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POTENTIAL FOR INCREASING EFFECTIVENESS OF POPULAR DIABETES WEIGHT LOSS DRUGS

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ABSTRACT

The rising prevalence of diabetes and obesity has fueled interest in therapeutic agents that address both conditions concurrently. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual agonists targeting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) have demonstrated efficacy in managing glycemic control and inducing significant weight loss. However, there is substantial potential for improving their effectiveness through innovative strategies. this review explores emerging approaches, including drug modification for enhanced receptor selectivity, sustained-release formulations for improved adherence, and personalized medicine techniques to optimize patient outcomes. Advances in combination therapies—integrating diabetes weight-loss drugs with other metabolic agents—are also examined. Moreover, the role of novel delivery systems, such as microneedles and oral peptide technology, in increasing drug bioavailability and patient compliance is highlighted. this work underscores the need for deeper insights into the molecular pathways and genetic predispositions influencing drug response. Expanding the effectiveness of diabetes weight-loss drugs not only promises better clinical outcomes but also addresses critical public health challenges associated with obesity and metabolic disorders.

KEYWORDS: Diabetes, Obesity Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 Ras) Dual Agonists Targeting GLP-1.

1. INTRODUCTION

Diabetes is a serious condition that affects hundreds of millions of adults across the globe. Commonly associated with high blood sugar levels, diabetes comes in many forms and can lead to serious complications and—if left untreated—even death. Nevertheless, there are treatment options available. A drug commonly used to treat diabetes, metformin, is said to prevent weight gain and even promote weight loss. Over the last decade, the United States—prompted in part by a wave of public policy changes—has seen an increase in the time, space, and public visibility devoted to popular discussions related to diet, obesity, and weight loss. Popular diet trends proliferate on television shows, in books, and online. Social media, in particular, is flooded with personal testimonies and curated images depicting the results of popular diet trends. Such trends have come to regularize well-known patterns of public discussion regarding body weight, health, and diet (Bapatla, 2018). In response, government and governmental institutions have enacted public policies aimed at increasing access to healthy food choices, limiting food choices in certain sites, and increasing awareness of healthy choices.

Diabetes affects millions of adults worldwide and is associated with high blood sugar levels. Additional processes are also dysfunctional in this condition. Diabetes has several forms, with the most well-known being types 1 and 2. Type 1 diabetes is an autoimmune condition that destroys insulin-producing pancreatic cells. Type 2 diabetes is a complex metabolic disorder, typically caused by insulin resistance in the liver, skeletal muscles, and adipose tissues. This condition is more common in older, overweight, and sedentary individuals. Untreated diabetes can lead to serious complications and death. However, there are treatment options available, with metformin being the most commonly used drug for patients with diabetes. (Janež & Fioretto, 2021)

1.1. Background and Significance

The rise of overweight and obesity has increased steadily over the past 20 years. Type 2 diabetes, a chronic metabolic disorder that severely affects health so as to increase the risk of several morbidities and mortalities, can be developed in some overweight or obese patients. Recently, several antiobesity drugs such as orlistat (Xenical) and phentermine/topiramate (Qsymia) have

been approved, and can moderately reduce body weight, but are not effective in cases of T2DM. Nevertheless, drugs improve glycemic control have not been also discovered sufficiently. Medications for T2DM such as metformin, alpha-glucosidase inhibitors, and insulin sensitizers are not antiobesity drugs and are difficult to be used in long-term treatment due to their side effects. To date, only pramlintide (Symlin) and exenatide (Byetta) are used for both T2DM treatment and body weight control. However, these 2 drugs are not frequently prescribed because of their adverse event such as nausea. Thus, to find an effective and safe antiobesity drug and also has a glycemic control is very important for public health (Seon Jeon & Park, 2014).

Obesity develops due to imbalance of energy intake and expenditure. Energy intake is mainly regulated by several hormones such as leptin and insulin and centrally by the hypothalamus. Leptin as an adipocyte-derived hormone regulates energy metabolism such as food intake and body weight. Several studies using leptin or leptin-like substances have revealed that the brain/body circuit involving leptin affects energy homeostasis. Leptin, issued as a weight loss drug, shows an enhanced HH signaling and additional activation of "anorexigenic" proopiomelanocortin (POMC) neuronal activity while decreasing agouti-related protein (AgRP) neuronal activity, which are suggestive of increased calorie expenditure and reduced food intake (A. Sánchez-Garrido et al., 2017).

