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Getting to precision psychopharmacology: Combining clinical and genetic information to predict fat gain from aripiprazole

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ABSTRACT

Introduction: All atypical antipsychotics are associated with some degree of weight gain. We applied a novel statistical approach to identify moderators of aripiprazole-induced fat gain using clinical and genetic data from a randomized clinical trial (RCT) of treatment resistant depression in older adults.

Materials and methods: Adults aged ≥60 years with non-response to a prospective trial of venlafaxine were randomized to 12 weeks of aripiprazole augmentation (n = 91) or placebo (n = 90). Dual energy x-ray absorptiometry (DEXA) measured adiposity at baseline and 12 weeks. Independent moderators of total body fat gain were used to generate two combined multiple moderators, one including clinical data alone and one including both clinical and genetic data to characterize individuals who gained fat during aripiprazole augmentation.

Results: The value of the combined genetic + clinical multiple moderator (M_{cg}) was 0.57 [95% CI 0.46, 0.68] (effect size: 0.57), compared to the combined clinical moderator (M_c) value of 0.49 [0.34, 0.63] (effect size: 0.49). Individuals who gained adiposity in this study were more likely to be female and younger in age, have lower weight, fasting glucose and lipids at baseline and positive for the HTR2C polymorphism.

Discussion: These results demonstrate a combined multiple moderator approach, including both clinical and genetic moderators, can be applied to existing clinical trial data to understand adverse treatment effects. This method allowed for more specific characterization of individuals at risk for the outcome of interest. Further work is needed to identify additional genetic moderators and to validate the approach.

1. Introduction

Atypical antipsychotics are used to augment antidepressants prescribed for treatment-resistant depression (TRD), a common and disabling condition in older adults that leads to increased medical comorbidity, decreased functionality, and early mortality(Barry et al., 2009; Callahan et al., 1998; Laursen et al., 2016). The efficacy of atypical antipsychotics in this population may account for their increasing use(Olfson et al., 2015; Wang and Farley, 2013; Wisniewski et al., 2009). But despite their clinical benefits, all atypical antipsychotics can cause varying degrees of weight gain and cardiometabolic risk leading to increased cardiovascular disease and related mortality(Colton and Manderscheid, 2006; Hjorthøj et al., 2017; Newcomer, 2004; Yood et al., 2009). Among the atypical antipsychotics, risk of weight gain, dyslipidemia and diabetes is highest with clozapine and olanzapine. More moderate risk is observed with quetiapine and risperidone. Aripiprazole and ziprasidone are observed to have low weight gain risk and may even be associated with weight loss and improvements in lipid profiles in individuals switching from higher-risk agents(Association et al., 2004; Haupt et al., 2007; Newcomer and Haupt, 2006). However, in treatment-naïve individuals, even these lower-risk agents can cause substantial weight gain and metabolic risk (Alvarez-Jiménez et al., 2008; Foley and Morley, 2011; Mitchell et al., 2013), primarily related to accumulation of excess adipose tissue(Han and Lean, 2016; Nicol

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et al., 2018). The metabolic risk associated with antipsychotic therapy may be greater in younger and in antipsychotic naïve populations (Nicol et al., 2018; Safer, 2004), but is poorly understood in older adults, where there may be age-related variability in the magnitude of treatment-related weight gain(Lenze et al., 2015; Smith et al., 2008). Furthermore, antipsychotic-induced weight gain (AIWG) may not be fully explained by increases in adiposity alone(Lenze et al., 2015; Nicol et al., 2018).

The National Institute of Health has highlighted the need for novel genomic techniques paired with well-phenotyped and diverse populations for developing personalized and effective treatment approaches to psychiatric illnesses(Health, 2018). Although a significant proportion of AIWG may be explained by genetic variants (Gebhardt et al., 2010; Theisen et al., 2005; Wehmeier et al., 2005), there is a paucity of data evaluating medication side effects using the combination of patient-level genetic and clinical data(Wallace et al., 2013). Thus far, approximately 38 single nucleotide polymorphisms (SNPs) within 20 genomic regions have been associated with AP-induced increases in body weight and body mass index (BMI), with SNPs in *ADRA2A*, *DRD2*, *HTR2C*, and *MC4R* having the largest effect sizes (Hedges' g's = 0.30–0.80) (Zhang et al., 2016). Greater degrees of weight gain have been reported with first exposure, especially early in treatment(De Hert et al., 2011; Fleischhacker et al., 2013). The interpretation of these results is limited, however, as direct measures of adiposity were not employed in the primary studies(Romero-Corral et al., 2008). Thus, genomic regions identified as associated with weight gain may or may not translate mechanistically to increased fat deposition and related changes in metabolic risk. Although there is clearly an increased risk for AIWG associated with younger age and first exposure, the genetic contribution to AIWG in older adults is poorly understood. Aditionally, the data evaluating antipsychotic clinical effectiveness as it relates to weight gain risk has been equivocal with respect to lower-risk agents like aripiprazole(Raben et al., 2017). Clinical tools that allow the prediction of who will experience larger increases in adiposity are needed to optimally utilize antipsychotics. This is a major unmet need in all age groups, including older patients who are likely to receive these medications and to suffer adverse metabolic effects.

