Psychiatry Research 348 (2025) 116452

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Unraveling antipsychotic induced weight gain in schizophrenia – A proof-of-concept study exploring the impact of the cumulative historical occupancy of different receptors by antipsychotics

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ARTICLE INFO

Keywords:
Antipsychotics
Obesity
Pharmacodynamics

ABSTRACT

Obesity is a common complication in schizophrenia contributing to increased mortality rates. We present a proof-of-concept study displaying a new method to investigate the impact of antipsychotic drugs (APs) on obesity in terms of their cumulative historical receptor occupancy (CHRO) in 150 selected from 174 patients with schizophrenia. Based on a thorough medication history, we estimated CHRO of serotonin 5-HT_{2C}, histamine H_1, dopamine D_2 and muscarinic M_3 receptors and studied their relationship with different metabolic outcome variables utilizing stepwise regression analysis and structural equation modelling (SEM).

Stepwise regression analysis revealed a significant positive relationship of Body Mass Index (BMI) with H_1-CHRO, but a negative relationship with M_3-CHRO. Moreover, H_1-CHRO was associated with increased triglyceride concentration, while 5-HT_{2C}-CHRO was associated with increased waist circumference and blood pressure. SEM, while confirming the diverging effects of H_1-/5-HT_{2C}- and M_3-CHRO on obesity, suggested that their effect on other metabolic variables was indirect, i.e. mediated by obesity.

Our results suggest that the metabolic side effects of antipsychotics can be described by their cumulative historical receptor occupancy with unique contributions of the different receptors. In particular, M_3 receptor antagonism seems to exert a protective effect, confirming findings from rodent M_3 receptor knock out models.

These findings may provide a framework for estimating the metabolic burden of future APs, guiding the development of drugs with more favorable metabolic profiles.

1. Introduction

Schizophrenia is a severe mental illness (SMI) that is associated with a broad range of physical health problems, including weight gain, obesity, and metabolic syndrome (Chen et al., 2022; Liang et al., 2022; Meyer and Stahl, 2009). These negative metabolic changes represent high-risk factors for cardiovascular diseases and can be seen as responsible for the mortality gap between patients with schizophrenia and the general population (Correll et al., 2022). Alarmingly, schizophrenia may decrease life expectancy of both men and women by >15 years (Laursen et al., 2014).

The interplay between metabolic alterations and schizophrenia is multifaceted. Straight forward lifestyle factors like limited physical activity, tobacco use, and poor diet choices, but also genetic predisposition, are highly prominent within this population (Olfson et al., 2015). However, the complex role of antipsychotics (APs) as substantial contributors to these metabolic changes must also be considered.

APs play an important role in ameliorating positive symptoms such as hallucinations, delusions, and disorganized thinking in patients with schizophrenia (Ceraso et al., 2022; De Bartolomeis et al., 2022; Tandon, 2011). One of their key characteristics shared by all currently available antipsychotics is dopamine D_2 receptor antagonism, or at least partial

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https://doi.org/10.1016/j.psychres.2025.116452
Received 26 October 2024; Received in revised form 16 March 2025; Accepted 19 March 2025
Available online 20 March 2025

agonism, which seems to be responsible for the antipsychotic effect (Pickar, 1995; De Bartolomeis et al., 2022). Dopaminergic neurotransmission is implicated in the modulation of appetite, but exerts divergent effects impeding unambiguous predictions on metabolic outcomes of D_2 receptor antagonism (Cannon et al., 2004; Szczypka et al., 2001).

However, almost all antipsychotics interact with a multitude of different neuroreceptors other than dopamine. Pleiotropic receptor profiles may contribute to both, antipsychotic effects, and metabolic side effects (Roth et al., 2004), such as changes in body composition and metabolism (Correll et al., 2011). Besides an increased risk for cardiovascular diseases, Antipsychotic-Induced Weight Gain (AIWG) may affect patients' quality of life (Faulkner et al., 2007). Hence, AIWG significantly contributes to nonadherence and discontinuation of antipsychotic medication, especially with agents exhibiting higher metabolic liability, emphasizing the importance of diligent clinical surveillance (De et al., 2024). Accordingly, obese patients were found to be more than twice as likely to miss their medication compared to those with a normal Body Mass Index (BMI) and noncompliance seemed to correlate with subjective distress from weight gain (Weiden et al., 2004; Dayabandara et al., 2017).

Among the different targeted receptors, histamine H_1 and serotonin 5-HT_{2C} receptors appear to be most relevant with regard to weight gain and disturbances of lipid or glucose metabolism (Montastruc et al., 2015). Adverse metabolic effects can be categorized by their site of action in the periphery as well as in the central nervous system (Ballon et al., 2014; Carli et al., 2021). Within the latter, the hypothalamus constitutes a key structure responsible for regulating appetite, food intake, and energy expenditure (Mukherjee et al., 2021). A growing body of evidence indicates that antagonism of H_1 and 5-HT_{2C} converges in increased stimulation of appetite in the hypothalamus (Roerig et al., 2011).

Conversely, antagonism at the muscarinic M_3 receptor may have an opposite effect on obesity-related outcomes, as rodent knock out models consistently exhibit reduced food intake, and potential benefits in glucose homeostasis and energy expenditure (Gautam et al., 2006). Despite this strong evidence for an anti-obesity effect of M_3 receptor knock out models, some researchers have assumed an obesity-promoting effect of M_3 receptor antagonism, given the fact, that olanzapine and clozapine exhibit a high affinity to M_3 receptors (Weston-Green et al., 2012; Yuen et al., 2021).

Considering drug-specific receptor binding profiles, it is not surprising that antipsychotics show different dose response curves with regard to weight gain (Wu et al., 2022). Given the physiological consequences of activating or blocking a particular receptor, the therapeutic effects or adverse reactions may thus be predicted by the degree of receptor occupancy. The receptor occupancy itself is a function of the drug concentration (which is proportional to the given dose) and its binding affinity at the respective receptor. Following this idea, Matsui-Sakata et al. (2005) demonstrated a correlation between H_1 receptor occupancy and weight gain as well as the manifestation of diabetes mellitus after 6 to 10 weeks of treatment with antipsychotics. Moreover, APs with higher binding affinities and antagonistic properties at both, histamine H_1 and serotonin 5-HT_{2C} receptors, showed a stronger association with diabetes than antipsychotics with distinct binding profiles, suggesting an elevated risk of glycaemic dysregulation (Montastruc et al., 2015).

Detached from acute effects of receptor occupancy, some effects may also cumulate over time. There is growing evidence for time-dependent effects of antipsychotics on weight gain (Nasrallah, 2003). However, current literature lacks comprehensive studies that focus specifically on time-dependent effects on the receptor level (Panariello et al., 2011). Addressing these gaps is crucial for the development of more targeted pharmacological interventions with reduced metabolic side effects.

