Pharmacogenomics of Medication-Induced Weight Gain and Antiobesity Medications

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Obesity is a chronic, multifactorial disease associated with a large number of comorbidities. The clinical management of obesity involves a stepwise integrated approach, beginning with behavioral and lifestyle modification, followed by antiobesity medications, endobariatric procedures, and bariatric surgery. Weight gain and subsequent obesity are common side effects of medications, such as prednisone or antipsychotics. In this era of precision medicine, it is essential to identify patients at the highest risk of weight gain as a result of medication use. Pharmacogenomics could play an important role in obesity management by optimizing use of antiobesity medications as well as minimizing adverse weight gain. This review aims to provide a comprehensive analysis of the current literature on the role of pharmacogenomics in obesity and medication-induced weight gain. In summary, there are more robust studies of medication associated with weight gain and pharmacogenomics, and more studies are needed to understand the role of pharmacogenomics in antiobesity medications.

Obesity (2021) 29, 265-273.

Introduction

Obesity is a chronic, multifactorial disease, defined as an abnormal or excessive accumulation of body fat that imposes a risk to the health of an individual. It is a major public health concern in the world, especially in the United States, with an enormous socioeconomic burden. The prevalence of obesity in the United States has trended upward of 39.4% in adults and 18.5% in youth as measured in the National Health and Nutrition Examination Survey 2015-2016 (3).The World Health Organization's global estimates have suggested that obesity prevalence has tripled between 1975 and 2016 (4). The estimated annual medical cost of obesity in the United States was a staggering \$480 billion in 2018, and it continues to rise (5).

Obesity is an imbalance between energy intake and expenditure. The deleterious effects of obesity are multisystemic, such as insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, stroke, sleep apnea, gallbladder disease, gout, osteoar-thritis, and some cancers, including colorectal and prostate in men and breast, endometrial, and gallbladder cancer in women (6). The etiology of obesity is a plexus of biological (genetics, brain-gut axis food intake regulation, prenatal determinants, pregnancy and menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, viruses), environmental (food abundance, built environment, socioeconomic status, culture, bias and discrimination, environmental chemicals), and behavioral (excessive calorie intake, eating patterns, sedentary lifestyle, reduced physical activity, insufficient sleep, smoking cessation) factors (7). Medications play a major role in weight gain, and the most important classes of drugs commonly associated with weight gain as a side effect include antipsychotic

Study Importance

What is already known?

- There are few reviews in the literature on pharmacogenomics and obesity drug therapy:
 - Precision obesity treatments including pharmacogenetic and nutrigenetic approaches (ref 1)

Pharmacogenetics of obesity drug therapy (ref 2)

What does this Review add?

In this review, we cover both aspects of pharmacogenomics in obesity: (1) the role of pharmacogenomics of commonly prescribed drugs with weight gain as side effects and (2) the role of pharmacogenomics in antiobesity medications and weight loss.

How might these results change the direction of research or the focus of clinical practice?

Our review in pharmacogenomics for obesity will guide providers and obesity experts to consider pharmacogenomics studies to prevent or stop weight gain from commonly prescribed medications and to enhance weight loss from antiobesity medications.

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© 2021 The Obesity Society. Received: 10 June 2020; Accepted: 29 September 2020; Published online 25 January 2021. doi:10.1002/oby.23068

drugs, antidepressant drugs, antiepileptic drugs, beta-blockers, antihyperglycemics, and glucocorticoids (8-11).

An integrated, multidisciplinary, and personalized approach is needed for obesity management. The Practice Guide on Obesity and Weight Management, Education, and Resources (POWER) program, a multidisciplinary, multisocietal effort to introduce a continuum of obesity care, recommends four phases for obesity management: (1) multidisciplinary assessment, (2) intensive weight-loss intervention, (3) weight maintenance, and (4) prevention of weight regain (12). In the weightloss intervention, the initial step is to provide all patients with lifestyle modification therapy. If the patient is unable to reach the weight-loss goal through lifestyle modification alone, a second-level therapy, such as medications, devices, or surgery, is recommended. The criteria for antiobesity medication (AOM) is BMI>30 kg/m² or BMI>27 kg/m² plus one obesity-related comorbidity. Currently, the Food and Drug Administration-approved AOMs for short-term use (up to 12 weeks) include phentermine, benzphentamine, diethylpropion, and phendimetrazine, and the AOMs for long-term use include phentermine-topiramate extended release, liraglutide (3 mg), orlistat, and bupropion/ naltrexone sustained release. Sibutramine, rimonabant, and lorcaserin were withdrawn from the market because of side effects. If the disease is severe and these management options have failed, bariatric endoscopy or surgery is considered as an option (12,13).