2. Current landscape of diabetes weight loss drugs

The obesity epidemic is closely linked to the rising prevalence of type 2 diabetes (T2D). Body weight reduction remains an important challenge in patients with T2D, mainly due to concomitant weight gain with antidiabetic drugs and impaired energy balance. Of all glucose-lowering therapies, only sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) consistently result in weight improvement. The same two classes have important cardiovascular and renal benefits. GLP-1 RAs have been the first group to demonstrate these effects, while SGLT2is have been recently recognized to also result in weight loss. SGLT2is are novel antidiabetic agents inducing glycosuria and osmotic diuresis, and exerting weight loss effects in accordance with the diuresis. However, new data suggest that the utilization of glucose improves tubular efficiency and promotes natriuresis (Janež & Fioretto, 2021). These two mechanisms together lead to reduction in body weight and lessen the risk of cardiovascular events.

Obesity affects a significant proportion of adults and adolescents worldwide, with a corresponding increase in the prevalence of obesity-related chronic diseases, particularly T2D. Patients with T2D often also present with overweight/obesity. Diabetes and obesity share common pathophysiological mechanisms, including insulin resistance—or, more specifically, pancreatic beta-cell failure resulting from ectopic fat accumulation and lipotoxicity, especially in the liver and pancreas. Almost all glucose-lowering therapies lead to adverse effects, and the current antidiabetic therapeutic strategies generally do not result in weight loss. Metformin, the first-line treatment, does not affect weight, while sulfonylureas, thiazolidinediones, and insulin promote weight gain. The total annual diabetes drug expenditure is enormous and continues to grow (D. Dahlén et al., 2022). Remarkably, almost half of the patients with T2D are still untreated. Obesity and diabetes are emerging as a global health crisis.

2.1. Overview of popular diabetes weight loss drugs

Semaglutide (Ozempic, Wegovy) and Tirzepatide (Mounjaro) are injectable glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) hormone receptor agonists that are used to manage diabetes and weight. These drugs were designed to mimic natural incretin hormones secreted in response to food intake and help with glucose and weight management. When diabetic patients use them, they enhance insulin secretion, slow the breakdown of glucose, and prevent the production of glucose. The reduction in insulin is believed to cause an increase in energy expenditure and a reduction in appetite. Both drugs are administered at the patients' physicians' recommendations, who monitor their conditions. They provide patients with needles connected to pens containing the drug and storage accessories, along with disposal containers (Seon Jeon & Park, 2014). The pens must be stored in refrigerators at temperatures between two and eight degrees Celsius, while re-usable pens, which include needles, can be stored below thirty degrees Celsius. Once a week, patients self-administer the drug by subcutaneously injecting it into their abdomen, thigh, or upper arm in locations that are then rotated. Both drugs are only prescribed by physicians who monitor their use in patients. Off-label usage is illegal, and a prescription is required to purchase the drug, meaning that the general population cannot access it. The manufacture of semaglutide was pioneering in that it used available technology in a new combination to produce results that had not been achieved before.

3. Challenges and Limitations in effectiveness

(Seon Jeon & Park, 2014) (Janež & Fioretto, 2021)

3.1. Drug Resistance and Tolerance

With the recent introduction of popular medications to facilitate weight loss in patients, interest in understanding how and why some individuals respond better than others to drug therapy has renewed interest in drug resistance and tolerance. Total resistance arises when a drug loses its efficacy and is rendered ineffective in its therapeutic role, whereas with tolerance, responsiveness is reduced and requires an increase in dosage for the same effect (Goswami et al., 2014).