Therefore, we created a new method to study long-term drug effects on a receptor level. While this approach might be applied to various research questions, we present a first use case assessing metabolic side effects of antipsychotics in patients with schizophrenia. For each patient, we tried to estimate its individual cumulative historical receptor occupancy (CHRO) based on self-reports and medical files. This allowed us to aggregate data from different drug treatments into a single analysis, thereby increasing the number of observations entering the statistical model.

Among the different receptors that are affected by antipsychotics, we focussed on four receptors implicated in weight gain and metabolic side effects: histamine H_1, serotonin 5-HT_{2C}, dopamine D_2 and muscarinic M_3 receptors. We investigated the consequences of the CHRO of each receptor on obesity as well as additional metabolic outcome variables while controlling for age, duration of illness and psychopathology.

We hypothesized that higher cumulative occupancy of H_1, 5-HT_{2C} and D_2 receptors is associated with obesity, high blood pressure and adverse effects on lipid and glucose metabolism, while we expected the opposite effect for M_3 receptor occupancy.

By expanding our understanding of the mechanisms underlying antipsychotic-induced weight gain, this research may contribute to the development of new strategies for the prevention and treatment of metabolic disturbances in patients with schizophrenia.

2. Materials and methods

2.1. Participants

Patients were recruited within the framework of a brain imaging trial (Gaebler et al., 2023, 2022a, 2022b), conducted at the Department of Psychiatry, Psychotherapy, and Psychosomatics of RWTH Aachen University Hospital, and four academically associated regional psychiatric hospitals. 150 in- and out-patients suffering from schizophrenia were included in the study despite clinical data being collected from 174 patients. The reason 24 patients were excluded was due to a lack of plausible and verifiable antipsychotic treatment history. The study protocol was approved by the ethics committee of the North Rhine medical association and by the local regulatory authority of RWTH Aachen University Hospital. Written informed consent was obtained from all participants. Diagnosis of schizophrenia was confirmed according to DSM-5 criteria by trained clinical psychiatrists using the structured clinical interview for DSM disorders. The clinical characteristics of the sample are provided in Table 1.

2.2. Medical history

All patients provided information about their current and past medications. Generic name of the antipsychotics, duration, dose, and route of administration were recorded. The data was collected to ensure the accuracy and reliability of antipsychotic treatment records. Patients who reported medication-free intervals exceeding 25 % and more of their disease duration were further explored to verify the plausibility of

Table 1
Clinical characteristics of patients with Schizophrenia.

	mean	standard deviation	range (min, max)
Age [years]	31.4	10.6	18, 61
years from first diagnosis	3.6	5.5	0, 24
PANSS positive total	16.7	7.1	7, 37
PANSS negative total	18.3	6.7	7, 40
blood pressure systolic [mmHg]	126.6	15.4	100, 181
blood pressure diastolic [mmHg]	80.6	13.2	40, 121
BMI [kg/m^2]	24.6	4.8	15.7, 44.1
waist circumference [cm]	97.6	27.5	55.0, 197.0
HbA1c [%]	5.2	0.5	4.5, 8.3
Triglycerides [mg/dL]	166.9	126.2	33, 754
Cholesterol [mg/dL]	177.5	47.0	79, 369
LDL/HDL ratio	2.4	1.1	0.7, 6.4
Gender	n	%	
male	113	75	
female	37	25	

their reported treatment. 24 out of the original 174 patients had to be excluded from the study due to a lack of plausible and verifiable antipsychotic treatment history. For each of the remaining 150 patients and each receptor of interest (roi, i.e. histamine H_1, serotonin 5-HT_{2C}, dopamine D_2 and muscarinic M_3 receptors), individual CHROs were calculated using the following formula

$$CHRO\ (roi) = \sum_{i=1,\ j=1}^{i=m,\ j=n_i} \frac{\mathrm{dose}_{i,j}(\mathrm{AP}_i) * \mathrm{t}_{i,j} * \mathrm{Kd}_{roi}(\mathrm{CPZ})}{\mathrm{Kd}_{roi}(AP_i)\ *\ \mathrm{M}(AP_i)}$$

with indices "i" and "j" denoting the "i^{th}" antipsychotic drug in the patient's medication history and its "j^{th}" treatment dosage given for a duration of "$t_{i,j}$" [days]. Kd denotes the receptor dissociation constant of the given drug which was obtained from the NIMH Psychoactive Drug Screening Program (PDSP) Database (Besnard et al., 2012). Chlorpromazine (CPZ), a widely recognized benchmark drug, considered as the prototypical antipsychotic, was chosen as the reference compound due to its broad spectrum of receptor affinities. Its selection ensures more relatable comparison, since it is often used as a standard for comparing the potency of other antipsychotics (chlorpromazine equivalent dose) (Davis and Chen, 2004). To further enhance the comparability, the molecular weight of the drug (M) was also included into the calculations. For participants receiving antipsychotics in long-acting parenteral form, the administered dose was converted into an equivalent daily dose to ensure consistency in the calculation of receptor occupancy.

Table 2 provides a comprehensive overview of the antipsychotic medications administered in the study. For each medication, the table lists the number of patients receiving the treatment, the average dose in milligrams per day (mg/d), and the average duration of treatment in days. Additionally for better comparison, the table includes a listing of patients who received no antipsychotic (AP) medication.

2.3. Statistical analysis

The statistical analysis was performed using SPSS (Version 29.0. Armonk, NY: IBM Corp) and R version 4.1.2 (R Core Team, 2013) including package "lavaan" (Rosseel, 2012). Since curve fitting analysis revealed a best fit for a logarithmic relationship between the cumulative historical receptor occupancy and the dependent metabolic variables, the CHRO measure for each receptor was log-transformed before entering the subsequent statistical analyses.

In order to determine the most significant receptor effects on the metabolic outcome variables, we conducted a stepwise regression analysis. This analysis also enabled us to account for correlated CHROs and to control for further influential variables, such as age, years since initial diagnosis (as a proxy for the duration of illness), and psychopathology. The analyses were carried out applying forward selection with a significance level of $p < 0.05$ for variable inclusion and listwise treatment of missing values.

Table 2
Overview of antipsychotic medication and treatment duration.

medication	N(patients)	dose [mg/d]		duration [days]	
		mean	SD	mean	SD
amisulpride	30	433.3	233.4	640.4	1258.3
aripiprazole	48	14.7	738.3	482.6	6.3
clozapine	16	330.5	159.1	1078.4	1624.2
haloperidol	10	6.5	4.4	327.8	912.6
olanzapine	52	15.9	5.8	390.4	861.9
paliperidone	9	12	2.8	593.8	691.5
quetiapine	21	383	308.6	1326	2229.6
risperidone	48	3.3	1.3	278.5	1003.0
ziprasidone	7	82	38.1	325.2	469.0
no APs	34	0		0	

AP = antipsychotic drug.