The use of AOMs is slowly becoming more common, and the current pharmacovigilance reports suggest that there are about 10 million prescriptions per year (14). Unfortunately, the response rate to AOMs is highly variable. On average, only 30% of patients will lose more than 10% of their total body weight in 1 year (15). The heterogeneity in response to AOMs may be explained by drug metabolism, absorption, and effect. Thus, the pharmacokinetics and pharmacodynamics of the drug may interact with an individual's genetic makeup, and this interaction with medications is defined as pharmacogenomics. Acknowledging the importance of AOMs in obesity management and the variability of response and potential role for pharmacogenomics, we decided to perform a literature review of the pharmacogenomics of obesity.

Search Strategies

A thorough review of articles was done from literature published on PubMed and MEDLINE using the following keywords: obesity, pharmacogenomics, antiobesity drugs, phentermine, liraglutide, lorcaserin, bupropion/naltrexone, phentermine/topiramate, orlistat, sibutramine, rimonabant, weight loss, weight gain, antipsychotic drugs, antidepressants, beta-blockers, glucocorticoids, antiepileptic drugs, antihyperglycemic drugs, sulfonylureas, gene variants, and gene polymorphisms.

Pharmacogenomics

Key definitions

It is essential to know some of the basic definitions to have a clear understanding of this review. The term pharmacogenomics reflects an amalgamation of pharmacology (the science of drugs) and genomics (the science of genes and their function). It is the study of the effect of genetic variation on response to a drug. Pharmacogenomics aims to advance the development of safe, effective pharmacotherapy tailored to the genetic makeup of the individual. Figure 1 illustrates pharmacogenomics as genes affecting at various levels, such as alteration in drug-metabolizing enzymes (a pharmacokinetic property) or variation in the drug target, a receptor or a protein, which in turn can lead to interindividual variation in therapeutic effect and adverse effect (a pharmacodynamics property).

Genetic polymorphism can be defined as the existence of two or more variants of a gene that occur in a population with at least 1% frequency of the less common variant (mutation). A genotype is the genetic constitution of an individual, either overall or at a specific gene. Phenotype is the observable characteristics of a cell or organism, usually being the result of the product coded by a gene (genotype). Single-nucleotide polymorphism (SNP) is a single base pair change in the DNA sequence at a particular point compared with the "common" or "wild-type" sequence. Each SNP receives a unique reference SNP ID number, recorded as "rs" number (example: rs25531) (https://en.wikipedia.org/wiki/DbSNP). An allele can be defined as one of the several variants of a gene, usually referring to a specific site within the gene. A variant allele is an allele at a particular SNP that is the least frequent in a population. A wild-type allele is the allele at a particular SNP that is the most frequent in the population. Locus/loci is a site on a chromosome at which the gene for a particular trait is located or on a gene at which a particular SNP is located (16).

Medications with weight gain as a side effect

Drug-induced weight gain is a serious adverse event of some of the commonly used classes of drugs that results in noncompliance to therapy as well as worsening of comorbidities related to obesity. Psychotropic medications, such as antipsychotics and antidepressants, have long been reported in the literature to cause weight gain and metabolic side effects (8,9). Similarly, antiepileptic drugs, such as valproate, are also commonly associated with weight gain, which constitutes a serious problem in treating patients with epilepsy (11). Steroidal agents, such as glucocorticoids and progestin oral contraceptives, are also commonly associated with weight gain (10,17). Apart from these drug classes, antiglycemic agents and beta-blockers are also known to cause weight gain (18). Table 1 summarizes pharmacogenomics of medications with weight gain as a side effect.

Antipsychotic drugs. Antipsychotic drugs are known to cause significant weight gain. The mechanism behind it involves the interplay of dopaminergic, serotonergic, histaminergic, and adrenergic systems. According to the weight gain profile, they can be grouped into those causing substantial weight gain (clozapine, olanzapine), moderate weight gain (risperidone, sertindole), slight weight gain (aripiprazole, iloperidone, amisulpride), and negligible or no weight gain (ziprasidone, quetiapine) (19).

Numerous trials have been performed, and robust data on the impact of the genetic profile on the metabolic adverse events of first- and second-generation antipsychotics have been collected. *HTR2C* is a commonly studied gene that is located on the X chromosome X. A study aimed at assessing whether there was an association between the rs518147 and rs3813929 polymorphisms of the *HTR2C* gene and olanzapine-induced weight gain reported a protective role of the -759 T variant allele of rs3813929 and the -697 C variant allele of rs518147 of the *HTR2C* gene against antipsychotics-induced substantial weight gain, defined as>10% increase in BMI (20).