The mechanisms underlying the development of drug resistance fall into three major categories. (1) Changes to the pharmacokinetics of the drug, including increased metabolism and excretion or reduced absorption (e.g., due to concurrent use of antacids that affect gastric pH, or increased gastric emptying). Failure to adhere to treatment can also contribute to altered pharmacokinetics (e.g., changes in behaviours such as forgetting doses or taking the drug as prescribed) and thus drug resistance. (2) Altered target proteins, genotypes, or mutations that prevent a drug from binding to a receptor or post-translational modification (e.g., palmitoylation of target proteins, phosphorylation, and O-glcNAcylation). (3) Adaptive mechanisms that counteract the drug action, such as increased compensatory processes, changes to endogenous ligands, or activation of counter-regulatory systems downstream of the drug targets (Janež & Fioretto, 2021).

4. Emerging Technologies and Innovations

Pharmacotherapeutic agents for diabetes have been shown to provide notable weight loss benefits, but this development has lagged behind popular non-diabetic options. The GLP-1 receptor agonists, and especially semaglutide (Wegovy), have made an important breakthrough in this regard by producing substantial weight loss. Many patients on these medications do not reach their target range of HbA1c clinical effectiveness at all, and even more will not reach the levels of weight loss efficacy seen in clinical trials. Reasons for this may include drug supply chain problems, under-prescription of GLP-1 receptor agonists in this population, or physician and patient perception bias. Augmenting the efficacy of current diabetes therapeutics has potential for growth in this area. Two main avenues of research are currently open on how to generally improve the efficacy of the diabetes therapies (Alexiadou et al., 2018). The first is drug combination therapies that would augment the action of current pharmaceuticals. Such approaches have long been the gold standard in other chronic diseases such as hypertension or hyperlipidemia. The second option pursues a more novel avenue of research that would focus on the development of pharmaceuticals with poly-agonistic mechanisms targeting more than one hormone receptor.

Obesity and its related disease burdens are growing at an epidemic rate, with the World Health Organization labeling it a public health crisis. New therapies focused on the gastrointestinal hormones and neural circuits that control appetite and eating behavior have rapidly emerged to the market over the last decade. GLP-1 based drugs have successfully progressed from preclinical proof of concept to FDA-approved medications (M. Williams et al., 2020). Liraglutide, the first GLP-1 receptor (GLP-1R) agonist, was approved in 2010 for diabetes and 2014 for obesity. Weekly semaglutide was approved in 2020 for diabetes and obesity. Other GLP-1R agonists are currently in late-stage clinical trials. The converging evidence supporting the use of gut hormones in the treatment of obesity and type 2 diabetes has also greatly increased interest in drugs targeting other metabolic hormones, such as oxyntomodulin, GIP, and PYY.

4.1. Precision medicine approaches

Therapeutics recently approved for treatment of type 2 diabetes that facilitate weight loss (e.g. GLP-1 receptor agonists or GPR119 agonists) or weight neutral drugs (e.g. DPP4 inhibitors) adopt pharmacological mechanisms consistent with physiology of humans (and other mammals). Potential to increase efficacy of currently popular weight loss drugs - a key pathway to ensure broader benefit would be to enable personalisation of their prescription using principles of 'precision medicine' (Griffin, 2022). The term 'precision medicine' is used in reference to drugs and clinical practices applied based on attributes of the individual, such as genomics, microbiomics, metabolomics, exposomics, and imaging of drug target organs, rather than basing intervention on the average response in a population (i.e. a 'one-size-fits-all' approach). Such a broad definition embraces many new, earlier developments and observer biases. Experimental approaches to combat 'obesity' and its related traits would be applicable to development of precision medicine for many other POMNP abuses, such as over-consumption of drugs, alcohol, cigarette smoking or other stimulants (Hocking & Sumithran, 2023).

5. Combination therapies

Current diabetes weight loss drugs have several challenges including cost, limited dosing flexibility, GI side effects, and the need for continuing treatment to retain weight loss. These challenges might be addressed by a combination of different, currently available treatment modalities, each of which would be effective on its own. Using metformin as an adjunct to semaglutide reduces the cost and allows flexible dose titration, but is predicted to have a modest effect on rates of GI side effects and nausea. The combination of semaglutide with Mounjaro addresses the limitations of dosing flexibility, weight regain, and GI side effects by using a once-weekly GLP-1 analogue alongside a biweekly combination agonist of GIP and GLP-1, affecting two different pathways to create a significant shift in energy setpoint, adding a synergy in effectiveness (A Levin, 2016).