In this framework, we conducted a separate stepwise regression analysis for each metabolic variable (body mass index (BMI)), waist circumference, systolic blood pressure, diastolic blood pressure, serum concentrations of triglycerides and cholesterol, LDL/HDL ratio and HbA1c) while the log-transformed CHROs of the four receptors of interest (histamine H_1, serotonin 5-HT_{2C}, dopamine D_2 and muscarinic M_3 receptors), years from first diagnosis, age, and PANSS positive and negative sum scores served as independent variables for potential inclusion in the model. To correct for multiple testing, each p-value corresponding to the F-test of overall significance of the final regression model of the respective dependent variable was corrected according to a false discovery rate (FDR) of $p < 0.05$.

To further explore the presumable hierarchical structure of the different variables, we applied structural equation modelling (SEM). To maintain sufficient simplicity of the model, the number of variables was reduced. Specifically, 'years from first diagnosis' was not integrated in the model due to its obvious dependence on age which itself is widely acknowledged as one of the most important factors contributing to obesity (Jura and Kozak, 2016). Based on the results of the stepwise regression analysis, all dependent variables that demonstrated a significant relationship with CHRO were included in the structural equation model (SEM). These variables comprised the systolic blood pressure, diastolic blood pressure, triglycerides, the LDL/HDL ratio, and HbA1c. Cholesterol was excluded from the model as it did not exhibit a significant relationship with any CHRO.

We assumed that the different explanatory variables (age, log-transformed CHROs) would exert a direct effect on obesity only, while the latter would affect the other metabolic variables. In this context, the latent variable "obesity" was defined by the two observed variables BMI and waist circumference. No other latent variables were used in the model. All observed variables were z-standardised before entering the model.

For a detailed view of the specific structure and analyses, please refer to Fig. 2.

3. Results

3.1. Stepwise regression

To identify the most relevant receptors contributing to the different metabolic outcome variables (while controlling for further influential factors), we conducted a stepwise regression analysis. For a comprehensive overview of the significant receptor occupancies entering the final stepwise regression model for each metabolic variable, see Fig. 1.

3.1.1. Measures of obesity

For the dependent variable BMI, the final regression model included four predictors in the following order: years from first diagnosis, age, histamine H_1, and muscarinic M_3-CHRO. The adjusted R^2 increased from 0.268 (only predictor "age" included) to 0.373 (all four predictors included) and the overall F-test indicated a significant fit ($F(4125) = 20.165$; p-FDR<0.001). Importantly, in the final model, years from first diagnosis, age and the cumulative H_1-CHRO exhibited a positive relationship with BMI (beta = 1.435, standard error= 0.515, standardized beta= 0.782, $p = 0.006$, see Fig. 1a.) whereas M_3-CHRO exhibited a negative relationship with the dependent variable (beta = −1.145, standard error=0.519, standardized beta= −0.606, $p = 0.029$, see Fig. 1b.) suggesting that a higher cumulative M_3 receptor occupancy was associated with a lower BMI. Notably, this negative relationship became only evident within the framework of the stepwise regression analysis, i.e. when controlling for the three other explanatory variables. In contrast, a standard bivariate regression analysis would have suggested a positive relationship which is explained by the correlation between H_1- and M_3-CHRO ($r = 0.961$, $p < 0.001$, $N = 150$)

When using waist circumference as the dependent variable, only serotonin 5-HT_{2C}-CHRO was included in the model (adjusted R^2=0.038;

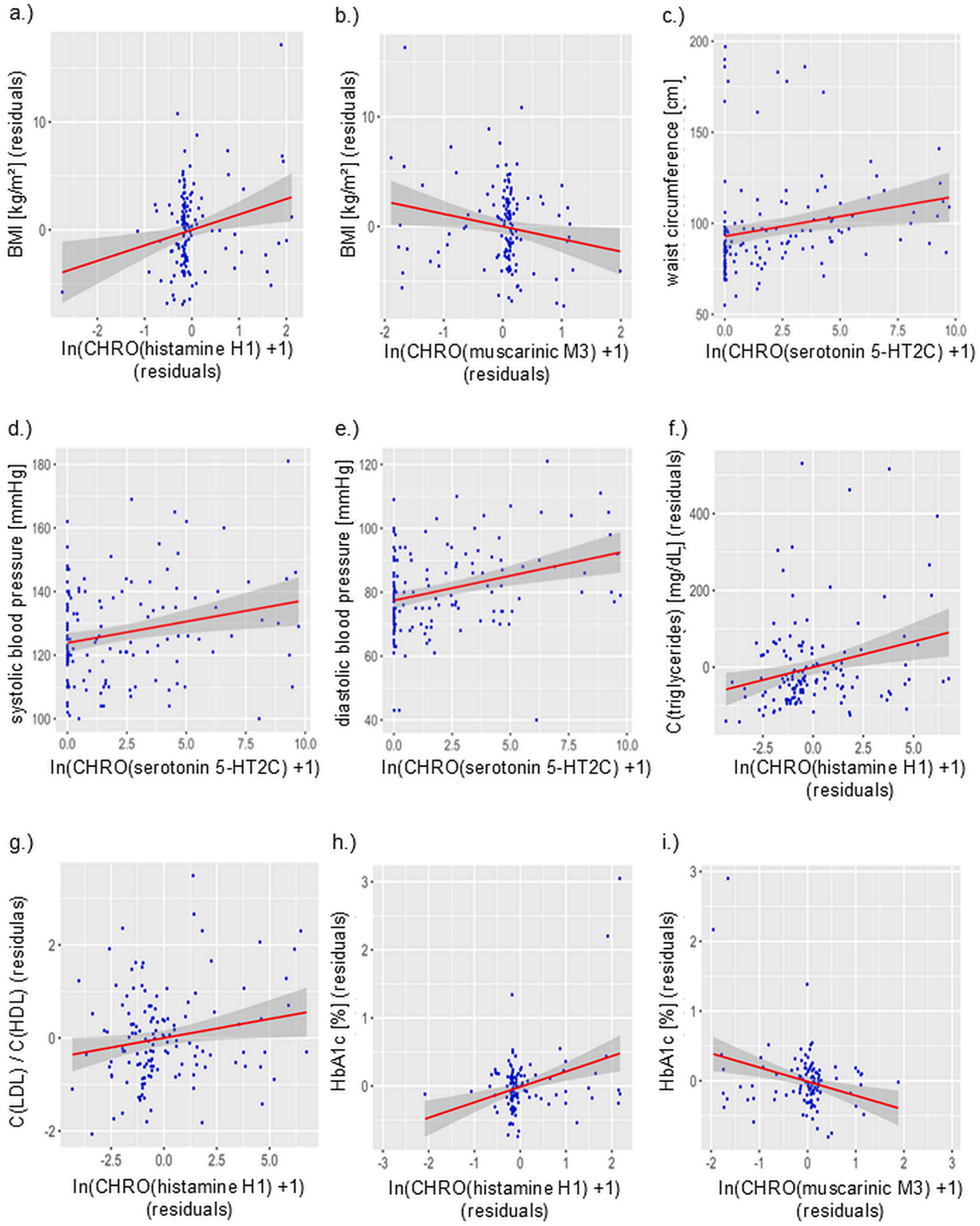

Fig. 1. Scatter plots demonstrating the relationship between the different metabolic variables and the significant cumulative receptor occupancies which were included as predictors in the stepwise regression analyses. If more than one predictor was included in the model, added variable plots were generated using the residuals obtained from a regression of respective metabolic measure (y-coordinate) or the respective receptor occupancy of interest (x-coordinate) on the other explanatory variables of the final model of the stepwise regression. Note the inverse relationship of muscarinic M_3 receptor occupancy and BMI in b) and i).