A statistical approach devised by Kraemer (Kraemer, 2013) utilizes existing data from completed randomized clinical trials (RCTs) to identify variables influencing treatment response(Niles et al., 2017a, 2017b; Smagula et al., 2016; Wallace et al., 2013). This method addresses several limitations of previous statistical methods applied to secondary analysis of data from placebo-controlled trials; namely that most predictors of treatment response in placebo groups will also be predictors in an active treatment group. The Kraemer approach identifies three types of baseline variable classes (non-specific predictors of treatment outcome, variables that are irrelevant to treatment outcome and moderators of treatment outcome), and selects an outcome that is relevant to harm/benefit balance. Once predictors are distinguished from moderators, a single broadly applicable correlation, accounting for scale and distribution, is calculated for each potential moderator - we refer to as the "Kraemer effect size." (Kraemer et al., 2008; Theisen et al., 2005) This is done to ensure that moderators are comparable to one another, regardless of the way in which the moderator is measured and its distribution in the population being studied. Thus, calculating a Kraemer effect size ensures that moderator values are uniformly applicable to the outcome of interest. A standardized Cohen's d effect size is then calculated for each moderator and used to inform variable selection for inclusion in the combined moderator(Kraemer, 2013). Then, a composite moderator is created by linearly combining the individual moderator values into a unitless multiple moderator value (*M*) ranging from −1 to 1. This combined moderator value is no longer interpreted as an effect size; but is understood on a scale with higher values indicating stronger moderation on the outcome of interest. To aid in interpretation, bootstrapping is used to create 95% confidence intervals around the combined moderator value (Wallace et al., 2013) (see supplemental materials for detailed description of the method applied in the present study). This approach has been championed as a way to cost-effectively utilize existing data in order to develop precision medicine tools for selecting treatments based on patient-level variables.

In the present study, we examined the multiple moderator approach to predict fat gain with aripiprazole use. The "IRL-GRey" (Incomplete Response in Late-Life Depression: Getting to Remission) study was an NIMH-sponsored, multisite, placebo-controlled RCT designed to test the efficacy of augmenting the antidepressant venlafaxine with the atypical antipsychotic aripiprazole in older adults with TRD(Lenze et al., 2015). In the IRL-GRey study, several measures of metabolic health were obtained, including fasting laboratory tests and body composition using dual energy x-ray absorptiometry (DEXA) to characterize cardiometabolic risk during initial exposure to aripiprazole. DNA was also collected and sequenced for 26 known common genetic variants associated with antipsychotic induced weight gain(Lett et al., 2012; Zhang et al., 2016). Previous analyses using data from the IRL-GRey study have examined moderators of treatment response with aripiprazole augmentation using the Kraemer method(Kraemer, 2013; Smagula et al., 2016). However, no analyses have been conducted to evaluate adverse treatment effects, namely, increases in adiposity. Here, we used the IRL GRey clinical data, including a gold-standard assessment of body composition, combined with single nucleotide polymorphisms (SNPs) associated with AIWG to demonstrate the application of the Kraemer method using both genetic and clinical moderators of aripiprazole-induced changes in adiposity.

2. Methods

2.1. Description of the parent study

The IRL-GRey study (Lenze et al., 2015) was a multisite, double-blind, placebo-controlled, RCT of aripiprazole augmentation of venlafaxine in antipsychotic-naïve older adults with TRD (n = 181 randomized participants; mean (SD) age 67.4 (6.10) years. Inclusion criteria were: age > 60 years and DSM IV criteria for a major depressive episode as defined by a Montgomery Asberg Depression Rating Scale (MADRS) score ≥15. Exclusionary diagnoses included dementia, bipolar disorder, schizophrenia, current psychotic symptoms, and alcohol or substance use within the past six months. Dementia criteria for exclusion included documented diagnosis of dementia upon review of medical records, a mini mental status exam (MMSE) score < 24, cognitive assessment using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Duff et al., 2008; Randolph et al., 1998) and a clinical interview applying formal DSM criteria for dementia in cases where the diagnosis was suspected but not supported by both of the first two criteria. Medical and physical comorbidities, assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Linn et al., 1968), were not exclusionary. In Phase 1 of the study, all participants (n = 468) received open-label treatment with venlafaxine extended release (ER), up to maximum dosage of 300 mg/day for 12 weeks. Those who did not meet the a-priori criteria for remission of depression during Phase 1 (i.e., a MADRS ≤10 on two consecutive assessments) were eligible for a double blind, 12-week augmentation phase (Phase 2) during which participants were randomized 1:1 to venlafaxine + flexibly-dosed aripiprazole (beginning at 2 mg/day, titrated as needed up to 15 mg/day) or venlafaxine + placebo. Total body fat (kg) was measured via DEXA scan before and after 12 weeks of aripiprazole augmentation.

Genomic DNA was extracted from blood lymphocytes in whole blood samples obtained prior to initiation of study medication. Genome Wide Association Study (GWAS) sequencing was performed to identify single nucleotide polymorphisms (SNPs) with an OpenArray® platform. Up to 10% of the genotypes for selected SNPs were re-genotyped for quality control. Additional quality control procedures included controlling for minor allele frequency > 5%, Hardy-Weinberg equilibrium

(p > 0.0001), genotype call rates > 98% and individual missingness < 10%.

