Interface between Pharmacotherapy and Genes in Human Obesity

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Key Words

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Abstract

Obesity is a polygenic chronic condition, and dysregulation in multiple underlying energy balance processes drives the obese phenotype. Lifestyle changes can be difficult to sustain long term, and anti-obesity drugs can be an advantageous component of a successful weight loss plan. However, due to lack of efficacy or adverse safety profiles, there is currently a limited selection of anti-obesity drugs on the market. This, coupled with the notable interindividual variability in efficacy of approved treatments, represents a significant unmet medical need. In this review, we will highlight this variability in weight loss response to these existing anti-obesity compounds and discuss how underpinning genetic variation is associated with weight loss outcomes. Existing research in the field of pharmacogenomics and obesity drugs will be highlighted, as will possibilities for future focus. We will conclude by exploring examples of successful pharmacogenomics studies, and also by asking how pharmacogenomics can be built into the drug development pipeline for the benefit of patients and pharmaceutical companies alike.

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Introduction

Obesity rates have risen sharply in recent years, doubling globally since 1980 [1]. More than 1 in 10 of the world's population is now considered obese [1], and obesity and overweight affect two thirds of adults in the US [2]. Prevalence of overweight and obesity is predicted to reach 86.3% by 2030 in the US if current trends continue [3]. This is alarming considering the toll which obesity exacts on quality of life and mortality. In fact, obesity is now considered the number one cause of preventable death in the US. Approximately 300 million adults die each year as a result of being overweight or obese [1]. Furthermore, obesity drives chronic diseases and lies at the root of 44% of the burden of diabetes, 23% of ischemic heart disease burden and 7–41% of the burden of specific cancers [1]. If obesity rates continue unabated, the number of new cases of chronic conditions such as type 2 diabetes, coronary heart disease, stroke, hypertension and arthritis is predicted to grow substantially (10-fold increase between 2010 and 2020) [2].

At its most fundamental level, overweight and obesity develop secondary to an imbalance between energy consumed and energy expended. Although simple when reduced to these terms, a highly complex web of social, dietary, environmental and genetic factors underpins energy balance regulation [4]. This results in a highly

heterogeneous set of factors driving a phenotype [increased body mass index (BMI) and adiposity] which on the surface appears similar between individuals. Individual genetic factors govern the risk of obesity and the ability of an individual to robustly defend a healthy body weight in an obesogenic environment. Data from twin and family studies suggest that 40–70% of interindividual body weight variability can be attributed to genetics [5]. However, unraveling the genetics of obesity is proving complex. Although extremely rare forms of monogenic obesity are documented, for example genetic leptin deficiency which responds to leptin treatment [6], in general, obesity is not the result of a single gene defect and is instead a polygenic condition with networks of gene-gene and gene-environment interactions. The advent of genome-wide association studies (GWAS) has added significantly to our knowledge of genetic factors underlying obesity and has led to the identification of novel loci linked with overall adiposity and visceral fat accumulation [7]. However, consistent with the multi-factorial nature of obesity development, individual single nucleotide polymorphisms (SNPs) identified by GWAS to date account for a very small percentage of phenotypic variance in test populations. For example, SNPs in Fat Mass and Obesity (*FTO*) and melanocortin-4 receptor (*MC4R*), which are among the most robustly replicated, account for less than 2% in adult BMI variance [8, 9].

Search Criteria

Literature searches were performed using PubMed for all original articles published using 'genotype', 'genetics', 'genomics', 'SNPs', 'pharmacogenetics' and 'pharmacogenomics' combined with 'weight loss', 'obesity', 'sibutramine', 'orlistat', 'phentermine', 'lorcaserin', 'Belviq', 'topiramate', 'Qsymia', 'GLP-1 receptor agonist', 'rimonabant' and 'CB-1 blockers'. All articles identified were English language full-text papers. To ensure that all relevant literature was captured, reference lists of previous reviews from peer-reviewed journals were searched for additional papers. Additionally, the authors drew from their knowledge of the literature in this field.