F(1137)=6,5; p-FDR=0.01). As expected, a positive relationship emerged between the two variables (beta = 2.192, standard error=0.860, standardized beta=0.213, $p = 0.012$, see Fig. 1c).

3.1.2. Other cardiovascular risk variables

Similar to waist circumference, for both, systolic and diastolic blood pressure, only serotonin 5-HT_{2C}-CHRO entered the step-wise regression model and in both cases, a positive relationship was observed (systolic blood pressure: beta = 1.343, standard error=0.473, standardized

beta=0.231, p = 0.005, adjusted R^2=0.047, F(1143)=8.048, p-FDR=0.008, see Fig. 1d; diastolic blood pressure: beta = 1.551, standard error = 0.396, standardized beta=0.312, $p < 0.001$, adjusted R^2=0.091, F(1143)=15.377, p-FDR<0.001, see Fig. 1e).

When using triglycerides as the dependent variable, in two steps, histamine H_1-CHRO (beta=13.380, standard error=4.461, standardized beta=0.267, p = 0.003) and age (beta=2.432, standard error=1.048, standardized beta=0.206, p = 0.022) entered the model while the adjusted R^2-value increased from 0.126 to 0.152 (F(2134)=13.21, p-FDR<0.001, see Fig. 1f).

For the dependent variable cholesterol, only age (beta = 1.969, standard error=0.338, standardized beta=0.446, $p < 0.001$) entered the model (adjusted R^2=0.193, F(1137)=33.955, p-FDR<0.001)

For the dependent variable LDL/HDL ratio, the final regression model included two predictors in the following order: age and H_1-CHRO. The adjusted R^2 increased from 0.231 (with only the predictor "age" included) to 0.252 (both predictors included), and the overall F-test indicated a significant fit (F (2132) =23.533; p-FDR < 0.001).

In the final model, both predictors exhibited a positive relationship with the LDL/HDL ratio: age (beta = 0.042, standard error = 0.009, standardized beta=0.400, $p < 0.001$) and H_1-CHRO (beta = 0.082, standard error = 0.038, standardized beta=0.184, p = 0.032; see Fig. 1g).

The last stepwise regression analysis examined HbA1c as the dependent variable, three predictors were included in the final model in the following order: H_1-CHRO, M_3-CHRO, and age. The adjusted R^2 increased from 0.091 (only predictor "H_1-CHRO" included) to 0.186 (all three predictors included), and the overall F-test indicated a significant fit (F (3116) =10.064, p-FDR < 0.001).

In the final model, H_1-CHRO showed a significant positive relationship with HbA1c (beta = 0.226, standard error = 0.060, standardized beta=1.231, $p < 0.001$, see Fig. 1h), whereas M_3-CHRO exhibited a significant negative relationship (beta=−0.202, standard error = 0.062, standardized beta=−1.066, p = 0.002, see Fig. 1i), suggesting that a higher cumulative M_3 receptor occupancy was associated with a lower HbA1c level. Additionally, age was positively associated with HbA1c (beta=0.011, standard error = 0.004, standardized beta=0.243, p = 0.013).

Since there is also evidence for a relevant contribution of $5HT_{2A}$ receptors to obesity, we conducted an additional exploratory stepwise regression analysis for which we also provided the 5-HT_{2A}-CHRO in addition to the other variables. Interestingly, the results remained unchanged: for none of the dependent variables, the 5-HT_{2A}-CHRO was included in the model. Accordingly, its contribution to explaining the variance in the respective metabolic outcome measures was not statistically significant when accounting for the other predictors in the model.

3.2. Structural equation model

To evaluate the potential hierarchical arrangement of the different variables assessed in this study, we employed a structural equation model (SEM). Our model assumed a direct effect of the cumulative historical receptor occupancy of 5-HT_{2C}, H_1 and M_3-receptors on the latent variable obesity based on the indicators BMI and waist circumference. The effects on the other metabolic outcomes (triglycerides, systolic and diastolic blood pressure, HbA1c, and LDL/HDL ratio) were considered as indirect, i.e. mediated by obesity. Moreover, we assumed a direct influence of age on all cumulative receptor occupancies, obesity and the other metabolic outcomes (triglycerides, systolic and diastolic blood pressure, HbA1c, and LDL/HDL ratio). Indeed, this model demonstrated a good fit to the data, as indicated by the non-significant chi-square test (χ^2 (23) = 23.335, p = 0.441) and other fit indices, including the Comparative Fit Index (CFI=1.000), the Tucker-Lewis Index (TLI= = 0.999), the Root Mean Square Error of Approximation (RMSEA= 0.012, 90 % CI [0.000, 0.080]), and the Standardized Root Mean Square Residual (SRMR= 0.032). Matching our hypothesis, the effect of M_3 receptor occupancy on obesity was the only one exhibiting a negative parameter estimate, indicating an inverse relationship. This means that higher M_3 receptor occupancy was associated with lower levels of obesity. This finding is particularly significant as it contrasts with the positive relationships observed for other receptors, such as H_1 and 5-HT_{2C}, which were associated with increased obesity. For more details, see Fig. 2.

4. Discussion

In the present study, we investigated the effect of different antipsychotic drugs on obesity and other metabolic variables by modelling their temporally cumulative receptor occupancy while controlling for further potentially influential variables such as age, duration of illness and psychopathology.

Our data suggest a temporally cumulative effect of serotonin 5-HT_{2C} and histamine H_1, but not dopamine D_2 receptor occupancy on obesity, serum triglyceride levels and blood pressure. In contrast, cumulative occupancy of muscarinic M_3 receptors exhibited a negative (i.e. protective) effect on obesity, matching studies on rodent knock out models. Finally, our structural equation model confirmed the opposing effects of the respective receptors (5-HT_{2C} / H_1 vs M_3) on obesity, but suggested that the other metabolic effects (affecting triglycerides and blood pressure) might be indirect, i.e. mediated by obesity itself.