2.2. Candidate clinical moderators considered for inclusion in the combined clinical moderator M_c

Based on supporting scientific literature and clinical relevance as described by Kraemer (Kraemer, 2013; Wallace et al., 2013), a pool of baseline, clinical and genetic variables were selected. Selection was based on previously identified moderators (Taylor et al., 2018) and risk factors of AIWG. These included age, sex, race, baseline weight, hemoglobin A1C, fasting insulin level, total DEXA-measured body fat, fasting glucose and lipid profile (including low density lipoprotein or LDL, total cholesterol, high density lipoprotein or HDL, and triglycerides)(Cortés et al., 2014; Fava et al., 2009; Strassnig et al., 2017; Taylor et al., 2018). We also included known markers of energy balance, including appetite and physical activity (Zimmermann et al., 2003), and psychiatric symptom severity, including the MADRS score and the quality of life values from the Medical Outcomes Study-Short Form (MOS-SF)(Raben et al., 2017). Concurrent treatment with medications known to promote weight loss or weight gain were also assessed as potential moderators (See supplementary materials for definition and list of medications considered)(Domecq et al., 2015). Finally, we included body mass index (BMI) change during Phase 1 of the IRL-GRey study (initial treatment with venlafaxine) as a potential moderator.

2.3. Candidate genetic moderators considered for inclusion in the combined clinical + genetic moderator M_{cg}

GWAS-identified regions associated with AIWG described above (Zhang et al., 2016) were considered as potential moderators. From this group, 26 SNPs in 19 genes that have been most strongly and consistently associated with AIWG were selected for inclusion(Arranz and de Leon, 2007; de Leon et al., 2008; Kao and Müller, 2013; Zhang et al., 2016). SNPs associated with AIWG included in the combined clinical + genetic moderator *(M_{cg})* were Adrenoceptor Alpha – 2A [*ADRA2A*], Adrenoceptor Beta 3 [*ADRB3],* Dopamine Receptor D2 [*DRD2*], Guanine Nucleotide Binding Protein [*GNB3*], *HTR2C*, Insulin-induced gene 2 [*INSIG2*], Melanocortin-4 Receptor [*MC4R*], Cannabinoid receptor 1 [*CNR1*], Methylenetetrahydrofolate reductase [*MTHFR*], Adiponectin C1Q and Collagen Domain Containing protein encoding region [*ADIPOQ*], leptin [*LEP*], Neuropeptide Y [*NPY*], Hypocretin Receptor 2 [*HCRTR2*], Acetyl-coenzyme A carboxylase alpha [*ACACA*], Acetyl-CoA carboxylase beta [*ACACB*], Fat mass and Obesity associated protein [*FTO*], NADH-ubiquinone oxidoreductase 1 [*NUDFS1*], Glucagon-like peptide 1 [*GCG*], and Opioid Growth Factor-like Receptor Like 1 [*OGFRL1*] gene (see Supplemental Table 4 for additional description of SNPs selected for inclusion).

2.4. Moderator selection for inclusion in the combined moderator

Analyses were conducted using the intent to treat principle. Available data from all 181 participants in the parent study was included in the present analyses. Multiple imputation was used to fill in missing data points for non-genetic variables. When genotype data was missing, we used the imputation server to fill in as many missing data points as possible. To create the combined clinical only (M_c) and clinical + genetic *(M_{cg})* moderators, 52 individual moderators (26 genetic and 26 clinical) were selected as described above. Kraemer correlations (see Supplementary Statistical Methods), as well as standardized Cohen's d effect sizes were calculated based on the interaction between the treatment effect and the moderator on DEXA-measured fat gain in a linear model (Kraemer, 2013). We then performed a factor analysis utilizing all relevant clinical and genetic variables in order to identify nonredundant latent variables. Considering completeness of data, clinical significance of the potential moderator, individual moderator standardized Cohen's d effect sizes, Eigen value factor loadings and moderator (interaction term) significance (p < 0.05), we chose one representative moderator from each factor for inclusion in the combined moderators M_c and M_{cg} (see Supplement for more details on moderator selection criteria).

2.5. Calculation of the combined moderators M_c and M_{cg}

Following individual moderator selection, the contribution of each individual moderator was optimized (Kraemer, 2004), (Kraemer, 2013) to yield a weighted sum of the individual moderators that maximized the interaction of treatment group and the combined moderator on the DEXA-measured change in adiposity as the outcome. Effect size estimates from this model were then used to calculate the combined moderator values(Kraemer, 2013; Wallace et al., 2013). Confidence intervals were estimated by bootstrapping the calculation of the combined moderator. Each of the combined moderators, M_c, and M_{cg}, were then used to determine moderating effect on treatment-related changes in DEXA-measured adiposity. A Kraemer effect size was then calculated for each of the combined moderators.

To visualize how the predicted treatment-related change in DEXA fat changed depending on an individual's M_{cg} value, model estimates were employed to plot the predicted change across the observed values of M_{cg} for the aripiprazole treated group (Fig. 1) (Kraemer, 2013).

