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Is polypharmacy the future for pharmacological management of obesity?

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Abstract

Despite the rapidly increasing prevalence and associated costs of obesity, treatment options have remained remarkably limited. Some 650 million people are estimated to be living with obesity, but until recently the lipase inhibitor orlistat was the only mainstay pharmacological option, alongside dietary restriction. However, with FDA approval of the glucagon-like peptide 1 receptor (GLP-1R) agonists, liraglutide and semaglutide, for the management of obesity, it is hoped the tide is beginning to turn. Roux-en-Y gastric bypass (RYGB) surgery remains the most effective intervention for weight loss, being attributable to changes in energy intake/expenditure. This is largely driven by substantial post-surgical modulation of circulating gut hormones, including GLP-1, as well as peptide tyrosine-tyrosine (PYY), oxyntomodulin (OXM), glucose-dependent insulinotropic hormone (GIP), cholecystokinin (CCK) and ghrelin. In order to mimic these effects of RYGB, there has been a recent surge of interest in pursuit of both administration of individual peptide combinations as well as development of unimolecular peptide hormone-based polypharmacy; single peptidic agents that co-activate several different receptor signalling pathways. Dual agonist therapies such as the GLP-1/GIP co-agonist Tirzepatide, are nearing regulatory approval for management of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM). Given the significant appetite and weight reductions attained with these agents, it is hoped that such unimolecular peptide hormone drugs, along with similar molecules in development, will ultimately yield successful modern polypharmacy to help manage the current obesity epidemic.

I. Introduction

Achieving control over the uncurbed prevalence of excess body fat remains one of the greatest global healthcare concerns of our time, with over 4 million deaths attributable to elevated body weight between 1990 and 2015 [1]. Obesity is defined by the World Health Organization (WHO) as an "abnormal or excessive fat accumulation that presents a risk to health", commonly classified by measurement of body mass index (BMI) [2]. Individuals possessing a BMI of >25 kg/m^2 are classified as 'overweight', while those with a BMI of >30 kg/m^2 are considered 'obese'. However, it is important to note that these cut-offs are based on observational studies in Europe and USA of primarily Caucasian populations, hence WHO recommends lowering the BMI threshold for obesity in South Asian populations to >27.5 kg/m^2 to account for the high prevalence of obesity in this ethnic group [3]. WHO global estimates suggest a staggering 1.9 billion adults are currently overweight, while 650 million are considered obese [1]. Obesity is a significant risk factor for over 200 disorders including cardiovascular disease [4], type 2 diabetes mellitus (T2DM) [5] and is becoming increasingly linked with development of Alzheimer's disease and dementia [6,7]. Most recent estimates state that the cost overweight- and obesity-related illness accounts for US $2.0 billion annually [8], equating to 2.8% of global gross domestic product.

In 2013 the American Medical Association officially recognised obesity as a complex, chronic disease in its own right [9], almost 15 years after the National Institutes of Health published guidelines supporting this same viewpoint [10]. Unusual cases of "hypothalamic obesity", in which hypothalamic injury results in hyperphagia, decreased energy expenditure and resultant weight gain [11], highlight the importance of complex central mechanisms regulating energy-balance. Furthermore, whilst rare monogenic classifications of obesity are known to exist (such as mutation of the leptin gene) [12], evidence from family, twin and adoption studies indicate that even in common, multifactorial obesity, multiple genetic

components play a more crucial role than previously considered [13-15]. As such, improved understanding of the physiological mechanisms underlying obesity and identification of additional drug targets hold the key to development of more effective therapies.

It is predicted that both newly developed and existing therapies will be employed in polypharmacy for the management of obesity. Traditionally, polypharmacy is considered as the use of multiple medicines to manage multi-morbidities [16], although several definitions are presented in the literature. In the context of this review polypharmacy is discussed as a multifaceted approach towards management of a single condition, obesity. This can involve administration of two or more individual drugs, co-administration of therapeutics in a single formulation or administration of unimolecular therapeutic compounds which can elicit several disease-modifying effects through actions at more than once receptor [17]. Importantly, overlap does exist, such as the combination of dual amylin and calcitonin receptor agonists (DACRA) with leptin or glucagon-like peptide 1 receptor mimetics [18].

II. Current management options

Despite the ever-increasing prevalence and spiralling economic burden of obesity, pharmacological treatments for the condition remain remarkably limited, especially when compared to related conditions like T2DM, or even dyslipidaemia. Lifestyle interventions through calorie reduction and increased physical activity remain first-line management options in overweight and obese individuals [19], and are important adjuncts to pharmacological or surgical intervention.