For a mechanistic explanation of our findings, it is necessary to understand the regulation of appetite and energy expenditure by the hypothalamus (see Fig. 3). Within this brain region, the arcuate nucleus (ARC) has emerged as a significant contributor to energy balance (Joly-Amado et al., 2014; Sainsbury et al., 2002). The ARC encompasses two primary neuronal subpopulations exhibiting opposing effects on appetite and energy balance (Kouidhi and Clerget-Froidevaux, 2018). First, ARC-POMC neurons are critical regulators of the pro-hormone pro-opiomelanocortin (POMC), which is converted to the biologically active anorexigenic α-melanocyte stimulating hormone (α-MSH) (Millington, 2007; Morton et al., 2006). α-MSH binds to melanocortin 3 and 4 receptors ($MC_3/_4R$), expressed in neurons within the paraventricular nucleus (PVN) of the hypothalamus and brainstem (Ellacott and Cone, 2004). This, in turn, reduces food intake and modulates autonomic nervous system pathways involved in adipose thermogenesis and energy expenditure (Adan et al., 2006; Kim et al., 2000; Labbé et al., 2015; Skibicka and Grill, 2009). The activity of ARC-POMC neurons is regulated by various hormones, including leptin, insulin, glucocorticoids, and thyroid hormones (Cone et al., 2001; Coppola et al., 2007; Harlan et al., 2011; Rahmouni and Morgan, 2007).

Second, ARC-AgRP/NPY neurons express the orexigenic molecules agouti-related peptide (AgRP) or neuropeptide Y (NPY), which inhibit ARC-POMC neurons as well as melanocortin 3 and 4 receptors, thus counteracting the anorexigenic effect of α-MSH (Gropp et al., 2005; Ollmann et al., 1997).

Fig. 3 shows a schematic representation of the links between the different receptors assessed in this study and the respective brain regions.

4.1. Serotonin 5-HT_{2C} receptors

Antagonism at 5-HT_{2C} receptors in the ARC of the hypothalamus is associated with reduced cleavage of the precursor hormone POMC, consequently leading to lower levels of the active anorexigenic hormone α-MSH (Baldini and Phelan, 2019; d'Agostino et al., 2018; Doslikova et al., 2013). Beyond the hypothalamus, recent findings from mouse models suggest the existence of a subpopulation of 5-HT_{2C} receptor expressing neurons within the VTA whose chemogenetic activation may lead to decreased incentive value of food (Valencia-Torres et al., 2017). Indeed, antagonistic properties at 5-HT_{2C} receptors may represent one of the major mechanisms of antipsychotic weight gain associated with olanzapine and clozapine (Kirk et al., 2009; Lord et al., 2017; Reynolds

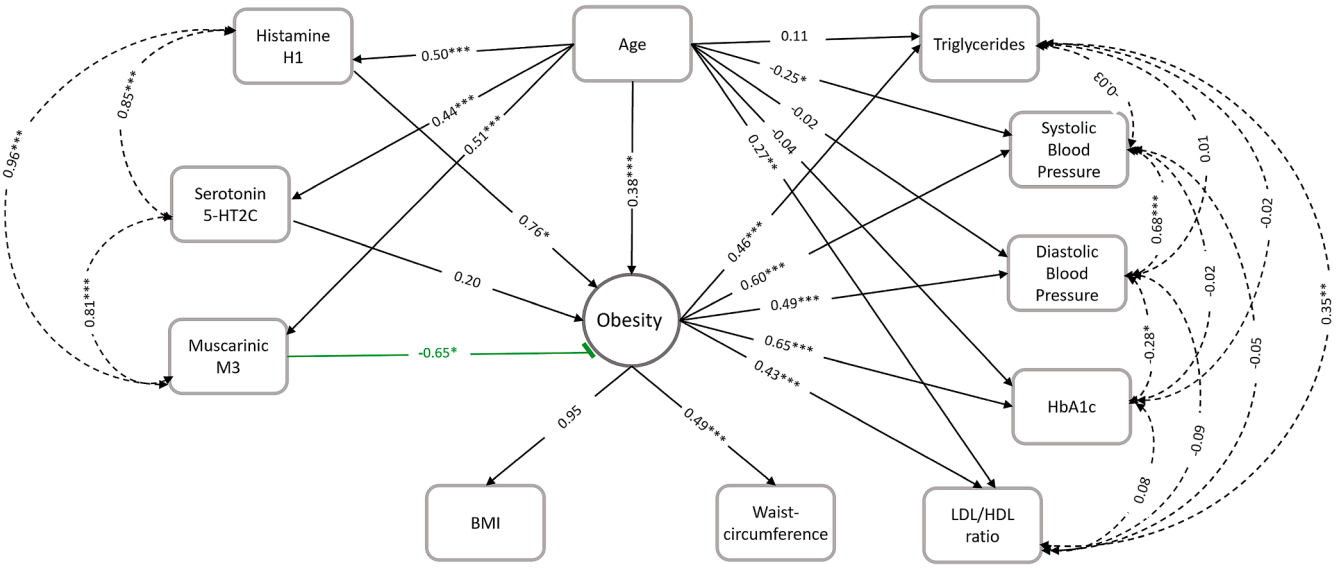

Fig. 2. Overview of our structural equation model (SEM) including standardized parameter estimates. Dashed double arrows represent correlation between variables. In this context, the latent variable "obesity" was defined by the two observed variables BMI and waist circumference. Note the green arrow indicating the inverse effect of muscarinic M_3-CHRO on obesity. ***$p < 0.001$ **$p < 0.01$ *$p < 0.05$.