Similar findings were proven in another study involving a prospective cohort of 48 female inpatients with schizophrenia given



Figure 1 Illustration of pharmacogenomics' role in drug metabolism. It reflects pharmacogenomics as gene variations/polymorphisms affecting an individual's response to a particular drug at various tiers, such as an alteration of drug-metabolizing enzymes (pharmacokinetics property) or variation in the drug target (pharmacodynamics property)

second-generation antipsychotics risperidone, clozapine, quetiapine, and olanzapine. Weight was measured at the time of admission and at the end of 6 weeks, with weight gain defined as an increase in weight greater than 7% of the baseline weight. The final results confirmed the protective role of a T allele of rs518147 in antipsychotics-induced weight gain (21).

Another longitudinal study was used to investigate the association between LEPR (leptin receptor) Q223R (rs1137101), LEP-2548 G/A, and HTR2C-759 C/T (rs518147) polymorphisms and BMI change following antipsychotic drug consumption. The study population included 141 patients, 58.2% of which were males, and the majority of the patients were either prescribed olanzapine or clozapine. An interesting finding in this study was the occurrence of an inverse relationship between the associations of LEPR rs1137101 with obesity in males and females. The LEP Q223R genotype is associated with a higher prevalence of obesity in females (P=0.03) compared with the LEPR 223QQ genotype, which is associated with a lower prevalence of obesity in females. The stratified analysis for the HTR2C rs518147 polymorphism demonstrated a protective role of the -759 T allele against obesity in both males and females, but the results did not reach statistical significance (22). A study was performed to establish the association of the tumor necrosis factor-alpha (TNF-alpha) -308 G>A (rs1800629) polymorphism and weight gain in patients with schizophrenia under long-term clozapine, risperidone, or olanzapine treatment. Five hundred patients from Yuli Veterans Hospital in Taiwan were enrolled in the study, each receiving a second-generation antipsychotic (clozapine-275, olanzapine-79, or risperidone-146) for at least 3 months. The body weight gain was determined as >7% of BMI. The body weight gain percentages in the individual genotype groups were: $GG=4.2\% \pm 15.7\%$, $GA=5.9\% \pm 18.2\%$, and $AA=-3.0\% \pm 10.1\%$. There was no significant association found between the body weight gain and TNF-alpha -308 G>A (rs1800629) polymorphisms (23).

Gene polymorphisms in *HTR2C* rs518147 and *LEPR* rs1137101 affecting weight gain response to antipsychotics can be potentially used to predict which individuals are likely to gain weight following the use of antipsychotic medications.

Antidepressant drugs. Antidepressant drugs are also responsible for altering the metabolic profile of the patients prescribed them. The older tricyclic antidepressants are more likely to be associated with obesity compared with the newer serotonin reuptake inhibitors (SSRIs) and atypical antidepressants. Mirtazapine can be placed between tricyclic antidepressants and SSRIs. Among the SSRIs, paroxetine is more likely to cause weight gain than the other SSRIs. Bupropion and nefazodone are least likely to cause weight gain.

Drug class causing weight gain	Drugs associated with weight gain	Gene	rs#	Outcome	References
Antipsychotics	Olanzapine	5-HTR2C	rs3813929	0% patients with T allele compared with 27% of patients with C allele >10% increase in BMI over 6 weeks	(20)
			rs518147	5% patients with C allele compared with 32% of patients with C allele >10% increase in BMI over 6 weeks	(20)
		DRD2	rs2440390	A allele: 2.1 kg greater weight gain over 8 weeks	(60)
	Clozapine	5-HTR2C	rs518147	T allele: 2.04 kg less gain in body weight at 6 months	(61)
		LEP-2548A/G	rs1137101	A allele: 1.4 kg/m ² greater change in BMI	(62)
	Atypical antipsychotics	TNF-α	rs1800629	A/G allele: no significant difference weight gain	(23)
	(olanzapine, clozapine,	HTR2C	rs518147	T allele: 2.34 kg greater weight gain at 6 weeks	(21)
	risperidone)	HTR2C	rs518147	T allele: no significant change in BMI after 18 months	(63)
Antidepressants	SSRIs/SNRIs	COMT	rs4680	G allele: GG genotype gained 4 kg more than AG genotypes at 10 weeks	(25)
		TPH1	rs1800532	A allele: AA genotype was 3.21 times more likely to gain weight compared with CA genotype at 10 weeks	(25)
		HTR2C	rs381929	No significant difference in body weight gain	(25)
		SCLC6A4	rs25531		(25)
Antiepileptics	Valproate	LEPR	rs1137101	A allele: 1.01 kg/m ² greater change in BMI at 6 months	(28)
		ANKK1	rs1800497	C allele: 0.65 kg/m ² greater change in BMI at 6 months	(28)
		PRKAA2	rs10789038	G allele : 0.54 kg/m ² greater change in BMI at 6 months	(28)
Antidiabetics	Rosiglitazone	PLIN	rs894160	G allele: 1.30 kg greater weight gain at 12 weeks	(33)

TABLE 1 Pharmacogenomics of medications causing weight gain as a side effect

The Clinical Pharmacogenetics Implementation Consortium has already established guidelines on dosing recommendations for SSRIs such as fluvoxamine, paroxetine, citalopram, and sertraline based on their associations with *CYP2D6* and *CYP2C19* phenotypes. The CYP450 isoforms are major metabolizers for SSRIs, but the direct role of these isoforms in affecting weight gain outcomes has not been studied so far (24).