1. Small molecule agents

In scenarios where effective weight-loss has not been attained through life-style modification, pharmacological intervention can be considered as an adjunct, rather than a replacement. At

present, the lipase inhibitor, Orlistat, is the only universally approved option. Orlistat inhibits the breakdown and absorption of dietary fat [20; Table 1]. However, since excess fat is then excreted in the stool, gastrointestinal side effects such as flatulence and incontinence are common and can severely impact quality of life. Such effects may result in changes of food preference, but Orlistat lacks direct effects on the mechanisms of appetite control [20]. Several attempts have been made in the development of oral anti-obesity agents which act through appetite suppression to bring about weight-loss, and avoid the quality-of-life issues associated with Orlistat. In that respect as described in more detail below, phentermine is available, although not readily accessible, in many world regions, with both naltrexone/bupropion and liraglutide now being approved almost universally.

Following on from this, Lorcaserin is a selective, small-molecule agonist for the serotonin 2C (5-HT_{2C}) receptor [21; Table 1], which utilises a central mechanism to decrease food appetite via modulation of the proopiomelanocortin (POMC) system of neurons [22]. Following promising initial outcomes such as sustained weight-loss over two years and improved biomarker levels for risk of cardiovascular (CV) events in the "Behavioural Modification and Lorcaserin for Overweight and Obesity Management" (BLOOM) trials [23], Locaserin achieved US Food and Drug Administration (FDA) FDA approval for management of obesity in 2012, but was not approved in Europe. However, due to concerns over an increased risk of cancer development in those receiving Locaserin [24; Table 1], the drug was withdrawn from the market in early 2020. This serves to highlight the lack of safe and effective prescribing options for obesity.

More encouragingly however, the therapeutic promise of the 5-HT_{2C} pathway for obesity continues with granting of orphan drug status for Tesomet® for management of hypothalamic obesity [25;Table 1]. Tesomet® combines tesofensine, a pre-synaptic reuptake inhibitor of dopamine, serotonin and noradrenaline previously investigated for

neurodegenerative conditions [26], with the beta-blocker metoprolol [25]. Phase IIb trials are presently underway in multiple regions for application in hypothalamic obesity, with early trial data indicating an average weight loss of 6.3% and a reduction in waist circumference of 5.7 cm following 24 weeks treatment in human participants [25].

Shortly after the approval of Locaserin, a second appetite-modulating oral medication achieved FDA approval, namely the synergistic phentermine/topiramate combination, Qsymia® [27; Table 1]. Phentermine is a centrally acting appetite suppressant, thought to reduce food-intake via enhanced release, as well as blockade of reuptake, of norepinephrine. In harmony with this, topiramate increases energy expenditure and decreases appetite through antagonism of alpha-amino-3-hydroxyl-4-isoxazole-propionic acid kainate (AMPA/KA) receptors [28]. Concerns over cognitive side-effects such as depression have hindered clinical uptake [29], with patients requiring careful monitoring and dose titration, while the risk of teratogenicity means a negative pregnancy test is required prior to initiation of therapy in females of child-bearing age. However, Qsymia® remains a treatment option in the US for obesity, but it has yet to gain approval in Europe.

In a similar vein, the oral cannabinoid receptor 1 (CB1) antagonist, rimonabant, was withdrawn in 2008 after just two years of regulatory approval in Europe for management of obesity [30; Table 1]. Despite promising rimonabant-induced appetite reductions, manifesting in significant weight loss in humans, the occurrence of severe cognitive adverse effects such as depression ultimately led to its withdrawal [30]. However, interest in modulation of the endocannabinoid system to manage is still of significant interest, provided safer agents with similar efficacy can be discovered. Indeed, the future here may well lie in the development of selective cannabinoid receptor 2 (CB2) agonists, which have been demonstrated to reduce weight gain in the preclinical setting [31; Table 1]. However, it is important to note that this

relatively recent discovery of non-immune cell CB2 receptor actions mean considerable further work is required to fully validate the efficacy and safety of this approach.

Another combination therapy, marketed as Mysimba® in Europe and Contrave® in US, combines naltrexone, an opioid antagonist licensed for the management of alcohol and opioid dependence, and bupropion, originally licensed as an antidepressant but now prescribed widely in smoking cessation [32]. The naltrexone/bupropion combination has a synergistic effect on appetite reduction, postulated to be mediated via action at hypothalamic centres to increase POMC cell production whilst disrupting beta-endorphin inhibitory feedback on POMC cells [32]. While still a prescribing option in the US and EU, naltrexone/bupropion was also approved in the UK but not recommended by the National Institute for Health and Care Excellence (NICE) due to concerns over long-term efficacy [33; Table 1], thus is not available through the UK National Health Service (NHS).

2. Peptide agents

2.1 POMC modulators

POMC modulation remains a viable target for obesity management, with leptin-based molecules mimicking actions of the endogenous polypeptide at hypothalamic POMC neurons to increase energy expenditure and satiety [34]. However, despite achieving regulatory approval for lipodystrophy, the leptin analogue metreleptin has not found application in obesity due to disappointing effects on weight loss [35]. Attempts were made to improve effectiveness of metreleptin through combination therapy with the amylin analogue pramlintide [36]. Despite improved weight loss when compared to monotherapy [36; Table 1], development was halted following phase II trials due to lack of overall efficacy. However, excitement is growing following promising phase III trial data with the melanocortin 4 receptor (MC4R) agonist,

setmelanotide [37; Table 1]. The injectable medicine has found application in rare, genetic forms of obesity which are attributed to POMC or leptin receptor deficiencies [11,37]. Administration over 12 months elicited a minimum of 10% weight loss, accompanied by >25% reduction in hunger scores [37].