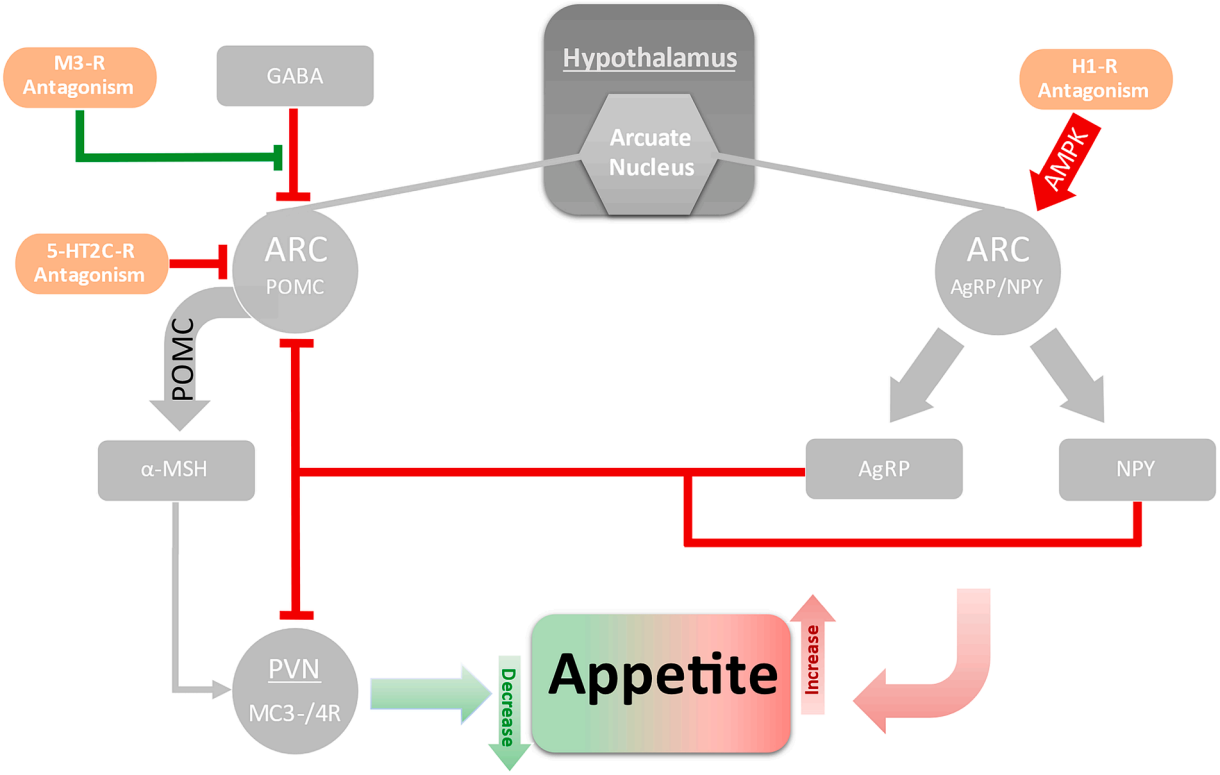

Fig. 3. Schematic overview of hypothalamic appetite regulation and the effects of the different receptors targeted by antipsychotics. The arcuate nucleus (ARC) in the hypothalamus, which is crucial for appetite and energy balance, consists of two opposing neuronal subpopulations: ARC-POMC and ARC-AgRP/NPY neurons. ARC-POMC neurons express pro-opiomelanocortin (POMC), which is cleaved to form the appetite-suppressing hormone α-MSH. The latter binds to $MC_{3/4}$ receptors in the paraventricular nucleus (PVN). 5-HT_{2C} receptor antagonism leads to inhibition of ARC-POMC neurons and accordingly reduced α-MSH production, thereby increasing appetite. In contrast, M_3 antagonism leads to reduced inhibitory GABAergic signalling to ARC-POMC neurons, reducing appetite. ARC-AgRP/NPY neurons co-express orexigenic molecules neuropeptide Y (NPY) and agouti-related peptide (AgRP), inhibiting ARC-POMC neurons and $MC_{3/4}$ receptors, thus counteracting the effects of α-MSH. H_1- antagonism activates 5′ AMP-activated protein kinase (AMPK), increasing the release of NPY and AgRP, and thus appetite. Red arrows indicate appetite increase, green arrows indicate appetite decrease.

et al., 2006). Accordingly, 5-HT_{2C} knock out mouse models are resistant against AIWG induced by olanzapine (Lord et al., 2017). Thus, it may not be surprising that in humans, AIWG also depends on the 5-HT_{2c} receptor genotype with certain alleles being more prone to weight gain during AP treatment than others (De Luca et al., 2007; Mukherjee et al., 2021; Reynolds et al., 2006; Sicard et al., 2010; Wallace et al., 2011;

Zhang et al., 2016).

Along these lines, selective serotonin 5-HT_{2C} receptor agonists have been explored as promising agents for promoting weight loss (Sargent et al., 1997). One of these agonists, lorcaserin, has been approved by the FDA for obesity treatment, demonstrating modest weight reduction with minimal notable side effects (Singh and Singh, 2020; Smith et al., 2009). Moreover, this drug suppressed hyperphagia and weight gain induced by olanzapine in a rodent model, suggesting treatment with this compound may evolve as a reasonable strategy to counteract weight gain related to APs (Lord et al., 2017). The role of serotonin 5-HT_{2C} antagonism as a cardiovascular modulator has been previously explored in the context of blood pressure and sympathetic regulation. Contrary to our long-term findings, short-term antagonism has been shown to decrease blood pressure (Dabire, 1991), whereas short-term agonism led to an increase in blood pressure (Ferreira et al., 2005). Our results suggest that the antihypertensive effects of 5-HT_{2C} antagonists may be counteracted by their obesogenic effects which may promote hypertension in the longer term.

4.2. Histamine H_1 receptors

The association between histamine H_1 receptor antagonism and weight gain is a widely acknowledged phenomenon (Kroeze et al., 2003; Sakata et al., 1988). As a major mechanism, H_1 receptor antagonism leads to phosphorylation of 5′ AMP-activated protein kinase (AMPK) in ARC-AgRP/NPY-neurons resulting in increased release of the orexigenic hormones NPY and AgRP (Kim et al., 2007).

Accordingly, betahistine, a H_1 receptor agonist and H_3 receptor antagonist, represents a promising drug for compensating weight gain mediated by the H_1 antihistaminergic properties of olanzapine (Barak et al., 2016). As expected, mitigation of olanzapine-induced weight gain by betahistine in rodents was associated with a decrease of AMPK-phosphorylation and NPY expression (Lian et al., 2014).

Besides its effect on BMI, our stepwise regression analysis revealed a positive relationship between H_1 receptor occupancy and triglyceride levels. Correspondingly, recent findings by Nikfar et al. (2022) suggest that H_1 agonists exhibit a hypolipidemic effect, leading to a reduction in triglyceride levels. Importantly, when H_1 antagonists were administered simultaneously, this hypolipidemic effect was abolished (Nikar & Rasouli, 2022). Even though our SEM suggests that the long-term effects of antipsychotics on triglyceride concentrations may be explained as a consequence of obesity, we cannot exclude the possibility of direct hyperlipidemic effects of antipsychotics with H_1 antagonistic properties.

4.3. Muscarinic M_3 receptors

The involvement of the muscarinic M_3 receptor in metabolic function remains an actively researched area with limited understanding so far. Most of the current knowledge can be derived from rodent studies. In particular, M_3 muscarinic receptor knockout mice (M_3R-/-) show reduced food intake, body weight and peripheral fat deposits as well as remarkably lower serum leptin and insulin levels (Yamada et al., 2001). Gautam et al. (2006) demonstrated that mice lacking M_3 receptors were protected from various types of experimentally provoked obesity and related metabolic imbalances impacting glucose regulation and insulin sensitivity. Moreover, these mice displayed a notable rise in both, basal and overall energy expenditure, possibly because of a heightened fatty-acid oxidation rate and amplified central sympathetic activity (Gautam et al., 2006). Acetylcholine's effect on food intake may be mediated by cholinergic neurons of the dorsomedial hypothalamus (DMH). Indeed, stimulation of cholinergic DMH neurons promotes food intake which is abolished by the selective M_3 receptor antagonist 4-DAMP (Jeong et al., 2017). Cholinergic DMH neurons project onto GABAergic axon terminals on ARC-POMC-neurons (see Fig. 3). Here, acetylcholine-mediated activation of presynaptic M_3 receptors promotes the release of GABA, thus inhibiting ARC-POMC-neurons and thereby increasing appetite. At a first sight, a valid counterargument against these potential benefits of M_3 receptor antagonists could be the well-known weight gain-related side effects of clozapine and olanzapine, although both drugs exhibit a relatively high affinity for M_3 receptors (Huang et al., 2006; Weston-Green et al., 2012). However, the present study suggests that weight gain associated with both drugs may be primarily mediated by antagonism of 5-HT_{2C} and H_1 receptors. Accordingly, efforts are made to explore new avenues for treating obesity through the development of selective antagonists targeting the M_3 muscarinic receptor subtype (Maresca and Supuran, 2008).