Few studies have evaluated the role of several gene polymorphisms that affect weight gain response to antidepressants. A study examined the role of *HTR2C*, *TPH1*, and *COMT* genes as well as *SLC6A4* rs25531 in body weight gain during antidepressive treatment with different classes of drugs, such as SSRIs, serotonin and norepinephrine reuptake inhibitors, and a combination of SSRI with serotonin and norepinephrine reuptake inhibitors. The study included a total of 301 patients out of which only 165 were included in the analysis. The results showed that *COMT* rs6480 significantly contributed to weight outcomes. The AG genotype was less likely (odds ratio [OR]=0.402, 95% CI:0.18-0.91) to gain more than 4 kg of weight during treatment than A homozygotes.

The GG genotype was four times (95% CI: 1.64-9.75) more likely to gain more than 4 kg of weight during treatment than heterozygotes. Moreover, *TPH1* rs1800532 also contributed to weight outcome (P=0.039). Upon correcting for multiple factors, only *COMT* rs4680 remained significant. Moreover, the genotypes *HTR2C* rs3813929 and *SLC6A4* rs25531 did not significantly contribute to weight outcome (25).

Currently, the *COMT* rs6480 polymorphism is not clinically used to predict weight gain outcomes of antidepressants. Lack of robust evidence in the literature warrants further research in pharmacogenomics of SSRI-induced weight gain.

Antiepileptic drugs. Antiepileptic medications have an impact on weight. A report studied weight changes associated with antiepileptic drug therapy, and it was found that levetiracetam and valproic acid cause significant relative and absolute weight gain, carbamazepine and lamotrigine caused nonsignificant weight gain, and topiramate was associated with significant weight loss (26).

The most common antiepileptic drug studied for the association of gene variation with weight gain as a side effect is valproate. A prospective study recruited 225 patients with epilepsy who were treated with valproate from the Chinese Han population to investigate the association of SNPs in CD36 and peroxisome proliferator-activated receptor gamma (*PPARy*) on valproate-induced obesity. A total of four SNPs, two in CD36 (rs1194197, rs7807607) and two in PPARy (rs10865710, rs2920502), were studied. The statistical interpretation from the data was that the CD36 rs1194197 C allele and rs7807607 T allele (OR=0.31; 95% CI: 0.13-0.72; P=0.009 and OR=0.38; 95% CI: 0.18-0.83; P = 0.02, respectively) were found to play a protective role in valproate-induced obesity. The PPARy rs10865710 C allele carriers were found less likely to have valproate-induced obesity compared with G allele carriers (OR = 0.04; 95% CI: 0.01-0.12; P < 0.001) (27). Another study examined the correlation of 19 SNPs in 11 genes on weight gain caused by valproate over 6 months in 212 patients with epilepsy treated with valproate. The observations were three polymorphisms-LEPR rs1137101, rs1800497 ankyrin repeat and kinase domain containing 1 (ANKK1), and rs10789038 protein kinase AMP-activated catalytic subunit alpha 2 (PRKAA2)that were associated with a BMI increase within 6 months after initiation of valproate treatment (P < 0.001, P = 0.017, and P = 0.020, respectively). Carriers of the A allele of LEPR rs1137101 gained significantly more weight compared with those with the GG genotype, whereas carriers of the C allele of ANK1 rs1800497 gained more weight compared with the wild genotype. Similarly, the G allele carriers of PRKAA2 rs10789038 had greater BMI change than the AA genotype (28). Apart from these prospective studies, a retrospective longitudinal study was conducted in 85 young patients with epilepsy who were treated with valproate and 93 who were treated with carbamazepine to study the impact of CYP2C19 polymorphisms. The final outcome was a greater incidence of weight gain in valproate-treated female patients with one or two loss-of-function CYP2C19 alleles than in females without the loss-of-function CYP2C19 alleles (29).

Glucocorticoids. Glucocorticoids have a multisystemic side effect profile, and one of the most common side effects is weight gain. Systemic steroids have a greater potential to cause weight gain compared with the topical preparations. A systematic review concluded that oral corticosteroids in the short term do not significantly affect body weight, appetite, energy intake, or body composition; however, long-term consumption of oral corticosteroids significantly affected these parameters (10).