2.2 Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone, released post-prandially from nutrient-sensing L-cells of the distal ileum and colon. Analogues based on this endogenous hormone have been successfully employed in the management of T2DM for over 15 years, due to beneficial effects on glycaemia via augmentation of glucose-dependent insulin secretion, reduced glucagon secretion and improved insulin sensitivity [38]. Formulation advancement has seen these agents evolve from twice-daily exenatide (Byetta®), to once-weekly preparations such as dulaglutide and semaglutide that employ half-life prolonging molecule attachment. Furthermore, a once-weekly preparation of exenatide utilises poly(DL-lactic-co-glycolic acid) microspheres to help form a peptide-depot upon subcutaneous injection [38]. GLP-1 receptor (GLP-1R) agonists have been demonstrated to promote satiety through actions at central and peripheral enteric neurons, which contribute to the "ileal brake" mechanism [39], to slow gastric emptying an intestinal transit. It is important to note that tachyphylaxis has been suggested for the GLP-1R agonist liraglutide in relation to gastric emptying [40], but this was not the case for the shorter-acting exenatide. In support of this, effects on gastric emptying in obese volunteers were most pronounced 60 minutes following administration of liraglutide, and appeared to be retained for longer periods when receiving 1.8 mg as opposed to the 3.0 mg dose of the drug [41], suggesting that this mechanism is less important for beneficial effects on body weight. These effects manifest significant weight loss,

hence, application of GLP-1R agonists as anti-obesity agents, in the absence of T2DM, has long been considered.

Positive strides have been made in this regard, as the once daily injectable preparation liraglutide, previously approved for the management of T2DM (Victoza®), became the first GLP-1R agonist to gain regulatory approval in USA, Europe and UK for management of obesity [42; Table 1], marketed as Saxenda®. Detailed investigation in human participants suggested the effects of liraglutide on weight loss are primarily mediated through reduced appetite and energy intake rather than increased energy expenditure [43], although glycaemic improvements undoubtedly have a role to play. Phase III trials (SCALE) demonstrated a sustained 2-year weight loss in participants without diabetes receiving liraglutide, in combination with lifestyle modification [44,45]. Moreover, 3-year follow-up in people with pre-diabetes indicated those receiving liraglutide took almost 3 times longer to develop T2DM [46].

Unsurprisingly, other GLP-1R agonists, previously approved for T2DM, are being pursued as treatment options for obesity. Results from the phase III STEP trials demonstrated subcutaneous, once weekly semaglutide manifested a substantial average weight loss of 14.9% following 68 weeks treatment [47; Table 1]. Furthermore, semaglutide elicited superior weight loss than liraglutide in comparative head-to-head studies [48]. As such, injectable semaglutide gained FDA approval for obesity in June 2021 marketed as Wegovy® [47,48], with regulatory approval in the UK and EU swiftly following. In addition to this, orally formulated semaglutide, marketed as Rybelsus®, has now been developed and FDA approved for T2DM [49]. With oral semaglutide demonstrating promising body weight reductions and tolerability in the PIONEER 8 trials in persons with T2DM [49; Table 1], phase III trials in participants with obesity are now recruiting. It is important to note that oral semaglutide, particularly at the lowest dose, had a greater incidence of adverse effects leading to discontinuation than

injectable semaglutide [49], and weight loss was also more pronounced with the injectable preparation [47-49]. Thus, careful consideration of the overall effectiveness of Rybelsus® will be required going forward.

3. Polypharmacy incorporating previously approved clinical agents

The trend of repurposing previously approved medicines towards obesity has seen investigation of the efficacy of GLP-1R agonists alongside other currently prescribed antidiabetic drugs. The combination of exenatide with the oral anti-diabetic, dapagliflozin, a sodium–glucose co-transporter 2 (SGLT2) inhibitor, was investigated in the DURATION-8 trial in poorly controlled individuals with T2DM [50]. A degree of synergy was uncovered between the two agents, with improvements in short- and long-term glycaemia and weight-loss exceeding either agent alone [51], and long-term efficacy confirmed over a two-year period [52]. Attempts are being made to confirm the mechanism behind this synergy [49], currently proposed to be related to the renal benefits elicited by both medications [53], but GLP-1-mediated reductions in energy intake coupled with SGLT2-mediated energy excretion in urine are likely implicated. Importantly, a 38-week randomised control trial, RESILIENT, is currently underway in persons with concurrent obesity and T2DM [54], seeking to uncover how this combination influences adiposity, energy balance, appetite and satiety. Such data will be invaluable in the confirmation of this therapeutic combination being a viable prescribing option in obesity.