All analyses were performed using SAS 9.4. (Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 468 eligible participants were started on open treatment with venlafaxine ER out of which 96 (20.5%) were non-completers due to withdrawal of consent, or withdrawal by the investigator, or for other reasons. 181 participants did not remit at the end of Phase 1; 91 of which were randomized to aripiprazole and 90 to placebo. Of the 91 participants randomized to aripiprazole, 40 participants remitted, 47 participants were non-remitters, 2 discontinued for adverse effects and 2 discontinued for other reasons. Of the 90 participants randomized to placebo, 26 participants remitted, 57 participants were non- remitters, 2 discontinued for adverse effects and 2 discontinued for lack of response. Table 1 contains the baseline and clinical characteristics of these 181 participants.

3.1. Individual moderator effects

The composition of each multiple moderator is listed in Table 2, along with the individual moderator Cohen's d effect sizes. The combined moderator with only clinical variables *(Mc),* was comprised of age; fasting insulin, triglycerides, and cholesterol values; concurrent treatment with medications associated with weight loss; MOS-SF physical and mental health related quality of life; total RBANS score; duration of depressive episode in weeks, and change in BMI during initial venlafaxine exposure in Phase I of the IRL-GRey.

The effect sizes of individual clinical moderators were small, ranging from 0.001 to 0.208. The largest clinical moderator effect size was the MOS-SF mental health-related quality of life (0.208), whereby better pre-treatment mental health-related quality of life explained a greater degree of moderating effect on change in adiposity with aripiprazole over placebo. The individual genetic moderator effect sizes were similarly small, ranging from 0.001 to 0.142. The genetic moderator with the largest moderating effect on fat gain was 5-Hydroxytryptamine Receptor 2C gene (*HTR2C*, 0.142), indicating individuals with this polymorphism experienced larger gains in adiposity with aripiprazole over placebo.

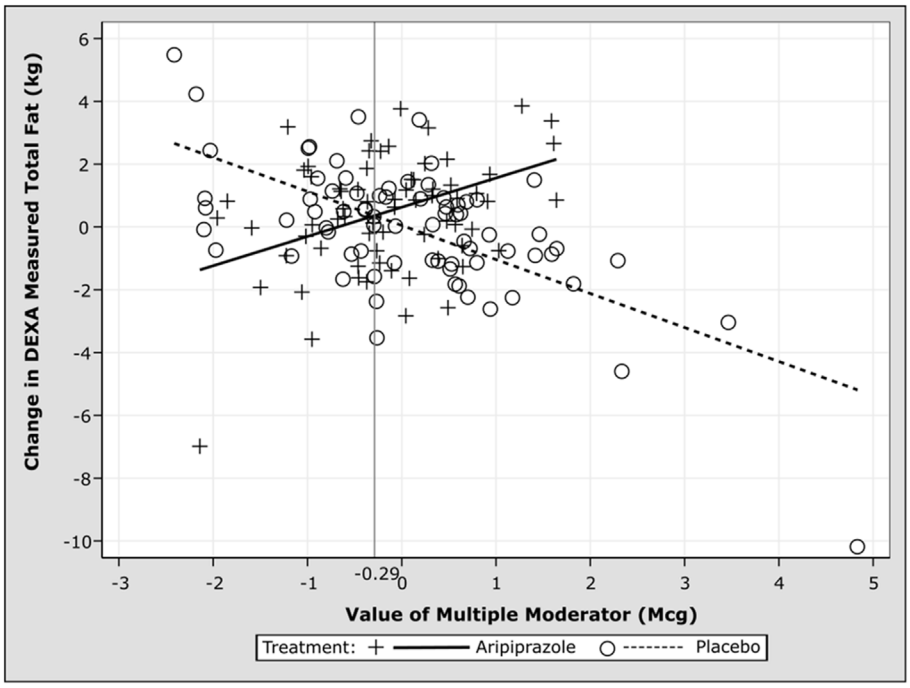

Fig. 1. Predicted DEXA-Measured Change in Adiposity for Aripiprazole versus Placebo Treatment Groups across Observed Values of the Combined Moderator M_{cg}. The plot shows the predicted amount of change in DEXA total fat (kg) on the Y-axis, across values of the combined moderator M_{cg} on the X-axis in both aripiprazole and placebo arms. At values above the crosspoint $M_{cg} = -0.29$, participants in the placebo group are predicted to lose fat, while participants in the aripiprazole augmentation group are predicted to gain fat. When stratified by M_{cg}, the effect size for those 57.4% with $M > -0.29$ was −0.45, and for those 42.6% with $M \leq$ -0.29, was 0.20.