Weight Loss Recommendations for Obesity

Overweight and obese individuals are encouraged to lose weight. More specifically, it is recommended that patients with obesity (BMI >30) lose at least 10% of their body weight as even this modest reduction has measurable benefits with respect to metabolic health and improvement of obesity-associated comorbidities [10]. Life-

style modification, such as increasing physical activity, decreasing energy intake, and cognitive behavioral therapy, is the preferred first line of treatment for obesity. Although the value of lifestyle interventions has been established [11–13], adherence to lifestyle changes can be problematic in the longer term. In general, even relatively small body weight losses are difficult to maintain and it has been estimated that significant weight regain occurs in 80–90% of individuals [14]. Pharmacological treatment options are indicated for individuals with a BMI >30 (obese) or those with a BMI >25 (overweight) with existing comorbidities such as diabetes, dyslipidemia or hypertension [10]. To improve weight loss outcomes, positioning pharmacological treatments in an individual's weight loss plan alongside diet and exercise may enhance body weight loss and be particularly beneficial for those unable to lose sufficient weight and/or maintain a reduced weight (i.e. 10%) through lifestyle modification alone.

Pharmacological Treatment of Obesity

Although the magnitude of the obesity epidemic continues to increase, there is a relative lack of efficacious pharmacotherapies approved for the treatment of this chronic condition, and thus there is a tremendous unmet medical need. Despite the fact that many anti-obesity compounds have made it to various stages of drug development over the past 2–3 decades, the vast majority have not been approved and thus not marketed, as a result of insufficient efficacy and/or adverse side effects. Currently, only 3 drugs [orlistat (Xenical, Alli), lorcaserin HCl (Belviq), phentermine and topiramate extended release (Qsymia)] are approved for continuous use in the US, and 1 drug, phentermine, is approved for short-term use (up to 12 weeks) (table 1). In comparison, ~34 drugs are approved and marketed for the treatment of diabetes [15] and ~79 for hypertension [16]. Several drugs such as sibutramine (US and Europe) and rimonabant (Europe) (table 1) have been marketed previously for weight loss, but have been withdrawn due to an inadequate cardiovascular disease safety profile or adverse neuropsychiatric symptoms, respectively. In addition, other pharmacotherapies are prescribed off-label for the treatment of obesity in the USA (table 1).

Alongside the relative dearth of pharmacological treatments for obesity, issues of compliance are important to consider. Meta-analyses of studies examining the weight loss effects of orlistat and sibutramine (Reductil,

Table 1. Weight loss drugs currently available on the market, previously withdrawn or used off label for weight reduction

Drug details	Proposed mechanism of action	Efficacy	Adverse effects
<i>Currently marketed weight loss drugs</i>			
Orlistat (Xenical, Roche; Alli, GlaxoSmithKline)	Pancreatic lipase inhibitor taken orally usually 3 times per day with meals. Prevents the hydrolysis and absorption of dietary fat. It is estimated that 30% of fat absorption is blocked.	In a 6-month study examining the efficacy of orlistat, 37% of subjects in the orlistat treatment group achieved the 10% weight loss goal, compared with 19% of subjects taking placebo [27].	Abdominal pain, flatulence, oily stools and diarrhea which can be avoided, at least in part, by reducing fat intake to <15 g per meal.
Phentermine hydrochloride (Adipex-P [®] , Teva)	Sympathomimetic amine. Acts centrally to increase dopamine, norepinephrine and serotonin activity resulting in reduced food intake and increased energy expenditure [80].	95.8 and 62.5% of subjects taking phentermine attained 10 and 5% weight loss, respectively, following 12 weeks of treatment (compared with 20.8 and 4.7% of subjects in the placebo group) [81].	Insomnia, anxiety and other central nervous system side effects, tachycardia, elevated blood pressure, palpitations and gastrointestinal effects. Associated with increased tolerance and dependency with long-term use.
Phentermine hydrochloride/ topiramate extended release (Qysmia [™] , Vivus)	Topiramate, originally developed as an anti-epileptic, has been shown to reduce body weight, although the mechanism of action is not exactly clear. Phentermine is a sympathomimetic amine (see above). Phentermine and topiramate are effective at inducing weight loss alone; however, adverse side effects prohibit individual long-term use. The lowered doses used in this combination facilitate weight loss while maintaining an adequate safety profile.	Approximately 62% of subjects taking 7.5/46 mg (phentermine/topiramate) lost 5% of their body weight and 37% lost 10% of their body weight during the 1-year treatment period (compared with 21 and 7% in the placebo group) [18].	Dry mouth, constipation, dysgeusia, paresthesia, insomnia, dizziness and irritability [18]. Approved with Risk Evaluation and Mitigation Strategy (REMS) based on an increased risk to infants of developing orofacial clefts if exposed during the 1st trimester [82].
Lorcaserin hydrochloride (Belviq, Arena, Eisai Inc.)	Selective serotonin 2C (5-HT _{2C}) receptor agonist which acts centrally to increase satiety and decrease food intake.	47.2% of subjects lost at least 5% of body weight compared with 20–25% of subjects taking placebo following 1 year of treatment [20, 28]. 22.6% of subjects taking Belviq lost at least 10% of their body weight compared with 7.7–9.7% of subjects in the placebo group [20, 28].	Upper respiratory infections, headache, dizziness, nasopharyngitis and nausea [28].
<i>Weight loss drugs withdrawn from the market after approval</i>			
Sibutramine hydrochloride (Meridia, Abbott)	Selective serotonin and norepinephrine reuptake inhibitor. Raises hypothalamic serotonin and noradrenaline concentrations by inhibiting their reuptake which results in decreased food intake. Revoked from EU and USA markets due to cardiovascular safety concerns.	5 and 10% body weight loss at 1 year was attained by 42 and 25% of individuals, respectively [26].	Increased blood pressure and pulse rate, constipation, dry mouth and insomnia.
Rimonabant (Acomplia, Sanofi-Aventis)	CB1 antagonist. Acts centrally to block CB1 receptors resulting in reduced food intake.	48.6–50.9% of subjects taking rimonabant lost 5% of their body weight in 1 year compared with 19.2–20% of subjects taking placebo. 25.2–27.4% of rimonabant subjects lost at least 10% body weight in 1 year compared with 7.3–8.5% in the placebo group [19, 29].	Failed to obtain FDA approval and was withdrawn from the European market due to adverse psychiatric side effects which included increased depression, anxiety and suicidal ideation [83]. Other side effects noted in phase III trials included nausea, dizziness, arthralgia and diarrhea [19].
<i>Peptide-based drugs used off-label for weight loss</i>			
Glucagon-like peptide 1 receptor (GLP-1R) agonist-based therapies, e.g. exenatide (Bydureon, Amylin; Byetta, Amylin)	Activates GLP-1 receptors in the central nervous system to reduce food intake.	Meta-analysis of randomized controlled trials investigating the impact of GLP-1R agonists on weight loss reported treatment induced greater weight loss than placebo in individuals with and without diabetes. Weight loss ranged from –0.2 to –7.2 kg [17].	Hypoglycemia, nausea, diarrhea and vomiting.