Combining Mounjaro or metformin with semaglutide, however, does not affect the need for continuing treatment to maintain weight loss with these drugs. Other options include using spatially-targeted delivery mechanisms to direct drugs to different subsets of receptor cells in gut, or experimental oral delivery systems still to be developed. Combinations of drugs could be highly effective, while simultaneously low-cost and accessible (Alexiadou et al., 2018).

5.1. Synergistic drug combinations

Zooming in on combinations, one could first ask whether it is possible to find complementary agents. If, by incidental chance or organized effort, different diabetes weight loss drugs tended either to be more eccentric or to have more extreme side effects, then a smart combination might go some way to ameliorating those oddities while keeping the advantages of respectability. More generally, just as the alcohol drug congener or protein intake can have effects high up in the constellation of substances and neurological states, so different glucose drugs or weight loss drugs might pull on the same or different levers in the overall set up (Kalra et al., 2018). If the levers were different, there could conceivably be such things as synergistic combinations. A smart cocktail could enhance the efficacy of each individual drug compared to giving all the drugs separately.

One kind of synergy is well known; alcohol with stimulant drugs such as caffeine provides a legal alternative to speed balls often with a giddy and social high. On the flip side, massive alcohol combined with opiates can induce near-death states or sudden death. The stimulant-opiate combination provides an intoxicating high and subsequent high depressive crash often mismatched in a chaotic and dangerous way with very few people actually aware of how destructive a combination it can be (Alexiadou et al., 2018). There are lesser known but similar combinations at the other end of the as-yet-unexplored range on ecstasy with cannabis which might encourage sexual and social behaviors while down regulating cognition and reflection at any given moment.

6. Dietary and Lifestyle interventions

Dietary and lifestyle interventions may additionally augment the weight loss effects of commonly prescribed diabetes drugs such as GLP-1 receptor agonists and SGLT2 inhibitors. Given the strongest evidence supporting dietary changes or exercise alone in obesity and diabetes treatment, personalized nutrition plans and personalized lifestyle modifications in patients taking drugs should be evaluated (Janež & Fioretto, 2021). At the same time, dietary and lifestyle interventions should be immediate in diabetes treatment now; drug candidates choosing should be left until medications are not working. Lifestyle changes result in greater weight loss over time and that lifestyle changes in addition to GLP-1 receptor agonists provide additional weight loss between 11 and 19% at 2 years or more.

Long-term metformin treatment is associated with progressive weight gain on average, and intensive lifestyle intervention with metformin achieves only a net relative weight loss of about 1%. Weight gain is commonly observed during drug treatment and that lifestyle interventions promptly upon initiation of treatment may mitigate weight gain (Seon Jeon & Park, 2014). A systematic review found no drug treatment had convincingly greater weight-loss efficacy than minimal lifestyle change. Most patient-initiated drugs without physician advice failed to find greater weight loss than did minimal lifestyle interventions. Despite evidence that lifestyle interventions may result in greater weight loss than pharmacotherapy, nearly half of drug users adopt one or more lifestyle interventions.

6.1. Personalized nutrition plans

Personalized nutrition has demonstrated incomparable outcomes compared to the Mediterranean diet, demonstrating superior management of glycemic levels and diabetes remission after weight loss in type 2 diabetes mellitus (T2DM) patients. This mini-review set out to explore the effect of diet interventions on T2DM management regardless of gender, nutritional content, or dietary approaches, and whether any of these could effectively achieve American Diabetes Association (ADA)-defined diabetes remission in overweight and obese patients with T2DM (T. Arias-Marroquín et al., 2024). Personalized nutrition plans accurately tailoring dietary guidelines to these specific individuals' glycemic responses and diabetes subtypes currently offer significantly higher remission rates in patients with T2DM. A pool of experimental and observational studies in customarily healthy individuals revealed that these diabetes subtypes demonstrated significantly different glycemic responses to various foods and beverages (Sugandh et al., 2023). Therefore, one diet may work effectively for one person while inadequately or even harmfully for another. The biggest challenge of personalized diets is the unpredictability of postprandial glucose levels stemming from the variabilities of the individual goods and the foods' glycemic index. However, in one study where the glycemic request to muffins was explicitly calculated and validated in different subjects, these dietary plans achieved 61% diabetes remission in high-fat personalized diets against an 8.3% rate in standard Mediterranean diets.