4.4. Dopamine D_2 receptors

Antagonism of dopamine D_2 receptors is a common mechanism of all currently available antipsychotics and changes in dopaminergic neurotransmission can lead to severe alterations of food intake. However, the role of dopamine in this context is rather complex involving different brain circuits with partially opposing effects. In general, dopaminergic modulation of food consumption is mediated by midbrain dopamine neurons projecting to the striatum and as well as hypothalamic dopamine neurons (Palmiter, 2007). Mice with a genetically engineered lack of tyrosine hydroxylase of their dopaminergic neurons become aphagic and starve by around 4 weeks of age (Zhou and Palmiter, 1995). They can be rescued by treatment with L-DOPA or selective restoration of dopaminergic signalling in the dorsal striatum (Szczypka et al., 2001). Even though dopaminergic signalling in the striatum seems to be essential for feeding, excessive dopamine concentrations in the synaptic cleft appear to inhibit feeding, too, as demonstrated by the effects of amphetamine, cocaine or dopamine receptor agonists (Cannon et al., 2004).

Within the hypothalamus, dopaminergic effects strongly differ between the respective sub-regions. For instance, in the arcuate nucleus, dopamine release by tyrosine hydroxylase (TH)-positive neurons leads to excitation of ARC-AgRP/NPY- neurons and inhibition of ACR-POMC neurons, yielding an overall orexigenic effect (Zhang and van den Pol, 2016). Conversely, activating cells in the lateral hypothalamic area and the zona incerta that express dopamine D_2 receptors leads to a reduction in body weight and promotes brown fat thermogenesis in rodents, irrespective of feeding (Folgueira et al., 2019). Among the different dopamine receptors, dopamine's modulation of food intake seems to be primarily mediated by D_1 and D_2 receptors (Zhu et al., 2016). Correspondingly, genetic polymorphisms of the D_2 receptor gene include various variants which may be associated with weight gain (Müller et al., 2012). Given this background, we decided to also assess the impact of dopamine D_2-CHRO on obesity in our study. However, our findings suggest that long-term occupancy of this receptor is of minor relevance with respect to AIWG. This may fit to the fact that more selective dopamine antagonists such as haloperidol or amisulpride are less prone to cause weight gain (Dayabandara et al., 2017). For these agents, weight gain may be influenced by individual differences in baseline striatal reward responses. Indeed, a longitudinal, prospective fMRI study found that patients with initially reduced dorsal striatal reward activity showed more pronounced weight increases after six weeks of treatment with the selective D_2 antagonist amisulpride (Nielsen et al., 2016).

4.5. Other mechanisms

Besides these direct effects on appetite, food intake and energy expenditure, it is important to also consider indirect obesogenic effects of antipsychotics through modulation of other physiological processes or systems such as the sleep wake cycle, motor activity (Arjona et al., 2004; Stefanidis et al., 2009), or the immune system (Fonseka et al., 2016).

Sedative effects of antipsychotics are especially common for agents with strong antagonistic properties at H_1 receptors (Hill and Young, 1978). Accordingly, these agents may promote daytime sleepiness (Loebel et al., 2014), which is considered to be a risk factor for obesity

(Liu et al., 2024). Potential obesogenic mechanisms of daytime sleepiness include changes of dietary preferences, low physical activity and reduced metabolic activity (Liu et al., 2024).

Even in the absence of daytime sleepiness, antipsychotics may still lead to reduced motor activity. At high levels of dopamine D_2 receptor blockade extrapyramidal motor symptoms such as parkinsonism may occur (Kapur et al., 2000), particularly for antipsychotics with tight binding to the D_2 receptor (Seeman and Tallerico, 1998). Preliminary evidence suggests that these antipsychotics may also cause more subtle or subclinical manifestations of parkinsonism: for instance, actigraphic data revealed that patients treated with risperidone were less active than patients on olanzapine despite similar levels of psychopathology (Walther et al., 2010).

Another mechanism of AIWG may be the reduction of pro-inflammatory cytokine levels which has been documented for different antipsychotics, particularly clozapine, olanzapine and risperidone (Sugino et al., 2009). Since pro-inflammatory cytokines are expected to exert anorexigenic effects, decreased expression mediated by antipsychotics may ultimately lead to weight gain. (Fonseka et al., 2016).

4.6. Psychopathology

In our study, psychopathology showed a surprisingly minor importance in relation to obesity. Contrary to our expectations, we did not observe a significant positive association between negative symptoms and obesity. This observation is consistent with the findings of Wang et al., who demonstrated that patients exhibiting features of metabolic syndrome had reduced PANSS negative scores (Wang et al., 2020). Interestingly, we identified a small negative association between the LDL/HDL ratio and positive symptoms, similar to the findings of Babatope et al., who reported a negative correlation with total cholesterol (Babatope et al., 2017). These findings contribute to a complex and nuanced understanding of the relationship between psychopathology and obesity, challenging some conventional assumptions.

4.7. Limitations

This study has several limitations. Given the relatively small sample size, the quantitative estimates of the here reported effects may be considered uncertain and driven by a small number of data points. As this is a proof-of-concept study, the findings should be interpreted with caution, and further research with larger sample sizes is necessary to validate these initial results.

Moreover, the retrospective nature of the study may introduce recall bias. Additionally, we did not control for factors such as baseline BMI, diet, physical activity, pharmacogenetic mechanisms and co-medication that could influence obesity (Newcomer, 2005). Relevant co-medication might include other antihistaminergic or anticholinergic drugs as well as antidepressants.

Furthermore, prolonged receptor occupancies appeared to be correlated indicating a problem of collinearity. To deal with this issue, we particularly chose the stepwise regression approach which avoids the inclusion of further predictors if they do not increase the explained variation as this is typically the case for highly correlated predictors (Goldberger and Jochems, 1961; Leigh, 1988). Nevertheless, in our final stepwise regression model of the dependent variable BMI, both H_1- and M_3-CHRO, which were highly correlated with each other, were included in the model. Moreover, the respective regression coefficients were statistically significant, both in the final stepwise regression model and in the Structural Equation Model, which also considered the correlation between the two variables (see Fig. 2). Indeed, only when regressing out the effect of H_1-CHRO, the negative impact of M_3-CHRO on BMI became apparent, both in the stepwise regression and structural equation model. Accordingly, previous assumptions on an obesity-promoting effect of M_3 receptor antagonism by olanzapine and clozapine may be rather explained by the associated H_1 receptor antagonism. By applying our method, the true obesity-protective effect of M_3 receptor antagonism as suggested by animal models may have been unmasked.