Meridia, Sibutrex) report that attrition rates can reach 50% [17]. This is similar to rates reported in large trials of phentermine and topiramate [18], rimonabant (Acomplia) [19] and lorcaserin [20]. Using pharmacy purchasing information from a large Health Maintenance Organization (HMO) serving over 1 million individuals, another group reports that adherence to therapy (orlistat, sibutramine) was substantially lower than that reported in clinical trials [21]. Although reasons for this noncompliance were not assessed due to the study design, age, gender or baseline BMI were not significantly associated with adherence [21]. A closer examination of published drug trials (rimonabant, sibutramine, orlistat) shows that among the top reasons for withdrawal/dropout from the trials were adverse effects, followed by patient request and noncompliance [18–20, 22]. Additionally, although not specific for anti-obesity drugs, lack of efficacy is often noted as a reason for withdrawal and noncompliance. These results highlight the need for efficacious pharmacotherapies targeting obesity which will be taken long term by patients.

Variability in Response to Weight Loss Drugs – A Justification for a Pharmacogenomics Approach

In an obese population, the underlying genetic and molecular processes promoting weight gain can vary significantly between individuals despite general phenotypic similarities within the group [23]. This has a substantial impact on potential therapeutic efficacy of pharmacological treatments which often target a single specific energy balance regulatory mechanism. Additionally, common genetic variation may alter the response to pharmacotherapy even if this variation is not associated with the risk of developing the disease itself [24]. Indeed, the weight loss response to drug treatments for obesity varies considerably. It has been noted that the overall data reporting quality of obesity drug trials is low, with poor and inconsistent reporting of standard error and standard deviation making it difficult to assess overall variability in weight loss response [25]. However, the number of subjects who achieve the goal weight loss during treatment is telling, with the majority of drug trials reporting that less than half of drug-treated participants met the 5% weight loss target, and a smaller proportion attain the more ideal 10% body weight loss.