III. Peptide co-administration – Learnings from RYGB

Roux-en-Y gastric bypass surgery (RYGB) is now regarded as a gold-standard management option for obesity-diabetes, with ~88% diabetes remission, increased weight loss and superior metabolic control being achieved, compared to current pharmacological interventions [55]. On

many occasions in as little as a few days post-surgery, before significant weight loss, there are marked improvements in glycaemic control [56] and insulin sensitivity [57], augmented beta-cell function [58], restored first phase insulin response [59] and decreased truncal fat deposition [59]. In this regard, post-surgery modulation of circulating gut-derived hormones such as GLP-1, peptide tyrosine-tyrosine (PYY), glucose-dependent insulinotropic hormone (GIP), oxyntomodulin (OXM), cholecystokinin (CCK) and ghrelin are thought to be strongly linked these benefits, advocating the use of peptide hormone-based polypharmacy for obesity [38,60; Figure 1]. Positive results from DURATION-8 and RESILIENT trials support use of peptide entities as part of polypharmacy for obesity, through combination of GLP-1R agonists and SGLT2 inhibitors in obese individuals [51,54]. However, polypharmacy employing multiple peptide preparations is certain to also become an important mainstay in the future management of obesity.

One such example is the combination of amylin and GLP-1, where combined amylin and GLP-1 receptor activation with separate entities brought about superior body weight loss in normal and obese rodents than monotherapy, reducing meal size and cumulative energy intake over in both acute and chronic scenarios [61]. Additionally, the study indicated stepwise, rather than concurrent, peptide administration was more effective [61], highlighting the advantage of dosing flexibility with co-administration of separate drugs when compared to unimolecular therapeutics. Further credence is given to the amylin/GLP-1 combination, with phase Ib data highlighting concurrent administration of the long-acting amylin analogue, cagrilintide, improved weight reductions attained with semaglutide [62; Table 1]. This effect has been attributed to proposed complementary effects of cagrilintide on appetite beyond that of GLP-1, such as positively affecting dietary decisions through modulation of hedonic regions within the brain [62]. This trial further highlighted the flexibility of co-administration, with the cagrilinitide dose titrated to varying degrees (0.16 – 4.5 mg maximum dose) across 6 cohorts,

while the semaglutide dose could be maintained at the clinically approved 2.4 mg [62]. Interestingly, a stepwise dosing regimen was not employed in this study.

Exploration of individual peptide co-administration continues, with Novo Nordisk again employing semaglutide, but this time in combination with a once-weekly GIP analogue termed NNC0480-0389 [63]. Phase I trials investigating the blood glucose and weight lowering potential of this combination in obese, overweight volunteers with T2DM are currently underway [63; Table 1]. The combination is expected to be a direct competitor for Eli Lilly & Co's unimolecular GIP/GLP-1 co-agonist, tirzepatide (discussed below). The comparison between these contrasting GIP/GLP-1R agonism strategies will provide a unique insight into the additive benefits of combined GIP and GLP-1 receptor activation for obesity.

IV. Unimolecular polypharmacy

Improved understanding of the hormonal component of weight loss post-RYGB has heralded pursuit of peptide-based polypharmacy. In addition to peptide co-administration, unimolecular polypharmacy has been investigated, employing single peptidic agents that can co-activate several independent regulatory peptide receptor signalling pathways to emulate post-surgery benefits [Figure 1].

1. Unimolecular dual acting agonists – Clinical studies

Enthusiasm has grown surrounding the anti-obesity effectiveness of several dual agonist peptides currently progressing through clinical trials. One such agent, a GLP-1/glucagon receptor co-agonist termed "cotadutide" incorporates important amino acid residues from each parent hormone to yield a molecule with a carefully balanced GLP-1/glucagon receptor activation profile [64; Table 1]. In phase II trials cotadutide-receiving individuals presented with significant reduction in liver fat, [65], which has seen a refocus of research toward

application in non-alcoholic fatty liver disease (NAFLD) [66; Table 1], a common eventuality in uncontrolled T2DM and obesity. Cotadutide has been demonstrated as superior to liraglutide in terms of weight loss and glycaemic improvement in rodents [64,65]. However, when directly compared in phase IIb trials in adults who were overweight or obese only the highest dose of 300 µg cotadutide surpassed weight loss attained with liraglutide at 1.8 mg [67]. Thus, if liraglutide was employed at the clinically approved 3.0 mg dose for obesity, it is likely it would significantly outperform cotadutide. Importantly, withdrawal from the clinical trial due to adverse reactions was more pronounced in the cotadutide treatment groups [67]. Whilst further development of cotadutide as an anti-obesity therapeutic is uncertain, the therapeutic promise of GLP-1/glucagon combinations for management of obesity is still apparent.