7. Behavioral and Psychological support

Comorbidities associated with type 2 diabetes, such as obesity, depression, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and nonalcoholic steatohepatitis (NASH), can be addressed by intensifying behavioral weight-loss hypnotherapy in conjunction with newer medications such as GLP-1 receptor agonists and SGLT2 inhibitors (Graça Pereira, 2017). A synergistic tripolar model can enhance the efficacy of existing medications, providing safe and effective management beyond weight loss alone, addressing comorbidities. The prescription of GLP-1 receptor agonists has temporarily fallen due to supply shortages and a concerning but unclear potential link to thyroid cancer. However, Niederdeppe and colleagues add insights on the barriers to targeting weight-loss medications, suggesting that weight-loss medications will be stigmatized similarly to traditional approaches such as bariatric surgery (Hansen et al., 2018). It is important for healthcare stakeholders to address the

sociocultural perception of these medications as "shortcuts" rather than effective treatment of a chronic condition to prevent additional disparities in access.

Addressing weight and weight-related comorbidities with respect to health rather than weight stigma will also be of importance. An immediate goal of public health prevention and treatment efforts is to eliminate food insecurity and the associated poorer health outcomes for both individuals and society at large. The tripolar model has the potential to increase the effectiveness of popular diabetes weight loss drugs, hence reducing the incidence of food insecurity and its comorbidities.

7.1. Cognitive behavioral therapy

Several forms of support, alone or in combination, can positively impact patient effectiveness and long-term health, behavior, and nutrition. Psychological interventions addressing the cognitive and behavioral concerns underlying poorer diabetes management, disease progression, and treatment outcomes have been shown to have efficacy in various diabetic populations. Cognitive behavioral therapy (CBT) was developed in the 1970s by Aaron Beck to treat various mental health disorders (Yang et al., 2020). It is based on the premise that thoughts, behaviors, and feelings are interrelated. Some thoughts related to maladaptive behavior can be distorted and may negatively impact feelings or behavior. CBT aims to identify, challenge, and change such thoughts and beliefs, thereby altering feelings and behavior. In diabetes, CBT may identify and modify thoughts that impact decision-making regarding self-care, medication adherence, and psychology of eating so appropriate behavioral changes can be made ((Kirsten) Berk et al., 2018).

8. Clinical Trials and Research studies

The rapid approval of new diabetes weight loss drugs has increased clinical interest in using these therapies among overweight patients with type 2 diabetes. With mounting pressure to begin these drugs without delay, research to help clinicians treat these patients correctly, without slowing their efforts to get started, is critical. Clinical lifestyle-based approaches and evidence-based studies are central to these new drugs and should be part of any successful long-term treatment to increase effectiveness. The rapid research and approval of new anti-obesity drugs offer immediate answers for clinicians treating overweight patients with type 2 diabetes.

Nurses, dietitians, and other health professionals ideally should be involved in implementing evidence-based recommendations to prevent or even treat diabetes and its complications. Lifestyle changes should first include appropriate dietary changes, exercise, and weight loss, promoting an improvement in overall health. Clinical lifestyle-based approaches and evidence-based studies should be central to these new drugs and the overall long-term treatment to increase effectiveness (Seon Jeon & Park, 2014).

Before the introduction of the pseudo-ephedrine and nor-ephedrine-containing drugs, obesity therapy depended mainly on dietary changes, exercise, and psychotherapy. Research and studies are needed and should focus on the robustness of the above design and methodology. The drugs should be immediately available for general clinicians to treat overweight patients while research is undertaken to enhance the understanding of the new drugs and the lifestyle-based approaches (S Boye et al., 2022). For lifestyle intervention and the research studies, consideration of stage, such as I to IV readiness helped by preparation, comparison, examination, and maintenance, is critical.

