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Glucagon-like peptide-1 agonists combating clozapine-associated obesity and diabetes

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Abstract

Clozapine is the most effective antipsychotic, but its use is tempered by adverse metabolic effects such as weight gain, glucose intolerance and type II diabetes. Current interventions do not facilitate compelling or sustained improvement in metabolic status. Recent studies suggest that glucagon-like peptide-1 (GLP-1) may play a key role in clozapine's metabolic effects, possibly suggesting that clozapine-associated obesity and diabetes are mediated independently through reduced GLP-1. As a result, GLP-1 agonists could show promise in reversing antipsychotic-induced metabolic derangements, providing mechanistic justification that they may represent a novel approach to treat, and ultimately prevent, both diabetes and obesity in patients on clozapine. GLP-1 agonists are already used for diabetes, and they provide a unique combination of glycaemic improvement and metabolically relevant weight loss in diabetic and non-diabetic patients, in the context of a currently favourable safety profile. Using GLP-1 agonists for clozapine-associated obesity and diabetes could be a potentially effective intervention that may reduce cardiometabolic morbidity and mortality in this vulnerable patient population.

Keywords

Clozapine, antipsychotic, GLP-1, metabolic, schizophrenia

Clozapine and its metabolic adverse effects

Clozapine has consistently been shown to be the most effective antipsychotic for treatment-resistant schizophrenia (TRS; Leucht et al., 2013). In addition to reducing positive and negative symptoms, clozapine is associated with multiple clinical advantages over other antipsychotics: low risk of extrapyramidal symptoms (Leucht et al., 2013), reduction of suicide in schizophrenia (Hennen and Baldessarini, 2005), reduced hospitalisation (Tiihonen et al., 2011) and reduced all-cause mortality (Tiihonen et al., 2009). However, clozapine's use has been tempered by side-effect liability, including cardiac adverse events, haematological risks, weight gain and metabolic disturbance (Leucht et al., 2013).

Although abnormalities in glucose metabolism, dyslipidaemia, type II diabetes mellitus (T2D) and weight gain are linked to all antipsychotics (Newcomer, 2005), there is a hierarchy of risk. Several meta-analyses provide consistent evidence that the atypical antipsychotics clozapine and olanzapine have the highest propensity to cause weight gain and metabolic impairment, followed by risperidone and quetiapine, whereas ziprasidone and aripiprazole appear less associated (Allison et al., 1999; Newcomer, 2005; Rummel-Kluge et al., 2010).

In naturalistic studies, the cumulative incidence of new-onset T2D in patients receiving clozapine was 43% at 10 years, with half of the cases reported within three months of initiation (Henderson et al., 2000, 2005). Clozapine-induced weight gain is likely a contributing factor, although there is considerable variation in the magnitude among individuals and between studies. Long-term naturalistic studies suggest the mean weight change is

11.6 kg over five years (Henderson et al., 2000). Reviews of randomised controlled trials (RCTs) report higher rates and frequency of weight gain, estimating mean weight increases of 4.45 kg over 10 weeks (Allison et al., 1999), with >20% of patients experiencing at least a 10% increase in body weight after 52 weeks (Wetterling, 2001). While most rapid weight gain occurs during the initial 6–12 months, statistically significant weight gain with clozapine may continue for four years before stabilising (Henderson et al., 2000; Umbricht et al., 1994).

Antipsychotic-associated obesity and T2D represent a major clinical issue that contributes to the increasing mortality gap between individuals with schizophrenia and the general population (Lawrence et al., 2013). Large epidemiologic studies have shown that cardiovascular mortality is approximately two to

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three times higher in people with schizophrenia compared with the general population, translating to a 16.4-year shorter life expectancy (Lawrence et al., 2013; Newcomer, 2005). Although antipsychotic-naïve individuals with schizophrenia have an elevated baseline risk of T2D due to possible genetic predisposition (Spelman et al., 2007), the metabolic adversities of antipsychotic treatment – particularly with clozapine or olanzapine – make a substantial contribution to the aetiology of this excess cardiovascular disease. Metabolic side effects also compromise adherence (Perkins, 2002) and quality of life (Allison et al., 2003) for clozapine-treated patients.

Current interventions for clozapine-associated obesity and diabetes

Evidence for current interventions for clozapine-associated obesity and T2D is limited. Treatment guidelines recommend three strategies for managing clozapine-associated obesity and diabetes: switching to another antipsychotic with a favourable metabolic profile, adjunctive behavioural treatments or adjunctive pharmacological interventions (National Institute for Health and Care Excellence, 2014). Although switching antipsychotics is effective (Mukundan et al., 2010), it is unfeasible for TRS patients receiving clozapine due to exacerbation of psychotic symptoms. Similarly, while non-pharmacological interventions cause modest reduction in weight, fasting glucose and lipids, adherence to exercise and calorific restriction is often poor in patients taking clozapine due to limited insight and clozapine's adverse effects of increased hunger, thirst and sedation (Caemmerer et al., 2012).