The literature on the correlation of glucocorticoid-induced weight gain with gene polymorphisms is scant. In one report, 68 patients with adrenal insufficiency treated with glucocorticoids were included in the study, and the genotypes investigated were active SNPs of the hydroxysteroid 11-beta dehydrogenase 1 (*HSD11B1*) and glucocorticoid receptor (GR) genes. The GR Bcl1 polymorphisms showed a significant association with both BMI and body weight. Homozygous carriers of BcII had significantly higher BMI compared with the heterozygous carriers (P=0.007). The rs4844880 polymorphism of the *HSD11B1* gene exerted a significant impact on BMI and weight gain compared with the noncarriers (17.5±9.87 kg and 4.05±9.95 kg, respectively; P=0.02) (30).

Greater research is needed to address the gene variants affecting weight gain due to glucocorticoids as it is prescribed for a multitude of conditions, and a prior pharmacogenomic profile can help prevent this adverse event. Antihyperglycemic agents. Among antidiabetic agents. sulfonylureas and thiazolidinedione are most commonly associated with weight gain (31). Currently, no studies are available in the literature that establish the direct effect of gene polymorphism on weight gain due to sulfonylureas; however, some studies see the role of these gene SNPs in treatment response to sulfonylurea. One such study was done to determine the influence of polymorphisms Gly972Arg, SNP43, and Pro12Ala of the genes insulin receptor substrate 1 (IRS1), calpain 10 (CAPN10), and PPARG2 on treatment response to sulfonylurea and metformin. The outcome suggested that polymorphism SNP43 may influence response to treatment with sulfonylurea and metformin (32). In the thiazolidinedione group, a study aiming to examine the effects of perilipin (PLIN) gene polymorphisms on weight gain with rosiglitazone (4 mg/d) treatment for 12 weeks in 160 patients with type 2 diabetes was performed. Four polymorphisms at the PLIN locus were genotyped: PLIN 6209TC (intron 2), PLIN 11482G A (intron 6) (rs894160), PLIN 13041AG (exon 8), and PLIN 14995AT (exon 9). Significant weight gain was observed with the PLIN rs894160 polymorphism with an additive dose-response relationship between the number of A alleles and the degree of weight gain (GG, 1.33 ± 1.59 kg; GA, 0.85 ± 1.89 kg; and AA, 0.03 ± 1.46 kg; P = 0.010) (33).

Beta-blockers. Beta-blockers have been associated with weight gain and counteract the cachexia induced by chronic heart failure. In a report assessing 293 patients with chronic heart failure on beta-blockade therapy and its association with weight gain, an increase of 0.9 ± 7.0 kg (P=0.03) weight gain was observed with beta-blockers (34).

Data are present on the effect of various beta-adrenergic receptor gene polymorphisms on weight changes, but no direct evidence supports the impact of gene variants on weight gain as an adverse event of this drug. A study investigated beta1AR polymorphisms—beta(1) Ser49Gly, beta(1)Arg389Gly, beta(2)Arg16Gly, beta(2)Gln27Glu, and beta(3)Trp64Arg—in 188 patients with type 2 diabetes. Beta(1) Ser49Gly was found to be significantly associated with obesity. The beta1Gly genotype group had higher BMI compared with the Ser49/ Ser49 genotype groups $(24.7 \pm 3.7 \text{ vs. } 23.4 \pm 3.3 \text{ kg/m}^2; P=0.031)$ (35).

Pharmacogenomics and AOMs

Currently, four Food and Drug Administration–approved medications are available for long-term management of obesity, which include phentermine-topiramate extended release, liraglutide, orlistat, bupropion-naltrexone, and lorcaserin. Furthermore, there are four additional drugs approved for short-term use (up to 12 weeks): phentermine, benzphentamine, diethylpropion, and phendimetrazine (14). The mechanism of action of AOMs is varied and has been extensively reviewed elsewhere (36). Here, we focused on the pharmacogenomics of AOMs (Table 2).

Phentermine-topiramate extended release. Phentermine has been approved for short-term management (up to 3 months) of obesity and its combination with topiramate is approved for long-term use. Phentermine is a trace amino acid receptor agonist (TAAR-1) that acts as a releasing agent of norepinephrine and dopamine. The increase in the biogenic amines in the hypothalamus mediates appetite suppression. The effects of pharmacogenomics profile on phentermine have not been studied thus far despite being the most widely prescribed medication for short-term management of weight that it has been in the market for more than six decades.