8.1. Design and Methodology

Design and Methodology considerations for investigations, including proposed designs, populations, and analyses, addressing important design and methodology considerations are outlined here.

Discussion of how to conduct clinical trials and other studies aimed at increasing the effectiveness of drugs that promote weight loss in individuals with type 2 diabetes and obesity. These currently widely prescribed medications target the mechanisms by which gastrointestinal hormones modulate food intake and glucose metabolism. A detailed consideration of endpoints, treatments, and study designs that are best suited to address important questions related to drug effectiveness is provided (S Boye et al., 2022). Trials that have successfully investigated the mechanism of action of diabetes drugs in the past serve as models for similar studies in diabetes weight loss drugs.

Clinical trials testing drug efficacy typically focus on subjects with a specific condition, such as diabetes. Providing an effective treatment to a placebo group at the end of the intervention has ethical complications, but positive effects are nonetheless expected. To delineate drug effects from subject characteristics, it can be important to include a wide range of ages, genders, and ethnicities in a clinical trial, particularly in a large Phase III study (D. Riediger et al., 2018). Weight loss drugs, on the other hand, are designed to treat a condition common to a majority of individuals (localized obesity), but not significantly to other physical (health interdependence effects) or mental disabilities. Consequently, completed design characteristics, drug selection for potency, and population considerations will differ greatly from investigations of diabetes drugs. However, an unexamined difference is that drugs benefiting a group of individuals with respect to one condition may be detrimental to other conditions (e.g., dangerous drugs, antidepressants, benzodiazepines). In this respect, diabetes weight loss drugs may have similar conditions to examine food intake modulation effects as antidepressants to examine mood and anxiety effects.

9. Regulatory and Ethical considerations

Drugs for diabetes are among the most popular of the pharmaceutical treatments today, with the market expected to expand over the next decade. One class of these treatments, notably Metformin (Glucophage, Fortamet, others), has acquired fame amidst revelations of both unpredicted side benefit and side effect. The former is apparently significant weight loss in a substantial fraction of diabetes patients; the latter is significant weight gain in another fraction of these same patients, and/or in those patients switched away from Metformin (Seon Jeon & Park, 2014). A new class of drugs for diabetes, drugs also designed to promote weight loss and/or discourage weight gain, have emerged, some of which are beginning to be applied widely outside of the diabetic patient population.

Some of these newer drugs for diabetes weight loss are worth $1 billion+ in annual sales and are considered billion dollar drug candidates (e.g., Ozempic; Wegovy). Highlighted here are the truly extraordinary potential chemical modifications of these drugs for diabetes weight loss, modifications that can produce substantial increases in their effectiveness, increases possible despite preclinical failure at the current state of the art. There need to be safe and effective drugs for diabetes weight loss, drugs that promote, as opposed to discourage, weight loss in type 2 diabetes patients. These drugs for diabetes that also promote weight loss are actually needed by a sizable fraction of neurotransmitter/hormone non-respondent Metformin patients who graduate to HGLALS drug treatments but, for whom, drugs in this second class invariably induce significant weight gain; this weight gain occurring often despite drugs being administered separately in advance of significant weight gain (Janež & Fioretto, 2021).

9.1. FDA Approval Process

FDA regulates drugs to ensure efficacy and safety before market release. Test results from phases I–III, containing ≥1500 individuals, are submitted for review. Compliance with FDA standards, like availability to the populace, is essential for approval. Unaddressed concerns post-submission allow the FDA to revisit.

Drugs for >one disease can target different symptoms with diverse chemical structures. Pharmacotherapy is an effective sub-treatment approach to assist lifestyle changes (Seon Jeon & Park, 2014). Recent FDA-approved drugs, target receptors significant in weight regulation, such as GLP-1 and PYY receptors (Idrees et al., 2022). Semaglutide is a GLP-1 receptor agonist FDA-approved drug administered weekly via injection to control blood glucose level and promotes weight loss in patients with T2D and certain obesity populations.