To date, clozapine-associated T2D is managed in line with national guidelines for diabetes in the general population (National Institute for Health and Care Excellence, 2014). However, there is some evidence that standard strategies provide less optimal outcomes in antipsychotic-associated T2D, suggesting differences in underlying causative pathways (Henderson et al., 2009; Schoepf et al., 2012). Additionally, many second-line antidiabetic agents cause weight gain or are weight neutral, potentially blunting the beneficial metabolic effects and exacerbating cardiovascular risk profiles (Sun et al., 2015). For example, when added to metformin, sulphonylureas, thiazolidinediones, basal insulin and biphasic insulin cause significant increases in body weight, while dipeptidyl peptidase-4 inhibitors are weight neutral and GLP-1 agonists are associated with weight loss (Liu et al., 2012). In addition, the incidence of hypoglycaemia is significantly elevated with sulphonylureas and insulins, whereas thiazolidinediones, dipeptidyl peptidase-4 inhibitors and GLP-1 agonists do not appear to affect hypoglycaemic risk when added to metformin (Liu et al., 2012).

Studies addressing pharmacological interventions for antipsychotic-associated obesity are limited and heterogeneous. Several meta-analyses in this area investigating more than 19 pharmacological interventions for attenuating weight gain caused by antipsychotics have found several agents across varying pharmacological classes which appear to be modestly more beneficial than placebo: antidiabetics (metformin), antipsychotics (aripiprazole), serotonin and/or noradrenaline reuptake inhibitors (reboxetine, sibutramine, D-fenfluramine) and anti-epileptics (topiramate, zonisamide; Fiedorowicz et al., 2012; Maayan et al.,

2010; Mizuno et al., 2014). Metformin has the most robust empirical evidence but may not have enduring maintenance effects. However, clozapine-treated patients may represent a distinct subpopulation of patients, since clozapine is reserved for TRS and, compared with other antipsychotics, clozapine is associated with greater metabolic disturbance which is more refractory to treatment (Whitney et al., 2015; Wirshing et al., 1999).

There are few high-quality clinical studies of pharmacological and behavioural treatments that specifically address clozapine-associated obesity and other metabolic adversities. A 2015 systematic review for clozapine-associated weight gain found that only topiramate, aripiprazole, fluvoxamine and metformin show modest benefit as adjunctive weight loss agents (Whitney et al., 2015). No agent has consistent evidence regarding improvement in other metabolic parameters. Notably, data are based on between one and three trials for each intervention, and the reliability of available studies is limited by methodological issues and small sample sizes. The authors also noted that of the four beneficial pharmacological treatments, all studies reported treatment-related side effects, and use of these agents may therefore be limited by problematic adverse effect profiles (Whitney et al., 2015). Additionally, although observed weight loss and isolated metabolic improvements reached statistical significance, the magnitude of these changes was not nearly great enough to offset the changes observed during treatment with clozapine. The authors concluded that no available modality has sufficient evidence to support sound clinical practice guidelines for managing clozapine-associated obesity (Whitney et al., 2015).

There is therefore a pressing need to investigate novel methods of treating and preventing clozapine-associated obesity and diabetes that are based on a physiological understanding of clozapine's obesogenic and diabetogenic mechanisms. This paper presents an overview of one such strategy involving the use of glucagon-like peptide-1 (GLP-1) analogues.

Methods

We searched the PubMed database for relevant published articles according to the following key terms: (psychosis OR schizophrenia OR clozapine OR antipsychotic) AND (liraglutide OR exenatide OR GLP-1 OR glucagon-like peptide). Articles were not restricted to any publication date. English was the only admissible language. Reference lists from original articles were also screened by title for additional sources. A systematic review and meta-analyses were not attempted, given the breadth of the topic.

Results

Our data search returned a total of 35 articles. Articles were initially screened for relevance by title and then by abstract, which resulted in 16 articles from the original search. After comprehensive full-text analysis, two articles addressing genetic variation as primary outcomes were excluded based on irrelevance, and two articles lacking primary measurements were excluded. One article was added by scanning references from the original search. Overall, there were 13 articles relevant for this research synthesis of the use of GLP-1 agonists for schizophrenia patients. Among them, seven articles reported preclinical results, three articles presented clinical studies investigating the effect of antipsychotic

administration on GLP-1 levels, two articles presented protocols for RCTs and one article was a case report.