The response to sibutramine treatment, for example, is known to be highly variable. Five and 10% body weight loss at 1 year was attained by 42 and 25% of individuals,

respectively [26]. In a 6-month study examining the efficacy of orlistat, 37% of subjects in the orlistat treatment group achieved the 10% weight loss goal, compared with 19% of subjects taking placebo [27]. A trial examining the efficacy of lorcaserin HCl reported that 47.2% of subjects lost at least 5% body weight compared with 25% of subjects taking placebo following 1 year of treatment [20]. 22.6% of subjects taking lorcaserin HCl lost at least 10% of their body weight compared with 9.7% of subjects in the placebo group [20]. These results agreed strongly with those of an earlier study which reported that 47.5% of subjects in the lorcaserin HCl arm lost at least 5% of body weight compared with 20.3% in the placebo group, and 22.6% of subjects taking lorcaserin HCl lost at least 10% body weight compared with 7.7% in the placebo group [28]. In the Phase III trial (CONQUER Trial) examining phentermine/topiramate extended release, 62% of subjects receiving a 7.5/46.0 mg (phentermine/topiramate) dose and 70% of subjects receiving a higher dose (15/92 mg) achieved at least 5% body weight loss over the 1-year treatment period compared with 21% in the placebo group. Seven percent in the placebo group, 37% in the 7.5/46 mg and 48% in the 15/92 mg group achieved greater than 10% weight loss [18]. Furthermore, in the RIO-North America Study which examined rimonabant-induced weight loss, 48.6% of subjects taking rimonabant lost 5% of their body weight versus 20% of subjects taking placebo at 1 year. 25.2% of rimonabant subjects lost at least 10% versus 8.5% in the placebo group [29]. In the European Study (RIO-Europe), 50.9% of subjects in the rimonabant group lost over 5% and 27.4% lost over 10% at 1 year compared with 19.2 and 7.3% in the placebo group (5 and 10% weight loss, respectively) [19]. The lack of clinically meaningful weight loss in a large proportion (typically over 50%) of drug-treated patients coupled with the risks of adverse effects (both known and potentially unknown that may become evident after approval with longer-term use) highlights the importance of identifying and targeting patients who will respond best to a specific pharmacotherapy.

It is reasonable to conclude that underlying genetic differences contribute to variability in response to treatment. This has led to a great deal of interest in the influence of genetics on responses to pharmacological interventions and to the study of pharmacogenomics. The internationally harmonized definition of pharmacogenomics (PGx) is the ‘study of variations of DNA and RNA characteristics as related to drug response’. Pharmacogenetics (PGt) is considered a subset of this and is defined as ‘the study of variations in DNA sequence as related to

drug response' [30]. As interindividual genetic differences have the capacity to influence all facets of a disease state, from pathogenesis to therapy, the Food and Drug Administration (FDA) has outlined three broad categories with relevance for drug development and pharmacotherapy: (1) genes relevant to the drug's pharmacokinetics [absorption, distribution, metabolism (including formation of active metabolites) and excretion (ADME)]; (2) genes that affect the drug's intended and unintended targets and therefore its effect on these targets, and (3) genes that predict the occurrence of disease development (e.g. genes that predict likelihood of tumor development or metastasis), sometimes called prognostic markers [31]. The value of PGx as stated by the FDA is to make drugs safer and more effective by identifying individuals who are most at risk for drug-induced adverse effects (safety PGx), are most likely to have an efficacious response or benefit from a genotype-modified dose or dosing interval (efficacy PGx) [31].

Considering the variability in weight loss response to pharmacotherapy, identification of drug-sensitive genotypes is important for several reasons. Targeted interventions will reduce unnecessary potential for adverse events in individuals unlikely to respond and may increase compliance with therapies as individuals will see a benefit to continued treatment. Additionally, a more focused approach may improve the cost/benefit and risk/benefit ratios of these treatments. PGt is becoming more prevalent in other health areas related to obesity, such as antipsychotic-induced weight gain (for review, see [32, 33]).

Safety and Efficacy PGx in Relation to Obesity Pharmacotherapies

Efficacy PGx and Sibutramine

Sibutramine is a serotonergic and noradrenergic reuptake inhibitor and acts centrally on 5-HT pathways, inhibiting the reuptake of serotonin and noradrenaline released from hypothalamic neurons [34]. Sibutramine is also associated with an increase in plasma epinephrine. The transmembrane 5-HT receptors signal to the intracellular environment through heterotrimeric guanine nucleotide-binding proteins (G-proteins). Activation of 5-HT_{2C} receptors in particular leads to hypophagia [35]. Considering that weight loss responsiveness is highly variable and the causes are unknown, several researchers have sought to segment responders and nonresponders to sibutramine based on genotype at key genes in sibutramine target pathways. Although not currently available in

the US or Europe, sibutramine is the most heavily studied anti-obesity agent in relation to PGx and provides an example of choosing candidate genes based on proposed target pathways.