TABLE 2 Pharmacogenomics of antiobesity medications

Antiobesity drugs	Gene	rs#	Outcome	References
Liraglutide	GLP-1 R	rs6923761	A allele- 1.8 kg more weight loss at 14 weeks	(41)
		rs6923761	A allele- delay in GE (adverse event)	(43)
		rs10305420	T allele - 5.7 kg less weight loss at 12 weeks	(42)
Topiramate	GRIK1	rs2832407	No effect on weight-loss outcomes	(64)
	INSR	rs4804428	T-C-A allele - 2.1 % greater body weight loss % at	(37)
		rs2396185	24 weeks	
		rs10419421		
Orlistat	GNB3	rs5443	T allele - 14.5% less fat mass reduction at 12 weeks	(45)
Bupropion	DRD2 Taq1	rs1800497	No polymorphisms predicted weight change during	(47)
	DRD2-141	rs1799732	treatment with bupropion at 12 months	
	C957T	rs6277		
	COMT	rs4818		
	SLC6A3			
Sibutramine	GNB3	rs5443	C allele- 7.2 kg greater weight loss	(50)
	ADIPOQ	rs266729	C allele - No difference in weight-loss outcomes at 12 weeks	(51)
	UCP2	rs28359178	G allele - No difference in weight-loss outcomes at 12 weeks	(52)
	SLC6A4		S allele- 2.2 kg greater weight loss at 12 weeks	(65)
Metformin	SLC22A1	rs1867351	No difference in weight-loss outcomes at 6 months;	(58)
		rs12208357	and 1.2% reduction in trunk fat	
		rs683369		
		rs3413415		
		rs2282143		
		rs34205214		
		rs34130495		
		rs628031		
		rs34888879		
		rs72552763		
		rs35270274		
		rs41267797		
		rs78899680		

Topiramate, initially an antiepileptic drug, potentiates the action of GABAergic neuron. The exact mechanism by which topiramate induces weight loss is not completely understood. However, clinical response to topiramate in individuals with obesity is highly variable (37). Variants in the insulin receptor gene (*INSR*) have been associated with differential weight loss in those treated with topiramate. In a clinical study of 445 patients with obesity, carriers of rs4804428 (**T**), rs2396185 (**C**), and rs10419421 (**A**) in *INSR* lost 9.1% of their baseline body weight compared with noncarriers (n=316) who lost 7.0% of their baseline body weight (37).

Liraglutide. Liraglutide is a glucagon-like peptide receptor (GLP-1R) agonist that causes weight loss centrally by inducing satiety and peripherally by delaying gastric emptying (38,39). The drug is subcutaneously (s.c.) administered. The safety and efficacy of

liraglutide have been evaluated in various trials. In a randomized, double-blinded, placebo-controlled trial comparing weight loss and cardiovascular outcomes following administration of 3 mg s.c. liraglutide versus 1.8 mg s.c. liraglutide versus placebo in 846 individuals with overweight or obesity, the total body weight-loss percentage at the end of 56 weeks was -6 versus -4.7 versus -2 (P < 0.001), respectively (40).

Few studies have been performed to establish the role of pharmacogenomics in treatment response to liraglutide. However, variants in GLP-1R have been associated with differential response. In a prospective study, 90 patients with type 2 diabetes mellitus and overweight were selected and initiated with the progressive treatment of liraglutide at a dose of 1.8 mg/d s.c. Of these participants, 51 of them had the genotype GG, and 39 had the GA/AA genotype of the GLP-1R SNP rs6923761. Parameters evaluated at the end of the study were BMI, weight, and a decrease in fat mass. The decrease was higher in A allele carriers, BMI $(-0.59 \pm 2.5 \text{ kg/m}^2 \text{ vs.} -1.69 \pm$ 3.9 kg/m²; P=0.05), weight (-2.78±2.8 kg vs. -4.52±4.6 kg; P=0.05), and fat mass (-0.59 ± 2.5 kg vs. -1.69 ± 3.9 kg; P=0.05) (41). Another report that studied the variants in the GLP-1R included the SNPs rs10305420 and rs6923761. The report involved 57 females with obesity diagnosed with polycystic ovarian syndrome who were assigned 1.2 mg s.c., four times daily liraglutide for 12 weeks. The results were measured in terms of strong responders who lost 5% or more of their initial body weight. Carriers of at least one T allele of rs10305420 had poor treatment response compared with those who carried two C alleles (OR = 0.27, 95% CI: 0.09-0.85, P = 0.025). Carriers of at least one A allele of rs6923761 tended to have a stronger treatment response compared with carriers of G alleles (OR = 3.06, 95% CI: 0.96-9.74, P = 0.05) (42).