Another recent success story is the GLP-1/GIP dual receptor agonist, termed tirzepatide [68; Table 1], based on the amino acid sequence of GIP with minor modifications to promote GLP-1 receptor activity. Phase II trials in people with T2DM indicated highly impressive body weight reductions of 5-10% and significant reductions in waist-circumference following 12 weeks of tirzepatide administration [69]. Reductions in body weight were over three times greater than those attained with the GLP-1 analogue, dulaglutide. Such effects were attributed to complementary modulation of appetite, gastric emptying and reduced emesis by GIPR to help improve overall effectiveness and tolerability [68].

Tirzepatide has been demonstrated as biased towards GIPR in the *in vitro* setting, activating the receptor with equipotency to native GIP [70], perhaps unsurprising given the high degree of amino acid sequence homology. Conversely, the peptide has 5-fold weaker affinity for the GLP-1R than the endogenous ligand [70]. The importance of dual receptor activation is paramount, however, given weight lowering effects of tirzepatide are annulled in GLP-1R knockout animals, but improvements in insulin sensitivity retained [71]. Thus, beneficial effects on appetite suppression and increased energy expenditure, mediated via the

central nervous system [72], are understood to be brought about through dual receptor agonism [68]. Further mechanistic analysis will be required to fully uncover the specific receptor activation ratios required to best impart potential synergy.

This is even more intriguing when considering the success of tirzepatide compared to a previously described balanced GIPR/GLP-1R co-agonist, namely NNC0090-2746 [73]. Thus, Phase II trials with NNC0090-2746 in people with T2DM demonstrated the co-agonist reduced blood glucose and body weight beyond placebo over 12 weeks, but was not more effective than liraglutide [73], hindering further clinical development. Additionally, while no direct comparisons have been made between NNC0090-2746 and tirzpeatide to date, the common occurrence of gastrointestinal disturbance with NNC0090-2746 would again allude to importance of the anti-emetic effects of GIPR activation to help offset GLP-1R induced adverse effects [68, 73].

Impressive Phase III (SURPASS-3) data have recently been published, demonstrating a 7.6-11.2% weight loss in patients receiving tirzepatide, in comparison to 5.7% induced by semaglutide alone [74; Table 1]. It is important to note that while poorly controlled T2DM was a prerequisite for inclusion in SURPASS-3, obesity was not. However, given the significant weight loss incurred, the potential for application of tirzepatide in obesity is clear.

2. Unimolecular dual acting agonists – Preclinical studies

It is noteworthy that while GLP-1R/GIPR co-agonism demonstrates obvious promise with respect to obesity, preclinical studies suggest that there may also be significant benefits of sustained GIPR blockade in combination GLP-1R activation [75]. Thus, the partial GIPR antagonist, (Pro^3)GIP, has originally been demonstrated to independently elicit a ~10% weight loss upon chronic administration in obese mice [76; Table 1]. Further related investigations demonstrated that combination of antibody-mediated GIPR blockade and GLP-1R agonism

elicited superior weight loss over monotherapy in obese mice and non-human primates [77]. Similar, but less pronounced, benefits of a peptide-based GIPR antagonist in combination with a GLP-1R agonist have been noted in high fat fed mice [78]. Optimised scheduling of delivery, to annul GIPR signalling and promote GLP-1R signalling, might lead to further improvements in beta-cell function [79]. However, a more recent study has characterised a bispecific antibody that combines GIPR antagonism and GLP-1R agonism within the same compound [80]. This bispecific antibody led to significant reductions of body weight in obese mice and monkeys [80], paving the way for further development of unimolecular GIPR antagonist/GLP-1R agonist combinations. Thus, in terms of GIPR signalling, the question remains as to what combines best with GLP-1 for the treatment of obesity – a GIPR agonist or a GIPR antagonist [75]?

Further dual agonist peptidic hormone agents are currently progressing through preclinical drug discovery, typically employing a GLP-1 element combined with other gut hormone agonists. Examples include a long-acting GLP-1/CCK1 receptor co-agonist, which brought about significant weight reduction when administered in obese, diabetic rodents, owing to appetite suppression [81; Table 1], although no human data on this combination is available to date. A GLP-1/secretin chimeric peptide, termed GUB06-046, was shown to decrease cumulative food intake more effectively than the GLP-1 mimetic taspoglutide alone in lean mice [82; Table 1]. Although when administered over 60 days in *db/db* mice reductions in food intake and were comparable to liraglutide [82]. However, confirmation of post-RYGB elevations in plasma secretin levels [83], combined with its established role in thermogenesis [84], warrant further investigation as a combination therapy with GLP-1 given complementary biological actions.