GNB3

The *GNB3* gene encodes the Gβ3 subunit of heterotrimeric G proteins. A polymorphism in this gene (rs5443), commonly known as the C825T variant, has received much attention within the context of obesity [36–38]. This is a synonymous SNP consisting of a substitution for C by T at position 825 in exon 10. The T allele is associated with a splice variant which is biologically active and linked with enhanced signal transduction [39]. Genotype at this SNP has also been associated with weight loss responsiveness to sibutramine. The initial report of this came from Hauner et al. [40] who retrospectively genotyped obese subjects (n = 111) who had participated in a 54-week randomized controlled trial of sibutramine versus control. All subjects received dietetic support, access to educational sessions and encouragement to increase physical activity. The 825T allele was found at a frequency of 35.1% which is comparable to that reported previously in obese Caucasian subjects [36, 41]. A strong effect of sibutramine was seen in the CC genotype group, wherein individuals in this group lost significantly more weight than the T allele carriers (TC and TT) (7.2 ± 2.2 kg compared with 4.1 ± 2.0 kg). The OR for 5 and 10% weight loss (sibutramine vs. placebo) in the whole group was 3.5 (95% CI 1.6–8.1) and 2.9 (95% CI 1.2–6.8) compared with 6.8 (95% CI 1.8–25.6) and 9.6 (95% CI 1.7–53.8) (5 and 10% weight loss, respectively) in the CC group (sibutramine vs. control). In contrast, Grudell et al. [42] showed that T allele carriers (TT/TC) exhibited greater weight loss than CC genotype in a study of 181 overweight or obese patients in a double-blind randomized controlled trial of sibutramine or placebo for 12 weeks. More recently, Hsiao et al. [43] sought to clarify this issue using Asian obese subjects (n = 131) who completed a 12-week intervention of placebo or sibutramine treatment. Similar to both previous studies, weight loss on the whole-group level was greater in the sibutramine group versus placebo (7.4 ± 1.2 vs. 3.5 ± 1.3 kg) after controlling for sex and baseline body weight and fat. Echoing the findings of Grudell et al. [42], TT and TC carriers lost significantly more weight on sibutramine compared to control, whereas CC carriers did not differ from control subjects in terms of body weight or fat loss [43].

PNMT

PNMT encodes the enzyme phenylethanolamine *N*-methyltransferase which is responsible for the conversion of noradrenaline to adrenaline. Considering its function, polymorphisms in *PNMT* have the potential to influence response to sibutramine. In a study of obese women ($n = 94$ 3-month completers), Peters et al. [44] report that a polymorphism consisting of a G to A transition, located in the *PNMT* promoter (-148 from the transcription start site), was associated with sibutramine-induced weight loss success. Subjects homozygous for either A (AA) or G (GG) lost significantly more weight than G/A heterozygotes [44]. G(-184)A polymorphism is commonly linked with G(-390)A (not measured), and functional assays indicate that the combination of these SNPs results in decreased promoter activity [45]. However, association between the G(-184)A variant in *PNMT* and weight loss response to sibutramine could not be confirmed in a subsequent, albeit smaller, 12-week intervention including 22 subjects taking sibutramine and 21 taking placebo [46].

SLC6A4

SLC6A4 encodes a protein that transports serotonin from the synaptic cleft to the presynaptic neurons, thereby terminating its effects. A repeat-length polymorphism (5-HTTLPR) in the 5' promoter region of this gene has been examined within the context of weight loss response to sibutramine. Alleles of the 5-HTTLPR promoter have either a short (S) or long (L) copy, with the S allele resulting in lower transcriptional activity [47]. The *SLC6A4* LS/SS genotype was shown to be associated with significantly greater weight loss following sibutramine treatment (6.1 ± 1.0 kg) compared with LS/SS or placebo (0.1 ± 0.9 kg). No effect of the LL genotype on weight loss responsiveness was reported [46]. The authors postulate that individuals with a partial functioning of the serotonin transporter have increased availability of serotonin for receptor-ligand interaction, leading to a more effective action of sibutramine [46].

ADRA2A (α 2A)

α 2A adrenergic receptors are involved in presynaptic inhibition of noradrenaline release, and activation has been shown to increase food intake [48]. It has been proposed that genetic variation in α 2A leading to decreased norepinephrine uptake would complement reuptake inhibition by sibutramine and result in enhanced weight loss [42]. However, no effect of genotype at α 2A-1291 C/G (rs1800544) on sibutramine- or placebo-induced weight loss following 12 weeks of treatment was observed [46].