We have to acknowledge that our results may strongly depend on the appropriate selection of receptors. The receptors assessed in this study were chosen based on a careful review of the scientific literature including both clinical and pre-clinical studies. However, other receptors (e.g. muscarinic M_1 acetylcholine receptors or adrenergic receptors) might exert relevant obesogenic effects, too (Panariello et al., 2011). Among the different 5-HT receptors which may be related to AIWG, the 5-HT_{2C} receptor has been studied most comprehensively (Ye et al., 2023). Moreover, there is a strong theoretical rationale given its established role in appetite regulation mediated by the hypothalamus (Baldini and Phelan, 2019; d'Agostino et al., 2018; Doslikova et al., 2013). Although there is additional evidence for a relevant contribution of 5-HT_{2A} receptors to obesity, it was not selected by our stepwise regression algorithm. Future studies should re-address this issue.

Furthermore, it remains uncertain whether the effects of the H_1 and 5-HT_{2C} receptors can truly be considered as independent from each other, or if a significant antagonism at both receptors must be present to induce weight gain. A possible argument against their independent contributions might be the fact that the 5-HT_{2C} receptor antagonist agomelatine is generally considered as weight neutral (Sansone and Sansone, 2011). However, this may be related to its additional agonistic effects at melatonergic MT_1 and MT_2 receptors and corresponding regulation of circadian rhythm. Moreover, in rodents, selective $5HT_{2C}$ receptor antagonists were sufficient to induce weight gain (Kirk et al., 2009). However, in the same study, a selective H_1 receptor antagonist did not cause significant increases in body weight. Further studies are needed to clarify this issue.

Moreover, our methodology does not account for active drug metabolites that may bind to the same receptors. In addition, individual differences in bioavailability and metabolism which may be related to genetic polymorphisms (Teng et al., 2023), drug-drug interactions (Conley and Kelly, 2007) as well as specific membrane transport proteins like P-glycoprotein (López-Muñoz et al., 2013; Moons et al., 2011) can alter the concentration of parent compounds and metabolites, potentially affecting receptor occupancy in the brain.

Furthermore, focussing on receptor occupancy alone may be an oversimplification of the pharmacodynamic effects of antipsychotics. Particularly our model does not differentiate between pure receptor antagonists, inverse agonists or partial agonists / antagonists. For instance, aripiprazole and cariprazine represent partial agonists of D_2/D_3 and 5-HT_{1A} receptors (Mohr et al., 2022). In addition, 5-HT_{2A} and 5-HT_{2C} receptors exhibit constitutive activityi.e. receptor signalling in the absence of any ligand. Since different antipsychotics have been demonstrated to also block this constitutive activity, they should be considered as inverse agonists rather than simple antagonists (Aloyo et al., 2009; Gaitonde et al., 2024). All of the receptors addressed in this study constitute G-protein coupled receptors (GPCRs) which are prone to biased agonism. This phenomenon refers to a ligand-dependent selectivity for certain signal transduction pathways relative to a reference ligand. Accordingly, different ligands of the same receptor may preferentially involve different G-protein subunits or β-arrestins (Komatsu et al., 2019). For antipsychotics, such differential effects on intracellular pathways were recently demonstrated for the 5-HT_{2A} receptor (Gaitonde et al., 2024).

Moreover, there is even preliminary evidence for antipsychotics-induced metabolic effects beyond receptor binding profiles. Due to their chemical properties, antipsychotics may disrupt lysosomal function, affect cholesterol trafficking and biosynthesis (Vantaggiato et al., 2019).

5. Conclusion

The present proof-of-concept study presents a new method to investigate side effects of drugs related to their cumulative historical

receptor occupancy. The data provide preliminary evidence that antipsychotics-induced metabolic side effects may be indeed described by our proposed measure of cumulative receptor occupancy and argues for unique contributions of different receptors. Particularly, prolonged 5-HT_{2C} and H_1 receptor antagonism may promote obesity and associated metabolic side effects whereas prolonged M_3 receptor antagonism may exert a protective effect. These findings may have clinical implications for the prevention and treatment of metabolic disturbances in patients with schizophrenia which should be confirmed in larger patient samples

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used The GPT 4 model as an editing tool for this paper to review and amend grammatical as well as spelling mistakes and ensure linguistic coherence and fluency. For literature research during the revision of the paper, the authors also used Elicit (https://elicit.com) and Perplexity (https://www.perplexity.ai/). After using these tools, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Federico Pacheco Sudar: Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Samar Samy Zekerallah:** Writing – review & editing, Visualization, Formal analysis. **Michael Paulzen:** Writing – review & editing, Supervision, Resources. **Klaus Mathiak:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Arnim Johannes Gaebler:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Formal analysis, Software, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Paulzen reports a relationship with Janssen Pharmaceuticals Inc, that includes: speaking and lecture fees. Dr. Paulzen reports a relationship with ROVI BIOTECH srl that includes: consulting or advisory and speaking and lecture fees. Dr. Paulzen reports a relationship with NEURAXPHARM UK Ltd that includes: speaking and lecture fees. Dr. Paulzen reports a relationship with Lundbeck LLC that includes: speaking and lecture fees. Dr. Paulzen reports a relationship with Otsuka Pharmaceutical Co Ltd that includes: consulting or advisory and speaking and lecture fees. Dr. Paulzen reports a relationship with www.psiac.de that includes: non-financial support. Dr. Paulzen reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was supported by the Federal Ministry of Education and Research (01EE1405A), Germany. AJG was supported by the Clinician Scientist grant of the Faculty of Medicine of RWTH Aachen University.

Acknowledgements

The authors thank Manuela Jülich for her contribution to blood sampling, and Michelle Schlingensief as well as Jasmin Mühlenberg for their organizational help.. Moreover, the authors thank the other members of the APIC Consortium for their contribution to the recruitment of participants and organizational help: Marc Augustin, M.D.; Joachim Cordes, M.D.; Emir Demirel; Thomas Dielentheis, M.D., Ph.D.; Jan Dreher, M.D.; Patrick Eisner, Ph.D.; Michelle Finner-Prével; Frederik Hendricks, M.D.; Jana Hovancakova; Peter Kaleta, M.*Sc*.; Fatih Keskin; Miriam Kirchner, M.D; André Kirner-Veselinovic, M.D.; Sarah Lammertz, Ph.D.; Christina Lange; Federico Maria Larcher, M.D.; Laura M. Lenzen, M.D.; Eva Meisenzahl-Lechner, M.D.; Jutta Muysers; Andrea Neff, M.D.; Michael Plum, M.D.; Erik Röcher, M.*Sc*.; Axel Ruttmann, M.D.; Sabrina Schaffrath, M.A.; Georgios Schoretsanitis, M.D., Ph.D; Lara Schwemmer, M.D.; Eva Stormanns; Antje Trauzeddel, M.D.; Lina Winkler, M.*Sc*.

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