3.2. Combined moderator values

The Cohen's d effect sizes and weights of the individual selected moderators used to calculate the combined clinical and genetic moderator M_{cg} are provided in Table 2. As noted above, the combined moderator values cannot be interpreted in the same way as the Kraemer or Cohen's d effect sizes. Rather, the strength of the combined moderator is interpreted in the context of the scale (−1 to 1) and the 95% confidence interval in which it lies. M_{cg} had a value of 0.57 [0.46, 0.68] (Kraemer effect size: 0.57), which was larger than any individual moderator value, and also larger than the M_c value, 0.49 [0.34, 0.63] (Kraemer effect size: 0.49). Fig. 1 illustrates the moderating effect of M_{cg} on treatment-related change in DEXA total fat (in kg) in both the aripiprazole and placebo groups. Higher M_{cg} values were associated with greater treatment-related increases in adiposity relative to the placebo group, which was predicted to lose adiposity at higher values of M_{cg}. At lower M_{cg} values, the aripiprazole augmentation group was predicted to gain less adiposity compared to those with higher values of

Table 1
Baseline Characteristics of Participants Randomized to Aripiprazole Augmentation versus Placebo in Phase 2 of IRL-Grey study (Lenze et al., 2015).

	N Missing	All N = 181 Median (25th/75th centile) or % (n)	Aripiprazole N = 91 Median (25th/75th centile) or % (n)	Placebo N = 90 Median (25th/75th centile) or % (n)
Age	0	66.0 (62.8/70.5)	66.4 (62.8/71.6)	65.7 (62.8/69.8)
Years				
% (n) > 70 yrs	0	27 (49)	[30 (27)	24 (22)
% (n) Female	0	57 (103)	57 (52)	57 (51)
% (n)White	0	88 (159)	88 (80)	88 (79)
Education (yrs)	0	14.0 (12.0/16.0)	14.0 (12.0/16.0)	14.0 (12.0/16.0)
CIRS-G	0	9.0 (7.0/13.0)	10.0 (7.0/13.0)	9.0 (7.0/12.0)
Total				
Count	0	6.0 (4.0/7.0)	6.0 (4.0/8.0)	6.0 (4.0/7.0)
% (n) diagnosed with diabetes	6	15 (26)	18 (16)	11 (10)
RBANS Total Index Score	3	95.0 (85.0/107.0)	98.0 (85.0/108.0)	94.0 (85.0/102.0)
% (n) with recurrent depression	0	71 (129)	68 (62)	74 (67)
Age at first depressive episode (yrs)	0	40.0 (20.0/57.0)	44.0 (24.0/57.0)	35.0 (17.0/57.0)
Duration of current episode (wks)	2	104.0 (35.0/364.0)	118.0 (45.0/364.0)	104.0 (28.0/317.0)
% (n) who have failed to respond to at least one adequate antidepressant trial during the current episode	3	74 (132)	73 (66)	75 (66)
MADRS	0	28.0 (25.0/32.0)	29.0 (25.0/33.0)	28.0 (24.0/32.0)
Enrollment				
Randomization	0	23.0 (18.0/28.0)	24.0 (18.0/29.0)	23.0 (18.0/26.0)
Venlafaxine dose at randomization (mg/d)	0	300 (300/300)	300 (300/300)	300 (300/300)

Abbreviations: RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CIRS-G = Cumulative Illness Rating Scale; MADRS = Montgomery-Asberg Depression Scale.

Table 2
Individual Moderator Cohen's d Effect Sizes for all 52 Baseline Clinical and Genetic Variables tested as Potential Moderators.

Individual Moderator	Effect Size[a]	Weight in the Combined Moderator M_{cg}
Selected for inclusion in the combined moderator based on effect size, factor loading, and significance of interaction term.		
Value for the final combined clinical + genetic moderator (M_{cg})	0.57	
MOS-SF Mental Component at randomization	−0.208	−0.274
BMI change during Phase 1, venlafaxine treatment	−0.187	−0.660
Age (years)	−0.177	−0.390
HTR2C_rs6318	−0.142	−0.191
HCRTR2_rs3134701	−0.133	−0.351
GNB3_rs5443	−0.116	−0.185
LEP_rs7799039	0.114	0.111
ADIPOQ_rs266729	0.111	0.250
Triglyceride level	−0.100	−0.122
OGFRL1_rs9346455	0.091	0.181
MTHFR_rs1801131	0.084	−0.107
MOS-SF Physical Component	0.076	0.036
*Concurrent treatment with medications associated with weight loss	−0.076	−0.083
Insulin level	−0.072	−0.125
Total Cholesterol Level	−0.071	−0.085
DRD2_rs1800497	0.069	0.163
ADRB3_rs4994	−0.035	−0.065
Venlafaxine dose at Phase 2 randomization	−0.034	−0.393
ADIPOQ_rs1501299	−0.015	−0.006
Sex (female vs. male)	0.010	0.042
Deselected from inclusion in the combined moderator based on collinearity, small effect size and/or low factor loading.		
MADRS	−0.197	
INSIG2_rs17047764	−0.113	
Age of onset of first lifetime episode	0.093	
Duration of current depressive episode (weeks)	−0.076	
ACACA_rs2229416	0.075	
HDL level	0.072	
Appetite (MADRS item 5)	−0.067	
Glucose level	0.065	
MC4R_rs489693	−0.059	
Weight (kg) at Phase 2 randomization	−0.057	
NDUFS1_rs6435326	0.052	
FTO_rs9939609	0.050	
ADRA2A_rs1800544	−0.045	
RBANS total index score	0.043	
ADIPOQ_rs2241766	−0.041	
Single or recurrent depressive episode	−0.041	
BMI at Phase 2 randomization	−0.034	
MTHFR_rs1801133	−0.039	
LDL level	0.038	
CIRS-G	0.037	
**Race	−0.035	
HCRTR2_rs4142972	−0.029	
DEXA - Total Fat (kg)	−0.026	
NPY_rs16147	0.025	
CNR1_rs806378	−0.015	
HTR2C_rs3813929	0.014	
GCG_rs13429709	−0.008	
*Concurrent treatment with medication associated with weight gain	0.003	
DRD2_rs6277	0.002	
Education (years)	0.001	
DRD2_rs1799732	−0.001	
ACACB_rs2241220	0.001	