ADIPOQ

Adiponectin is an adipose-derived plasma protein (adipokine) linked with glucose homeostasis and insulin sensitivity. Increased plasma adiponectin concentrations have been reported following sibutramine treatment [49]. Adiponectin is encoded by the *ADIPOQ* gene. *ADIPOQ* variant rs266729 has received attention due to its association with obesity and type 2 diabetes [50]. In a study of obese Taiwanese patients taking sibutramine ($n = 87$) or placebo ($n = 44$) for 12 weeks, C allele homozygosity was shown to associate with significantly greater body fat loss and total body weight loss with sibutramine treatment compared to the GG or GC genotypes [51].

Safety PGx and Sibutramine

CYP Enzymes

Risk/benefit in medicine approvals is of importance; however, individual safety is oftentimes at the core of regulator decisions. Safety PGx, distinct from efficacy PGx, seeks to determine underlying factors driving adverse response to a drug and, in combination with efficacy PGx, can identify segments of the population likely to experience a positive risk/benefit ratio. Again, the literature of safety PGx as it relates to obesity drugs centers around the study of sibutramine. In humans, sibutramine is rapidly metabolized to *N*-mono-desmethyl sibutramine (M1) and *N,N*-di-desmethyl sibutramine (M2), and the in vivo effects are primarily due to the actions of these metabolites, rather than sibutramine itself [52]. Several CYP enzymes are involved in the metabolism of sibutramine including CYP3A4, CYP2B6, CYP3A5 and CYP2C19 [53]. These genes are highly polymorphic and impact the levels of substrates and their pharmacokinetic properties [54, 55]. A study investigating the impact of genotype at *CYP2B6*, *CYP3A5* and *CYP2C19* on pharmacokinetics of sibutramine found that genotype at *CYP2B6* and *CYP3A5* did not contribute to the pharmacokinetic variability of sibutramine. On the contrary, *CYP2C19*, which was thought to play a minor role based on in vitro data, was shown to significantly impact the disposition of sibutramine and the appearance of the M1 metabolite. Carriers of the PM genotype at *CYP2C19* had a significantly greater area under the curve ($+252.2\%$) and $C_{\max}$ ($+179.8\%$) sibutramine in plasma than other genotypes. Additionally, the $C_{\max}$ and area under the curve of the M1 metabolite was significantly raised [56]. A subsequent study investigated the impact of genotype at *CYP2B6*, and pharmacokinetics of sibutramine and active metabolites was conducted with 57 subjects each given a single dose of either 10 or 15 mg with blood collected for 72 h after ad-

ministration. Genotype at *CYP2B6* did not significantly impact area under the concentration time curve or maximum plasma drug concentration; however, a relationship between the *CYP2B6**6 allele and a lower metabolite clearance of the M1 metabolite was observed. No differences in blood pressure were observed across genotype groups [57]. These studies have highlighted the impact of variants in genes encoding CYP enzymes and sibutramine pharmacokinetics. However, the contribution of these variants to the development of adverse events has not been adequately addressed.

Other Potential SNPs Impacting Drug Efficacy

Although PGx studies for obesity drugs other than sibutramine are lacking, genetic variants in genes associated with drug mechanism of action with the potential to influence response have been identified.

Orlistat

SNPs have been identified in the gene encoding pancreatic lipase (*PNLIP*), the enzyme responsible for the hydrolysis of triglyceride in the intestine. Sequencing *PNLIP* exons in a cohort of patients with pancreatic lipase and control deficiency identified 3 silent SNPs associated with pancreatic lipase deficiency. Subsequent genotyping of Caucasian, Asian, African and Native American cohorts identified that two of these SNPs were relatively common in Caucasian populations, and one appears to be African decent specific [38]. Orlistat targets pancreatic lipase and inhibits its activity, thus impairing triacylglycerol hydrolysis and subsequent absorption by the intestine. Unabsorbed lipid is passed in the feces, and the presence of this excess lipid in the gastrointestinal tract is the cause of Orlistat-induced adverse effects. Hence, this variation has relevance for the treatment of individuals with Orlistat, as genotype at *PNLIP* may contribute to variability in triacylglycerol hydrolysis and so to the degree of efficacy and adverse effects experienced.