A correlation between the genetic variants of GLP-1 R and transcription factor 7 like 2 (*TCF7L2*) to delayed gastric emptying and weight loss in individuals with obesity was established using data from two randomized, double-blinded placebo-controlled trials. The data reflected that within *GLP-1R* (rs6923761), patients carrying the minor allele who received exenatide or liraglutide had larger mean retardation in gastric emptying relative to baseline (117.9±27.5 minutes and 128.9± 38.3 minutes, respectively) compared with those with the wild-type allele G (GG) (98.5±30.4 minutes and 61.4±21.4 minutes, respectively; *P*=0.11). However, for *TCF7L2* (rs7903146), genotype (major vs. minor) changes in GE at 5 weeks (*P*=0.93) and weight loss at 5 weeks (*P*=0.72) were not different (43). There is a consensus among all studies that patients with A allele carriers of *GLP-1R* SNP (rs6923761) respond more favorably to treatment with liraglutide.

Orlistat. Orlistat acts by inhibiting gastric and pancreatic lipase and henceforth inhibiting the breakdown of intestinal triglycerides into fatty acids and monoglycerides for absorption by the intestinal mucosa. A 4-year, double-blinded placebo-controlled study looked at the effect of orlistat on various parameters and included 3,305 patients with obesity with BMI>30 who were subjected to lifestyle changes plus either orlistat or placebo. The mean weight loss at the 4-year end point was 5.8 kg with orlistat compared with 3.00 kg with placebo and was statistically significant (P<0.05), proving its strong clinical utility in weight-loss management (44).

Variability in weight-loss response to orlistat alone and its association with gene polymorphisms has not been studied so far; however, there is one clinical trial that investigaed genetic variations affecting response to the additive effect of orlistat on sibutramine therapy for weight loss. The 12-week trial evaluated variation in rs5443 in the guanine nucle-otide–binding protein beta polypeptide 3 (*GNB3*) and drug response. After the intervention, fat mass proportion in total weight loss was significantly lower in subjects with a T allele than in those without a T allele (P = 0.034), suggesting blunted fat mass reduction in females with obesity with T allele carriers (45).

Bupropion-naltrexone. Bupropion potentiates dopaminergic and noradrenergic neurotransmission by inhibiting the dopamine and norepinephrine transporter, respectively, at the neuronal endplate. Naltrexone and its active metabolite 6B-naltrexol is an antagonist of the μ -opiod receptor. Bupropion, in combination with naltrexone as a sustained-release preparation, is approved and proven to cause significant

weight loss likely by reducing the desire to eat and food cravings (46). Very limited information is available on the pharmacogenomics of weight-loss response to bupropion. The studies available have evaluated only gene variations affecting bupropion for smoking cessation and alcohol consumption. A trial studied the impact of five candidate genes on weight gain response to bupropion versus placebo in smoking cessation. Variants in five candidate genes were studied and included D2 dopamine receptor gene (*DRD2*), Taq1 (rs1800497), DRD2-141 (rs1799732), C957T (rs6277), catechol-o-methyltransferase (*COMT*) (rs4818), and solute carrier family 6 member 3 (*SLC6A3*). Weight was recorded at baseline, end of 6 months, and 12 months. The results did not support the role of these genotypes in weight changes and treatment response (47).

Abundant evidence is available on gene polymorphism correlation with naltrexone on response to its different indications, such as pain management, analgesia, opioid intoxication, and alcohol dependence, but no data have been collected on gene variants affecting weight-loss response to bupropion/naltrexone extended-release preparation, which warrants further studies.

Lorcaserin. Lorcaserin is a serotonin receptor (5-HT2C-R) agonist that activates the proopiomelanocortin (POMC) pathway in the brain, which promotes satiation. A multicenter randomized double-blinded trial included 3,182 patients who were randomized to receive either placebo or lorcaserin. The primary end points in the study were weight loss at 1 year and 2 years. Patients in the lorcaserin group lost an average of $5.81 \pm 0.16\%$ of the baseline body weight, as compared with $2.16 \pm 0.14\%$ in the placebo group (*P*<0.001), which indicates it to be an effective drug (48).

Plenty of studies have been performed on the gene *5HTR2C* and its variants on the weight outcomes following antipsychotic and antidepressant medications. However, research on the influence of gene polymorphisms in weight-loss response to lorcaserin is scant, and the *5HTR2C* gene holds excellent potential as a candidate gene for future research for alternative 5HTR2c agonists, as lorcaserin was recently withdrawn from the market.

Sibutramine. Although subutramine is no longer on the market, the pharmacogenomics studies of sibutramine are useful and might be of value to be replicated in other AOMs. Sibutramine influences both noradrenergic and serotonergic pathways within the hypothalamus, inhibiting the release of both noradrenaline and serotonin from the hypothalamic neurons. It has a dual physiological action, reducing food intake by enhancing satiation and reducing the decline in metabolic rate that occurs with weight loss (49).

