP and the consequent absence of guideline recommendations, they remain the most frequent pattern in clinical practice.

This study has important clinical implications. Despite initiating treatment with metabolically problematic medications, a substantial number of individuals (40/92) experienced an escalation of medications, in 90% of cases, an addition of another medication. The main concern with using metabolically less problematic medications may be their presumably lower efficacy [51]. This is not necessarily supported by meta-analytical evidence [52, 53]. If these medications were less effective, we could expect even more switches if commencing treatment with metabolically less problematic options. However, it might not be a significant concern since early switches did not impact weight gain. Starting individuals on metabolically less problematic medications could offer a greater number of people a better chance of avoiding weight gain. For this reason, advocating for the less metabolically problematic medications as a first-line treatment early in the course of illness is warranted, even if they were less effective, which is not clear. Unfortunately, in some countries, including Czechia, insurance companies do not cover prescription of the safer medications to those with low to normal baseline BMI.

The strengths of this study include the real-life setting of a large psychiatric hospital, a range of medications, and a broad representation of individuals with psychotic disorders in novel prospective design. The inpatient setting minimizes possibility of medication nonadherence and dietary differences among individuals, thereby ensuring abstinence from other psychoactive substances. Research on early psychosis brings advantages and minimizes the impact of past medication exposure and illness, creating more sensitive circumstances for detection of medication-related alterations. In our study, all diagnostic and clinical assessments were conducted by clinical psychiatrists, thereby minimizing other potential sources of error. Furthermore, we had access to daily chart notes and had the opportunity to precisely measure medication exposure, which is uncommon in real-world studies on FEP. We applied a novel method, which allowed us to track the trajectory of prospectively tracked medication changes and evaluate their impact on weight.

This study has the following limitations. This was not an RCT. However, clinical practice may significantly differ from controlled trials, and certain questions may only be addressed in naturalistic designs. We can only assume the reasons for changes in medication, and there is a potential for patient/prescriber bias. Although our study provides a detailed and precise description of AP usage day by day, physical measures and psychopathology were assessed only at the end of the study during the research visit, thus limiting our temporal resolution. Physical activity, diet, substance abuse, and socioeconomic factors prior to hospitalization could not be controlled. We screened for illegal substance use and misuse, as well as alcohol and nicotine consumption, during a clinical assessment, but not by a standardized questionnaire. At the same time, information about substance abuses, especially in people who are acutely psychotic may not be accurate by any means. Of note, in the Czech Republic, smoking is allowed on psychiatric wards, so there was no change in smoking habits during hospitalization that could possibly lead to additional weight changes. Weight gain during hospitalization may be higher than it would be in an outpatient setting. The average duration of follow-up was relatively short, but it was sufficient for people to gain weight. In addition, it allowed us to establish the most sensitive, fastest predictor of weight changes.

To conclude, we demonstrated that early in the course of illness, during inpatient treatment, baseline BMI remains the strongest predictor of weight gain on APs and is a better predictor than type of medication, initial medication, polypharmacy, or medication switches. Remarkably, baseline BMI may also be one of the fastest predictors, as it predicted weight change over a very short period of

time, that is, just weeks, when other traditional predictors did not yet demonstrate an effect. Type of medication or treatment duration early in the course of treatment are relevant only when comparing extremes of weight change, so are likely slower to impact weight gain than the baseline BMI. The study supports the use of metabolically less problematic medications as a first-line treatment early in the course of illness, especially in people with low baseline weight. This approach would give more people a greater chance to prevent/delay medication-related weight gain.

**Supplementary material.** The supplementary material for this article can be found at <http://doi.org/10.1192/j.eurpsy.2024.1761>.

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**Competing interest.** The authors declare none.

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