Lorcaserin

Lorcaserin is a 5-HT_{2C} selective agonist. 5-HT_{2C} receptors are expressed in the brain and neurotransmission via these receptors has been implicated in ingestive and appetite behaviors [58]. 5-HT_{2C} receptors are postsynaptic with classical 7-transmembrane spanning domains associated with G-protein coupled receptors and linked to phospholipase A2 and C [58]. 5-HT_{2C} receptors are unique among the 7 transmembrane receptors in that 5-HT_{2C} pre-mRNA is the subject of RNA editing [59]. The human brain exhibits diversity in the type of 5-HT_{2C}

mRNA expressed and this diversity and differences in editing can impact G-protein coupling and downstream intracellular signaling and has been demonstrated to decrease agonist potency [59]. Variability in regulation and expression of adenosine deaminases acting on RNA (ADARs) (editing machinery) as well as in 5-HT_{2C} itself (editing template) could have a significant impact on response to treatment with 5-HT_{2C} agonists [59]. Additionally, a number of SNPs (–995G/A, –759C/T and –697G/C) and a tandem repeat sequence (–1027GT) located in the 5-HT_{2C} promoter give rise to a series of haplotypes associated with obesity and type 2 diabetes [60], and have also been reported to be associated with high receptor expression rates [61]. Although these SNPs have not been studied within the context of response to weight loss drugs which target 5-HT_{2C} such as lorcaserin or sibutramine, these 5-HT_{2C} polymorphisms have been associated with variability in response to antipsychotic drugs and the risk of antipsychotic-induced weight gain [58, 62]. Furthermore, the 5-HT_{2C} gene product undergoes posttranslational modification leading to amino acid substitutions which can alter efficacy of interaction between receptor and G protein and can decrease agonist binding efficacy (antagonist not affected) [58].

Cannabinoid Receptor Type 1 Blockers

Cannabinoid receptor type 1 (CB1) blockers such as rimonabant have been shown to decrease body weight in some individuals albeit with significant neuropsychiatric side effects. SNPs located within the gene encoding CB1 (*CNR1*) have been linked with obesity phenotypes [63]. There are currently no reports of the impact of genotype at *CNR1* and weight loss response to CB1 blockers such as rimonabant. However, CB1 is also a target of psychiatric drugs, and genotype at rs1049353 has been linked with response to antidepressant treatment. Specifically, G allele carriers (GG/AG) may be resistant to antidepressant treatment relative to AA genotype at rs1049353 [64].

Glucagon-Like Peptide 1 Receptor Agonists

It is possible that variability in *Glucagon-Like Peptide 1 Receptor (GLP-1R)* contributes to the variability in weight loss response to GLP-1 treatment (e.g. exenatide or other GLP-1 analogues) [24]. For example, a heterozygous *GLP-1R* missense polymorphism that resulted in a substitution of threonine 149 by methionine (T149M) and which was associated with diabetes has been identified [65] and studied in vitro [66]. This polymorphism was observed to reduce binding of GLP-1 and exendin-4 [66]. In addition to downregulated agonist potencies, the

polymorphic receptor induced significantly less cAMP production (GLP-1 and exendin-4 stimulated) cells compared to the wild type receptor [66].

Building PGx into Drug Development – Prospective Efficacy PGx

There are a number of cases where PGx information has been added successfully to a drug label after marketing. For example, the label of clopidogrel (Plavix) [67], used to prevent blood clots in patients recently suffering from myocardial infarction or stroke, was updated to include information on the impact of SNPs on *CYP2C19* efficacy. This was based on postmarketing information linking a loss of function mutation in *CYP2C19* to reduced antiplatelet response to clopidogrel and an increased risk of death or nonfatal myocardial infarction or stroke [68, 69]. Abacavir (Ziagen), used in HIV infection, is another example of postmarketing PGx label changes to identify patients at risk of toxicity-related side effects [31]. Warfarin (Coumadin) has also been updated to include PGx information useful in the selection of a suitable therapeutic dose [31].

Although these postmarketing developments have significant benefit, the recognition of population subgroups before approval would be advantageous for patients and pharmaceutical companies alike. The utilization of PGx approaches early in the drug development pipeline may aid in optimal drug and dosing selection, as well as help to predict and select individual responders and nonresponders. The early identification of responders and nonresponders serves to increase confidence in a molecule and promote those with potential for further study [70]. This in turn increases the potential for obesity drug approvals, by enriching subsequent phase III trials for individuals likely to respond positively and by preempting populations in which the drug may be contraindicated due to an increased risk of adverse events. Achieving a greater weight loss may help to offset some of the risk associated with these drugs, improving the risk/benefit ratio. This enrichment also serves to decrease sample size in the larger phase III trials (due to larger effect sizes), thus reducing cost and time [31, 70]. Ultimately, this can provide patients with earlier access to targeted, safer and more efficacious treatments.