Combination of GLP-1/fibroblast growth factor 21 (FGF21) has shown promising weight- and lipid-lowering potential in rodent models of obesity and is being investigated for

NAFLD [85; Table 1], however the large molecular mass and complex tertiary structure of FGF21 make it somewhat unattractive as a therapeutic due to heightened production costs. Additionally, combination of GLP-1R agonism alongside neuropeptide-Y2 receptor (NPY2R) activation has been explored, due to pro-satiating and weight-loss potential of both signalling pathways [86; Table 1]. Indeed, the chimeric exendin-4/PYY(3-36) analogue has shown initial *in vitro* promise [87], and this rationale is strengthened by recent findings employing long-acting NPY2R and GLP-1R agonists in combination, which has recently demonstrated synergistic weight loss in obese-diabetic mice [88; Table 1]. As with GLP-1 and GIP, it will be interesting to determine whether co-administration or unimolecular development represents the ideal strategy. Finally, a long-acting GLP-1 and xenin dual-agonist, exendin-4/xenin-8-Gln, reduced appetite and body weight, while augmenting insulin secretion and restoring GIP sensitivity in obese mice [89,90; Table 1]. The recent resurgence of interest in GIP, largely brought about through the success of tirzepatide [74], could be predicted to increase interest in xenin compounds, given their ability to restore GIP sensitivity in obesity [89].

3. Unimolecular triple acting agonists – Clinical studies

Unsurprisingly, following positive strides in the development of dual agonists, several triple-acting agents, which can further emulate the multifaceted hormonal changes post-RYGB, are at various stages of development. One such example, HM15211, a once-weekly, antibody-conjugated GLP-1/GIP/glucagon receptor co-agonist was superior to liraglutide in terms of increasing energy expenditure, promoting weight-loss and reducing hepatic inflammation markers in rodent models of obesity [91; Table 1]. However, while a dose equivalent to the clinically approved 3.0 mg of liraglutide was employed, further comparison as to these effects in human participants are required. That said, phase II trials to examine HM15211 as a treatment option for NAFLD are currently recruiting, with the ultimate hope to realise clinical

application in obesity. A similar tri-agonist, termed LY3437943, recently began recruitment for phase II trials in T2DM, following promising preclinical findings such as reduced food intake and 45% weight loss following chronic administration to obese mice [92], with the weight-loss being primarily attributed to adipocyte lipolysis. Additionally, early pharmacokinetic profiling suggests suitability for once-weekly dosing [92], further compounding interest in this molecule.

4. Unimolecular triple acting agonists – Preclinical studies

Unimolecular exendin-4/gastrin/xenin-8-Gln has been shown to improve glycaemia, insulin and GIP sensitivity in rodents, coupled with encouraging reductions in fat mass, triglycerides and cholesterol levels [93; Table 1]. However, the exact mechanisms behind these effects still require elucidation. Additionally, preclinical data relating to several unimolecular tri-agonists targeting glucagon, GLP-1 and GIP receptors such as [DA^2]GLP-1/GcG [94; Table 1], and the similar tri-agonist, first reported by Finan and colleagues [95,96; Table 1], have shown potent weight-reducing effects leading to clear improvements of metabolism [94-96]. The latter compound outperformed GIP/glucagon or GLP-1/glucagon receptor agonists in body weight reduction following sub-chronic administration in obese mice, as well as liraglutide, but a relatively low dose was chosen for liraglutide, thus further study is required [95]. Finally, given incorporation in dual agonists [87,88], it is likely PYY will find application in triple agonists. Indeed, a recent study employing a continuous subcutaneous infusion of GLP-1, together with the dual GLP-1/glucagon receptor agonist OXM and PYY, termed "GOP", demonstrated significant weight loss following 4 weeks treatment in persons with obesity [97]. Moreover, glucose tolerance improvements were superior to those achieved with RYGB [97]. While GOP provides tangible proof-of-concept for development of similar single-entity agonists for these targets, development of a unimolecular compound or co-administration

formulation which does not require continuous infusion is required for the therapeutic promise of this combination to be realised.

V. Conclusion

Despite many years of stagnation regarding prescribing options in obesity, it is hoped that the recent approval of liraglutide and semaglutide [46,49; Table 1] represents a shift towards availability of a new generation of highly effective anti-obesity agents. Positive weight loss outcomes in people with T2DM receiving combined GLP-1 agonism with SGLT2 inhibitors [50,51] provide proof-of-principle for traditional polypharmacy in obesity with concurrent diabetes, although at present this combination is unlikely to be employed in persons without diabetes. Moreover, the therapeutic potential of unimolecular peptide polypharmacy is close to being realised for NAFLD and T2DM, with several such agents edging their way towards approval [63,65,67,68; Table 1]. Such progress and outcomes are clearly translatable to treatment of obesity. In truth, the previous lack of pharmacological options has made polypharmacy virtually impossible in obesity to date. However, development of single peptidic entities, with carefully balanced dual- or triple-hormone receptor activation profiles, represents a highly attractive approach to realise the obvious potential of polypharmacy for the management of obesity.

VI. Declaration of interests

PRF, and NI are named on patents filed by Ulster University for the exploitation of incretin-based drugs and other peptide therapeutics.