Abbreviations: BMI, body mass index; MADRS, Montgomery Asberg Depression Scale; LDL, low-density lipoproteins; HDL, high-density lipoproteins; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MOS-SF = Medical Outcomes Survey - Physical Component; CIRS-G = Cumulative Illness Rating Total.
*See Supplemental materials for list and definitions.
**Race was defined as white/non-white in the original dataset.
[a]Calculated from Kraemer effect size = d3/(2 ((d2^2 + (d3^2)/4 + 1)$^{.5}$)), see Supplemental Statistical Methods for additional details.

M_{cg}.

3.3. Individual participant characteristics across values of m_{cg}

The pattern of observed moderation allowed us to categorize participants into two groups based on whether their computed moderator score fell above or below the cross-point value of M_{cg} (−0.29). When the sample was stratified by the value of M_{cg}, the effect size for those 57.4% with M > −0.29 (the crossing point of the aripiprazole and placebo treatment group regression lines, Fig. 1) was −0.45, and for those 42.6% with M ≤ -0.29, was 0.20. Characteristics of patients above and below the cross-point differed (Table 3), whereby those above the cutpoint gained more fat on aripiprazole; were more likely to be female, younger, and had lower fasting insulin, triglyceride levels, and higher MOS SF-36 physical scores. They also received a lower terminal venlafaxine ER dose and had a decrease in their BMI during Phase 1 of the IRL-Grey study. Patients above the cross-point had higher frequencies of DRD2_rs1800497, OGFRL1_rs9346455, LEP_rs7799039, ADIPOQ_rs266729, and HTR2C_rs6318 risk variants, and lower frequencies of GNB3_rs5443, HCRTR2_rs3134701, and ADIPOQ_rs1501299.

3.4. M_{cg} and treatment response

Finally, to determine whether M_{cg} also moderated aripiprazole treatment response (e.g., achieving MADRS ≤ 10 on two consecutive assessments), we evaluated participants treated with aripiprazole whose individual characteristics placed them above (i.e., likely to have fat gain) vs. below (i.e., unlikely to have fat gain) the combined moderator cut-point. Remission rates did not differ significantly based on M_{cg} value: 47.1% for those above the cut-point, vs. 46.9% for those below the cut-point ($\chi_1^2 = 0.001$, p = 0.98).

4. Discussion

This study represents a proof-of-concept application of a combined moderators approach, utilizing both clinical and genetic markers of cardiometabolic risk to identify indicators for increased adiposity during treatment with aripiprazole in older adults. This approach allowed us to characterize participants at elevated risk for gains in adiposity during aripiprazole treatment based on their clinical characteristics and genotype for known genetic predictors of AIWG. Although not statistically significant, the combined moderator including genetic information, M_{cg}, accounted for larger moderating effect on changes in adiposity than any individual moderator alone or the combined clinical moderator. These results are important because they demonstrate how existing clinical data and genetic samples from RCTs can be integrated into a composite measure and used to deconstruct what factors may be most important in moderating adverse treatment outcomes. In this study of older patients, those with greater treatment-induced gains in adiposity were more likely to be female, younger in age, with lower baseline fasting insulin, cholesterol, and triglyceride than those who did not gain significant body fat during treatment. This may be an important distinction from other age groups, where risk characteristics may differ. Moreover, fat change was not associated with treatment response. Prior reports testing robustly obesogenic antipsychotics had suggested a relationship between antipsychotic treatment response and weight gain(Raben et al., 2017). However, our results with aripiprazole do not support the idea that depression treatment response is related to weight gain.

As noted earlier, unbiased GWAS approaches have successfully identified many genomic regions associated with AIWG, but the

Table 3
Moderator profiles (dichotomous and continuous variables) based on the combined moderator (M_{cg}).