A published example of this ‘prospective efficacy PGx’ [70] approach in action is the use of a GI181771X (GlaxoSmithKline), a cholecystokinin A1 (CCK-A1) receptor agonist, in the treatment of obesity. Cholecystoki-

nin (CCK) is a gut hormone and neurotransmitter which is released from the I-cells of the small intestine in response to luminal nutrients [71]. CCK promotes digestion [71] and in addition functions as an anorectic, suppressing food intake by decreasing meal size [72–74]. Roses [75] described a small phase II-A trial of obese individuals randomized to receive placebo ($n = 41$) or drug ($n = 40$). Following the 2-month treatment period, a clear group of hyperresponders, losing between 5 and 9% of their body weight, could be distinguished, showing that this compound was efficacious in a targeted population. This study contained a significant PGx element, and genotype at 112 SNPs (in 21 candidate genes) which represented potential polymorphic sites in the mechanism of action were tested. An analysis of allele segregation of the 21 candidate genes across the drug and placebo populations identified 3 SNPs that segregated with the drug response variation. One allele of each of these 3 SNPs (2 related to the drug-proposed mechanism of action and 1 related to obesity generally) associated with the hyperresponder group (denoted as 2–2 homozygotes) and the other allele associated with the nonresponder group (denoted as 1–1 homozygotes). The hyperresponders lost on average 3.3 kg during the study and nonresponders gained an average of 1.3 kg. 1–2 heterozygotes (considered as potential responders) fell in the middle for weight change. This example represents a proof-of-concept PGx study which was taken forward into a larger phase II-B trial. However, failure to adequately incorporate this preliminary PGx data into the study design of the subsequent trial [75] resulted in a negative outcome, in that there was no significant weight loss difference in the drug-treated compared with the placebo-treated groups [76]. In addition to GlaxoSmithKline, other pharmaceutical companies also had CCK-1 receptor agonists in development and did not report taking advantage of genetic differences to better understand and potentially improve the efficacy and risk/benefit of these compounds.

The rationale of the company at the time to incorporate data from the PGx phase II-A trials in subsequent larger trials may be understood by the fact that the FDA ‘Voluntary Exploratory Data Submission’ (VXDS) was not yet in existence, hence this change in design would have represented a departure from existing process [75]. The newer guidance on this area from the FDA, in conjunction with the European Agency for the Evaluation of Medicinal Products (EMA), and the so-called ‘safe harbor’ for the submission of pharmacogenomic data [77], facilitates communication between the sponsor and the regulators early in the process. The creation of this review

infrastructure allows the sponsor to gain a clear understanding of how the FDA will react to genomic, or indeed other ‘omics’ data, and can guide future planning steps on the road to registration [77].

Conclusions

Although application of PGx testing may not be as prevalent in primary care as it was predicted to be at this stage after the completion of the human genome project [78], the relevance of genomic analysis and its relationship with therapeutic drug responses is becoming more prevalent in the consumer/public mindset. Many direct-to-consumer genotyping services now provide information on genotype and adverse event risk as well as drug efficacy. Although these may currently be premature and limited in scope and utility, this is a growth area and the adoption of next-generation sequencing technologies will significantly enhance the information available to consumers [79].

The majority of PGx studies in the area of obesity to date have been hampered by small sample sizes which are most likely underpowered. Additional issues include retrospective genotyping, meaning that studies were not powered specifically for the analysis of a genotype effect, analysis of a small set of targeted candidate genes based on proposed mechanism of action, and analysis of one or very few genetic variants at a given locus [24]. Published reports of PGx and obesity drugs have been carried out

largely at academic or clinical centers with only one report highlighting the use of PGx in the drug development pipeline. This reflects the problem on the ground of variable response to drug treatment of obesity and the attempt to understand and predict response or nonresponse to therapy, and the need for safer more efficacious targeted therapies.

Considering the direct negative impact of obesity on health and health care costs, it is essential that effective, safe and long-term treatments are developed. Treating a complex, multi-factorial condition such as obesity with a single drug and expecting it to be safe and efficacious in all obese individuals is unrealistic and to date has failed to effect positive change in obesity prevalence. Pharmacotherapies have a clear place in obesity management. Lifestyle changes alone are difficult to maintain, and the inclusion of drugs targeting food intake and energy expenditure pathways has the potential to enhance and maintain weight loss success. The polygenic and multifaceted nature of weight gain and obesity can make the development of treatment plans problematic. However, it is necessary to accept and address this complexity, with the goal of understanding which segments of a population (representing disease subtypes) will respond to treatment by either identifying underlying genetic drivers or characterizing response phenotypes. Targeting interventions at those who will benefit from them most in a safe manner may improve compliance and ultimately will play a meaningful role in the management of obesity.

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