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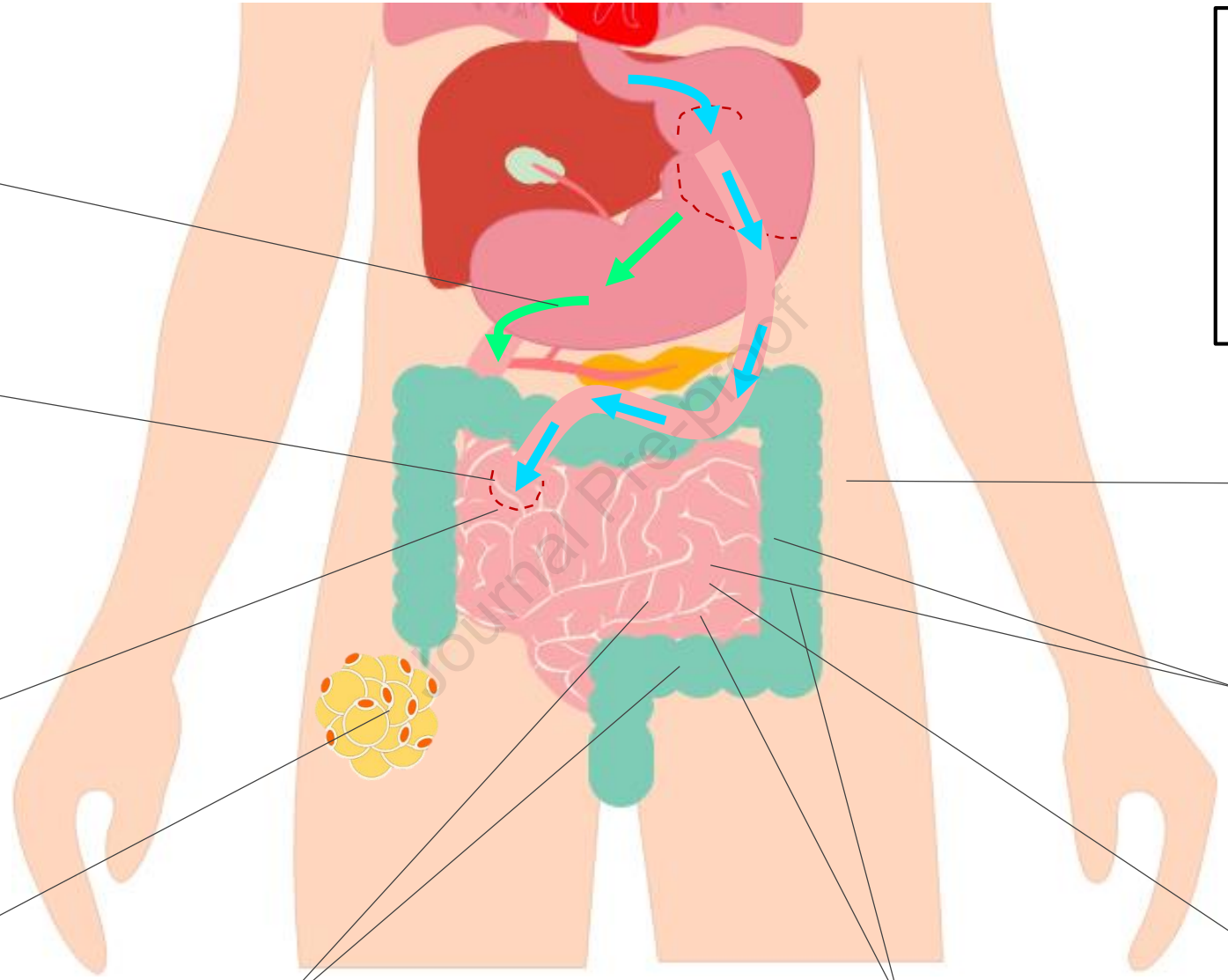
Figure legend

Figure 1. An overview of post-prandial hormone changes following Roux-en-Y gastric bypass surgery (RYGB). RYGB involves rerouting of the digestive tract, via creation of the "Roux limb", to bypass much of the stomach and duodenum and directly feed nutrients into the jejunum. Food passes through the Roux limb (shown by blue arrows), while digestive juices continue to flow through the stomach to the duodenum (shown by green arrows). Hormonal modulation is presented for pancreatic insulin and glucagon, duodenum-derived cholecystokinin (CCK), jejunum-derived glucose-dependent insulinotropic hormone (GIP) and neurotensin, ileum and colon-derived glucagon-like peptide 1 (GLP-1), peptide tyrosine tyrosine (PYY) and oxyntomodulin (OXM) and adipose-derived leptin. Post-prandial increases are indicated by green boxes, decreases are indicated by red boxes and no discernible change is indicated by grey boxes.