Variable	Aripiprazole augmentation associated with larger increases in total fat gain ($M_{cg} > -0.29$; n = 85) Mean (SD) or %	Aripiprazole augmentation associated with smaller increases in total fat gain ($M_{cg} < -0.29$; n = 96) Mean (SD) or %	Cohen's d Effect Size
Insulin level	10.9 (9.1)	14.8 (14.3)	−0.32
Total Cholesterol Level	187.8 (50.6)	192.1 (41.8)	−0.09
MOS-SF - Mental Component	29.1 (10.2)	31.4 (9.0)	−0.24
MOS-SF - Physical Component	44.6 (12.2)	40.2 (11.8)	0.37
Triglyceride level	137.1 (83.7)	150.0 (84.5)	−0.15
Venlafaxine dose	271.8 (50.1)	283.2 (39.9)	−0.25
BMI Change	−0.6 (1.9)	0.5 (1.5)	−0.64
Age (yrs)	65.7 (4.9)	68.9 (6.6)	−0.55
Sex (% Female)	62.4	52.1	0.20
Weight loss drug	15.3	15.6	−0.01
GNB3_rs5443	27.6	35.2	−0.23
HCRTR2_rs3134701	18.2	33.5	−0.52
MTHFR_rs1801131	34.7	31.3	0.09
ADRB3_rs4994	7.6	9.3	−0.09
ADIPOQ_rs1501299	27.1	29.1	−0.06
DRD2_rs1800497	22.4	20.3	0.07
OGFRL1_rs9346455	11.2	8.2	0.15
LEP_rs7799039	46.5	39.8	0.18
ADIPOQ_rs266729	32.4	23.3	0.27
HTR2C_rs6318	11.2	15.9	−0.20

Abbreviations: MAF, minor allele frequency; SD, standard deviation; BMI, body mass index; MOS-SF = Medical Outcomes Survey - Mental Component; MOS-SF = Medical Outcomes Survey - Physical Component.

combination of all known SNPs to date explains only a small degree of observed AIWG (Zhang et al., 2016). Participants in the present study who experienced treatment-related increases in adiposity, similar to what has been observed in other population samples experiencing increase in weight or BMI, exhibited higher frequencies of DRD2_rs1800497, OGFRL1_rs9346455, LEP_rs7799039, ADIPOQ_rs266729, and HTR2C_rs6318 polymorphisms, as has been reported by others(Zhang et al., 2016). HTR2C has been most extensively studied in antipsychotic-induced weight gain (Tiwari et al., 2016) and has known effects on appetite, satiety, and hunger(Lett et al., 2012). ADRB3 genes are associated with the adrenergic system and have are thought to contribute to the development of obesity through adipocyte hyperplasia(Lett et al., 2012). GNB3 has been previously associated with both hypertension and obesity in non-mentally ill populations(Lett et al., 2012). The genetic moderators selected for inclusion in this study were common known variants with relatively large effect sizes. However, as has been reported in other samples, these factors individually accounted for a relatively small degree of moderating effect on change in body weight. Unbiased, sequencing-based approaches combined with GWAS, like exome or whole-genome sequencing, have the potential to identify not only the common variants influencing a patient's phenotype and treatment response, but also those that are rare or even unique. Future studies employing combined genomic approaches to account for rare or new genetic variants in extensively phenotyped RCT samples may be more likely to detect a greater degree of the genetic contribution to AIWG.

This analysis has both strengths and limitations. We used data from a controlled clinical trial that employed direct measures of adiposity and included well-characterized clinical and genetic data. Second, we employed a novel statistical approach designed to optimally use such data in exploring complex relationships between variables on the adiposity outcome. Finally, we studied older adults with TRD – a population in whom the safety of antipsychotic medications is already of concern, given the risk for adverse cardiovascular outcomes. This initial analysis demonstrates, from a single study, that a combined multiple moderator has the potential to differentiate those who are most susceptible to treatment-induced adiposity changes. Future work should include the analysis of data from multiple clinical trials to arrive at a replicable, clinically useful way of personalizing treatment decisions. Additionally, a combined moderator approach does not confirm the validity of each individual moderator variable in the composite. Instead, the combined moderator calculation is a pragmatic approach for working with numerous patient-level variables (e.g., 52 clinical and genetic measures) and reducing them to a smaller number of particularly impactful variables that can then be combined into a composite. While the combined moderator effect was much higher than any individual variable, the effect size of both combined moderators was moderate. Additionally, individual genetic moderator values were predominantly small to moderate. This suggests either the genetic risk for experiencing treatment-induced fat gain is low in general, or that the genes we studied may not represent all potential genetic contributions (eg rare variants or combinations of genes). A number of relevant variables that might predict fat gain, such as family history of diabetes or obesity, lifestyle, antipsychotic treatment adherence etc. were not included due to limitation of available data, and their inclusion could have contributed to larger combined moderator values. The relatively small genetic contribution to fat gain in our results may also be explained by the limited generalizability of our sample. Additionally, while some participants gained fat during the course of this study of aripiprazole, the number of participants and the amount of fat change overall was small. Finally, we did not include gene-environment interactions in this model for simplicity while illustrating the application of the method. However, future analyses would ideally address the issue of gene-environment interactions with larger samples. That genetic moderators played a relatively small role in fat gain here compared to prior reports highlights the need for further study of the genetic contributions to antipsychotic-induced increases in adiposity to validate our selected moderators in an independent sample. These limitations should be carefully considered in the interpretation of results.

This study demonstrates that a combined moderator approach can assist in understanding the moderating effect of both clinical and genetic characteristics on treatment-related side effects. This approach is theoretically a useful method for post-hoc analysis of existing clinical trial data, as it allows for the exploration of the intricate relationships between potential moderators. This is relevant in the study of complex, chronic health conditions like obesity, where the relationships between genetic and environmental factors remain poorly defined. Replicating these results in other samples as well as with other second-generation antipsychotics is essential, as is further study of genetic contributions in

broader age ranges and diverse racial and ethnic populations. Thus, our findings are not an end-point, but rather the first step on the path towards developing a precision medicine approach for using antipsychotics.