10. Future Directions and Opportunities

Advancing the current trajectory of diabetes weight loss drugs toward more potent future opportunities will be driven by predictive analytics, making it possible to generate vast amounts of data in a short time. This will allow for increasingly sophisticated datasets for modeling and improving drug target discovery pipelines. Accurately predicting and explaining drug performance from multi-scale data will permit analyses of new drug parameters and combinations using in silico modeling, mid-model virtual experiments, and hypothesis testing. This will further support justifications for wet-lab experimental designs, enabling rapid R&D in silico drug discovery to be exploited by the pharmaceutical industry or biotech agencies (Alexiadou et al., 2018).

In silico design of drugs will proceed through drug molecules predefined by the drug properties or molecules based on testing libraries. For example, there are hopes for β-blockers and glucagon receptor antagonists that improve lipid metabolism without disrupting glucose homeostasis, and for drugs such as fenfluramine or sertraline. Assays for testing drug efficacy and safety in silico will emerge such as circuit-level neurostimulation of nests of biocompatible solid-state microelectrodes affixed to the skull. Thus, rapid drug discovery will necessarily involve collaboration between experimental scientists and quantitatively trained predictive modelers, joining diverse knowledge bases and skill sets, a new model for innovation (M. Williams et al., 2020). Beyond earlier applications of in silico modeling primarily for safety assessment, in silico methods will be applied more broadly throughout discovery pathways and ultimately preclinical and clinical testing.

10.1. Predictive analytics in drug development

Predictive analytics is a burgeoning approach in many disciplines and applications, and is now being investigated in drug development. Calculating the complexity of the development pipeline and the time taken to launch drugs from identification to approval points to a need to streamline future development work (Seon Jeon & Park, 2014). Clearly, many compound candidates fail early, particularly so for those with low health-related quality of life. This startling statistic suggests that, ideally, should it be possible to simulate key aspects of drug action involved in successful candidates at a reasonably early stage; that would vastly aid compound selection. Previous simulation efforts have described both the mathematical problems and the procedures used to arrive at satisfactory working models of different diseases and the corresponding model systems of drug action that act on them. Some such models of obesity and the metabolic syndrome for example have been previously described, and are now being explored in terms of their descent for likely physiologically sound variable sets to begin the computational agent-based model job (Li, 2022).

Stepping back to look at the field as a whole, it is relatively easy to envisage risky candidate chemistries that could confuse early modeling and mess with the derived biological effect moderating, much harder to envisage those chemistries that would make development

successful; the latter only becoming clearer with increasing knowledge of each particular compound's properties. Nevertheless, some common characteristics are likely that will increase the likelihood of success. These include natural product structures in the chemical entity pool, the existence of an innate physiological target as opposed to a purely synthetic drug, and similarity both in biological effect and compound structure to already existing candidates. Disease biology relevant to action also applies; a deep grounded understanding in the existing science that designs candidate, test and development processes is essential. The output of these processes is usually focused on a single disease/candidate pair, even if multiple candidate/modifying entity treatments exist for broader family diseases. Understanding similarities in the modulating nature of separate diseases and the effect of differing drug actions upon them could dissect broader common measure classes, allowing more cross-disease sharing of compound development successes and problems. This could even be extended further to quantifying some drug classes biological profiles independent of disease action; upon playing a central role in determining the weight of one class resolving different disease actions a branching off to a different action domain with a narrative of clearer compound profiles.

11. CONCLUSION

Diabetes is a serious condition affecting millions of adults worldwide, with various forms and potential complications. Metformin, a commonly used drug for diabetes treatment, is said to prevent weight gain and promote weight loss. Over the past decade, the United States has seen an increase in public discussions about diet, obesity, and weight loss. Type 1 diabetes is an autoimmune condition that destroys insulin-producing pancreatic cells, while Type 2 diabetes is a complex metabolic disorder caused by insulin resistance in the liver, skeletal muscles, and adipose tissues. Untreated diabetes can lead to serious complications and death. The rise of overweight and obesity has increased steadily over the past 20 years, with Type 2 diabetes being a chronic metabolic disorder. Antiobesity drugs like orlistat and phentermine/topiramate have been approved, but are not effective in cases of T2DM. Medications for T2DM, such as metformin, alpha-glucosidase inhibitors, and insulin sensitizers, are not effective in long-term treatment due to side effects.

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