Therapeutic Name	Administration Route	Mechanism of Action	Regulatory Approval/Development Stage	Reference
Orlistat	Oral	Lipase Inhibitor	2007	20
Locaserin	Oral	5-HT_{2C}R agonist	2012 - Withdrawn 2020	21-24
Tesofensine/Metoprolol (Tesomet®)	Oral	Monoamine reuptake inhibition/ß1 receptor blockade	Phase IIb (Hypothalamic Obesity)	25,26
Phentermine/topiramate (Qysmia®)	Oral	AMPA/KAR agonist	2012 (US,EU)	27-29
Rimonabant (Acomplia®)	Oral	CB1 antagonist	2006 (EU) – Withdrawn 2008	30
JWH-015	Injectable	CB2 agonist	Preclinical	31
Naltrexone/bupropion (Mysimba®/Contrave®)	Oral	POMC/beta-endorphin modulation	2014 (US,EU)	32,33
Metreleptin/pramlintide	Injectable	POMC/LEPR modulation	Abandoned 2011 - Phase II	36
Setmelanotide	Injectable	MC4R agonist	Phase III	37
Liraglutide (Saxenda®)	Injectable	GLP-1R agonist	2019	41-45
Semaglutide (Wegovy®)	Injectable	GLP-1R agonist	2021	47,78
Semaglutide	Oral	GLP-1R agonist	Phase III	49
NNC0480-0389	Injectable	GIPR agonist (combined with semaglutide)	Phase I (T2DM)	63
Cotadutide	Injectable	GLP-1R/GCGR co-agonist	Phase II (NAFLD)	64-66
Tirzepatide	Injectable	GLP-1R/GIPR co-agonist	Phase III (T2DM)	68-71
NNC0090-2746	Injectable	GLP-1R/GCGR co-agonist	Phase II (T2DM)	73
Cagrilintide/Semaglutide	Injectable	AMYR/CTR/GLP-1R agonists	Phase Ib	75
(Pro^3)GIP	Injectable	GIPR partial antagonist	Preclinical	76
mur-GIPR-Ab	Injectable	GIPR antagonist	Preclinical	80
[Lys^{12} PAL]Ex-4/CCK	Injectable	GLP-1R/CCK1R co-agonist	Preclinical	81
GUB06-046	Injectable	GLP-1R/SCTR co-agonist	Preclinical	82
GLP-1-Fc-FGF21 D1	Injectable	GLP-1R/FGFR co-agonist	Preclinical	85
EP45	No *in vivo* data	GLP-1R/NPY2R co-agonist	Discovery	87
Fc-GLP-1/Fc-PYY(3-36)	Injectable	GLP-1R/NPY2R co-administration	Preclinical	88
Exendin-4/xenin-8-Gln	Injectable	GLP-1/NTSR1 co-agonist	Preclinical	89,90
HM15211	Injectable	GLP-1/GIPR/GCGR co-agonist	Phase II (NAFLD)	91
LY3437943	Injectable	GLP-1/GIPR/GCGR co-agonist	Phase II (T2DM)	92
Exendin-4/gastrin/xenin-8-Gln	Injectable	GLP-1/CCK2R/NTSR1co-agonist	Preclinical	93
[DA^2]GLP-1/GcG	Injectable	GLP-1/GIPR/GCGR co-agonist	Preclinical	94
Monomeric GLP-1/GIP/GCG	Injectable	GLP-1/GIPR/GCGR co-agonist	Preclinical	95,96

Table 1. A summary of therapeutic interventions for management of obesity. Drug names (brand names), administration routes (where applicable), mechanism of action and regulatory approval dates are provided. For therapeutics yet to reach regulatory approval, stage of development is indicated, including specific conditions being pursued, where known. Abbreviations: serotonin 2C receptor (5-HT_{2C}), cannabinoid receptor 1 (CB1), alpha-amino-3-hydroxyl-4-isoxazole-propionic acid kainate receptors (AMPA/KA), proopiomelanocortin (POMC), leptin receptor (LEPR), melanocortin 4 receptor (MC4R), glucagon-like peptide 1 receptor (GLP-1R), glucose dependent insulinotropic peptide receptor (GIPR), glucagon receptor (GCGR), cholecystokinin 1 receptor (CCK1R), cholecystokinin 2 receptor (CCK2R), secretin receptor (SCTR), amylin receptor (AMYR), calcitonin receptor (CTR), fibroblast growth factor receptor (FGFR), neuropeptide-Y 2 receptor (NPY2R), neurotensin 1 receptor (NTSR1), non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), palmitic acid (PAL), amino acid enantiomer [DX].

A Summary of Hormonal Changes Following RYBG



Key
Increase
Decrease
No Impact

CCK
↑ Satiety

GIP
↑ GIP Sensitivity

Neurotensin
↑ GIP Sensitivity
↑ Insulin Secretion

Leptin
↓ Adiposity

PYY(3-36)
↑ Satiety

GLP-1
↑ Insulin Secretion
↑ Satiety

Insulin, Glucagon
↑ Insulin sensitivity

OXM
↑ Energy expenditure

FGF-21
↑ Peripheral glucose tolerance