5. Conclusion

Atypical APs are widely used for their broad clinical effectiveness, account for upwards of $13B in healthcare expenditures in the last decade(Crystal et al., 2009). Older adults are more likely than adults in younger age cohorts to receive AP medications, predominantly for the treatment of agitation in the setting of dementia, or for treatment resistant depression(Olfson et al., 2015; Wang and Farley, 2013). Given the significant side effects of this drug class, including weight gain and increased overall cardiometabolic and cardiovascular disease risk, a precision approach to prescribing is needed. A multiple moderator approach including genetic characteristics accounted for a greater degree of moderating effect on changes in adiposity during aripiprazole treatment than any individual genetic or clinical moderator. The value of the combined clinical and genetic moderator M_{cg} was also larger than that of the combined clinical moderator M_c, indicating that the addition of genetic moderators may increase the utility of such modeling. The direct and precise measurement of the outcome of interest (i.e., change in adiposity), combined with detailed phenotypic and genetic data in an antipsychotic-naïve population sample, represent strengths of this study. Participants predicted by M_{cg} to gain fat during aripiprazole treatment had specific baseline characteristics including gender, age, baseline fasting metabolic values and genetic factors associated with known derangements in cardiovascular, metabolic and adipose tissue function. These results should be interpreted with caution, as further studies using multiple moderator analyses in populations inclusive of broader age range, and racial, ethnic and gender diversity are needed to validate this approach. Nonetheless, these results demonstrate the feasibility of using existing clinical and genetic data in such models, and sets the stage for future research focused on developing pharmacogenetic decision support tools for clinical care(Abbott et al., 2018; Arandjelovic et al., 2019).

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Declaration of interests

JPM has received research funding from the National Institutes of Health, The Food and Drug Administration and the Patient-Centered Outcomes Research Institute. EJL receives or has received support from NIH, FDA, Takeda, Lundbeck, Janssen, Aptinyx, Alkermes, the Taylor Family Institute for Innovative Psychiatric Research, the McKnight Brain Research Foundation, the Center for Brain Research in Mood Disorders, the Barnes/Jewish Foundation, and PCORI. CFR has received pharmaceutical support for NIH-sponsored research studies from Bristol-Myers Squibb, Eli Lilly, Forest, and Pfizer; grants from NIMH, the National Heart, Lung, and Blood Institute, the Center for Medicare and Medicaid Services (CMS), PCORI, the Commonwealth of Pennsylvania, the John A. Hartford Foundation, the National Palliative Care Research Center, the Clinical and Translational Science Institute, and the American Foundation for Suicide Prevention; he has also served on the American Association for Geriatric Psychiatry editorial review board. CFR also receives an honorarium for serving as Editor-in-Chief for the American Journal of Geriatric Psychiatry, and he has received a speaking honorarium from MedScape/WebMD; is the co-inventor of psychometric analysis of the Pittsburgh Sleep Quality Index (licensed intellectual property PRO10050447). BHM receives research support from Brain Canada, the Canadian Institutes of Health Research, NIH, the Centre for Addiction and Mental Health Foundation; he has received medications for NIH-funded clinical trials from Bristol-Myers Squibb, Eli Lilly, Pfizer, and Pfizer/Wyeth and software used in studies from Capital Solution Design and HAPPYneuron; he owns stock in General Electric. JWN has received research funding from the NIH and Otsuka. He has served as a consultant for Auris, Sunovion, Indivior, Otsuka, Alkermes, and as a consultant to litigation, and served on a Data Safety Monitoring Board for Amgen. He has received honoraria for CME from the American Diabetes Association and the American Society for Clinical Psychopharmacology. DJM has received research support from the Canadian Institutes of Health Research, NIH, the Centre for Addiction and Mental Health Foundation (CAMH, Joanne Murphy Professorship), the Canadian Biomarker Integration Network in Depression, and the Ontario Brain Institute. GEN has received research funding from NIMH, Otsuka America, Inc., Alkermes, The Sidney R. Baer, Jr. Foundation, the Center for Brain Research in Mood Disorders (CBRiMD) and the Center for Diabetes Translational Research (CDTR) at Washington University, and serves as a consultant for Alkermes, Sunovion and Supernus Pharmaceuticals, Inc. HO, YZ. AEL and TRP have no disclosures.

Author contributions

EJL, CFR and BHM designed the parent study and wrote the protocol. HO, EJL, JPM and GEN developed the hypothesis and secondary data analytic plan. JPM, AEL, MDY and YZ conducted data analyses. HO, GEN, EJL, JPM, MDY and YZ had access to all the data and analyzed the data. HO, EJL, DJM and GEN were responsible for the decision to submit the report, and drafted it. All authors read, critically revised, and approved the report. The corresponding author, GEN, confirms that she had full access to all the data in the study and final responsibility for the decision to submit the manuscript for publication.

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Appendix A. Supplementary data

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