Out of numerous polymorphisms studied so far, one of the important ones is the *GNB3* C825T polymorphism. In a retrospective study, patients who had participated in a multicenter double-blinded placebo-controlled trial were selected. The trial consisted of 348 participants, 174 of which were in the sibutramine group and 174 in the placebo group. Only 111 participants could be traced, and blood samples and buccal samples were obtained from them. The samples were genotyped for the *GNB3* C825T (rs5443) polymorphism. The results demonstrated a strong effect of sibutramine in individuals with CC genotype (P=0.003). This group lost an additional 7.2±2.2 compared with 4.1±2.0 kg in the subjects with the TT/TC genotype (P=0.0013) (50). Another interesting gene that is important to note is the *ADIPOQ* gene. Adiponectin is an adipose-derived plasma protein known for modulating insulin sensitivity and glucose homeostasis and is encoded by the adiponectin CQI and collagen domain-containing (ADIPOQ) gene located on chromosome 3q27. The study consisted of 131 individuals from the Taiwanese population in a randomized clinical trial, including 87 in the sibutramine group and 44 in the placebo group. The first end point was body fat loss percentage, and the second end point was weight loss compared with baseline weight at the end of 12 weeks. The samples were genotyped for ADIPOQ rs266729. The strong effect of sibutramine on the percentage of body fat loss was indicated for patients with the CC genotype $(4.6\% \pm 0.5\% \text{ vs. } 1.9\% \pm 0.3\%; P=0.001)$. In contrast, sibutramine had no significant effect on the percentage of body fat loss in subjects with the GG and GC genotypes (P=0.383 and P=0.814, respectively) (51). With a similar study design by the same author in the same Taiwanese population, a different genotype was studied. This time a common SNP, in the uncoupling protein 2 (UCP2) gene -866G/A (rs659366), was under investigation. Data concluded that sibutramine had a strong effect on weight loss and body fat percentage in AA+GA genotype groups (P < 0.001) compared with the GG genotype, which had no significant effect on weight loss and body fat percentage in response to sibutramine (52). The GNB3 C825T (rs5443) polymorphism and ADIPOQ rs266729 gene variations are the key players in determining weight-loss outcomes with sibutramine.

Metformin. In recent years epidemiological and preclinical studies have shown the favorable effect of metformin in body weight loss, for which it is usually used as an off label medication (53). The Metformin Study Group showed a decrease of 3.8 kg of body weight in the metformin group compared with sulfonylureas, at 29 weeks (54). The BIGRO study group examined weight-loss treatment with metformin 850 mg twice a day for 1 year and found a 2-kg weight loss compared with controls (55). Additionally, the Diabetes Prevention Study, the largest study to show the weight benefits of metformin, showed that patients at high risk for type 2 diabetes randomized to metformin experienced a 2.1-kg weight loss (56). Even though the evidence suggests an effect of metformin in weight loss, there is considerable inconsistency regarding this outcome.

The interpatient variability to metformin response in terms of weight reduction has been attributed to several factors, including genetic polymorphisms of metformin transporters, such as the organic cation transporter member 1 (OCT1, encoded by SLC22A1), the plasma membrane monoamine transporter (PMAT), and the multidrug and toxic compound extrusion proteins (MATEs) (57). Waio Johnn Sam et al. found that the SLC22A1 polymorphism detected in children with obesity did not significantly affect the 6-month response to metformin in terms of body weight; however, SLC22A1 variant carriers had smaller reductions in percentage of total trunk fat after metformin therapy (58). The genetic variation of the metformin transporters OCT1, MATE1, and MATE2-K has also been studied in women with polycystic ovarian syndrome; nevertheless, none of the polymorphisms significantly affected the clinical response to metformin to weight loss, lipid profile, or insulin sensitivity. However, these previous findings should be interpreted carefully because of the small sample size and the short duration of both studies (59).

Conclusion

Further research on gene polymorphisms associated with antiobesity drugs can play a pivotal role in understanding the variability in response

to these drugs. Incorporating those genetic variants from the evidence into commercially available pharmacogenomics testing can help individualize obesity treatment. Translating the current knowledge and evidence of weight gain as a common side effect of certain medication into clinical practice may help achieve better patient outcomes and prevent weight gain as an adverse event of a drug. Knowing the pharmacogenomic profile of a person can guide the provider away from drugs that would be more likely to cause weight gain as a side effect and hence help them make the right choice of drug for that patient.**O**

Funding agencies: AA is supported by the National Institutes of Health (K23 DK114460, C-Sig P30DK84567), ANMS Career Development Award, Center for Individualized Medicine – Gerstner Career Development Award, and Mayo Clinic.

Disclosure: AA is a stockholder in Gila Therapeutics and Phenomix Sciences; he serves as a consultant for Rhythm Pharmaceuticals and General Mills. The other authors declared no conflict of interest.

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