The endogenous GLP-1 system and GLP-1 physiology

GLP-1 is an endogenous peptide hormone secreted by enteroendocrine L-cells of the gastric mucosa (Drucker, 2006). GLP-1 is produced by proteolytic processing of the proglucagon pro-hormone, with the major active form being the 30-amino acid peptide GLP-1 (GLP-1 7–36 amide; Holst, 2007). GLP-1 is essential for normal glucose tolerance, and as an incretin hormone, it contributes to amplification of insulin secretion in response to food intake (Iepsen et al., 2014). The GLP-1 receptor (GLP-1R) is widespread throughout the body, including the pancreas, gastrointestinal tract, kidney and brain (Iepsen et al., 2014). GLP-1R agonism promotes weight loss and improves glucose homeostasis in both animal models and humans (Holst, 2007). Peripherally, GLP-1 acts on the pancreas to enhance insulin secretion, via β -cells, and inhibit glucagon secretion, via α -cells. These effects are glucose dependent, and they abate when glucose falls below 4–5 mM, thereby circumventing hypoglycaemia (Drucker, 2006). GLP-1 control of glucose homeostasis likely involves complex regulation of both the peripheral and central nervous systems in addition to direct control of pancreatic islets (Figure 1; Heppner and Perez-Tilve, 2015). GLP-1 also exerts islet-independent effects to reduce hepatic glucose production, suggestive of a direct effect on peripheral tissues (D'Alessio et al., 1994; Prigeon et al., 2003). Decreased GLP-1 action, causing increased hepatic glucose production, has been suggested to be an important mechanism contributing to the development of T2D (Iepsen et al., 2014). In addition to its insulinotropic effects, GLP-1 has a multitude of actions, including regulation of satiety, lowering of food intake and slowing gastric emptying, which contribute to its broad glucoregulatory actions (Drucker, 2006). These mechanisms also contribute to an anorectic effect of GLP-1 which is responsible for GLP-1-induced reduction in body weight (Heppner and Perez-Tilve, 2015).

Although GLP-1 delays gastric emptying, which reduces postprandial glucose excursions and post-meal satiety (Madsbad, 2014), rapid tolerance develops to this effect, and therefore it is not central to the long-term body weight lowering mechanism of GLP-1 (Holst, 2007). The primary body weight lowering effect of GLP-1 and its analogues resides in its central effects in several areas of the brain involved in appetite regulation, which peripherally administered GLP-1 and GLP-1 analogues can access via leaks in the blood–brain barrier (Heppner and Perez-Tilve, 2015; Kastin et al., 2002). The arcuate nucleus of the hypothalamus has been implicated as a major site mediating the action of GLP-1R on energy intake, and blockade of GLP-1Rs in the arcuate nucleus attenuates GLP-1-induced anorectic action and weight loss (Secher et al., 2014; Tang-Christensen et al., 1998). The parabrachial nucleus, the nucleus of the solitary tract, amygdala and the circumventricular organs have also been suggested as important areas for GLP-1 regulation of feeding and associated body weight loss (Alvarez et al., 2005; Dossat et al., 2011). Interestingly, GLP-1R agonism may also mediate weight loss in part through interaction with the leptin system, causing increased leptin levels and thereby mediating satiety (Iepsen et al., 2015). Such diverse

physiological effects make GLP-1R agonism an attractive mechanism for glycaemic control and weight management.

GLP-1-based therapies

Despite the attractive physiological effects of native GLP-1, its therapeutic application is limited by its rapid degradation following release from gut L-cells (Drucker, 2006). Active GLP-1 (7–36 amide) does not persist long in the circulation (plasma half-life: 1–2 minutes) due to its susceptibility to the catalytic activity of the enzyme dipeptidyl peptidase-4 (DPP-4; Holst, 2007). DPP-4 rapidly cleaves the two amino acids at the N-terminus to produce inactive GLP-1 (9–36 amide) which cannot signal to the pancreas (Holst, 2007). There are two commercially available therapeutic approaches to prolong the *in vivo* actions of GLP-1: GLP-1 receptor agonists (GLP-1RAs) and inhibitors of DPP-4 ('gliptins'). Compared with gliptins, GLP-1RAs provide superior glycaemic control and weight loss, whereas gliptins are weight neutral (Deacon et al., 2012). Gliptins have also recently been shown to have no effect on major cardiovascular events in T2D (Udell et al., 2015; White et al., 2013).

Presently, six different GLP-1RAs, administered via subcutaneous injection, have been examined in phase III clinical trials for T2D: exenatide, liraglutide, albiglutide, tasoglutide, lixisenatide and dulaglutide (Ebdrup et al., 2012). Several other agents with optimised pharmacokinetics allowing extended dosing regimens (daily or weekly administration) are in advanced clinical development (Ryan and Acosta, 2015). However, most clinical data and experience relate to exenatide and liraglutide, and these are the primary GLP-1RAs used clinically for T2D (Ebdrup et al., 2012). Twice-daily exenatide (exenatide BD), a synthetic peptide with 53% homology to GLP-1, was the first GLP-1RA granted market authorisation for T2D by the United States in 2005 and has since been approved in more than 87 countries (Therapeutic Goods Administration, 2013). Subsequent to exenatide BD approval, long-acting GLP-1 agonism has been achieved with fatty acylation (liraglutide) and a long-acting exenatide formulation (exenatide LA), thereby allowing daily or weekly administration, respectively (Heppner and Perez-Tilve, 2015). Exenatide LA, first approved in Europe in 2011, was synthesised through encapsulation of exenatide into extended-release polymeric microspheres (Fineman et al., 2011).

Liraglutide 3 mg is the first GLP-1RA to be granted approval for chronic weight management indications in non-diabetic patients (FDA in December 2014). Liraglutide has since been approved for weight management in Europe (March 2015), and registration is being pursued in several other countries (Ryan and Acosta, 2015). Notably, the approved dose (3 mg/day) is higher than that used in T2D (1.8 mg/day), reflecting that higher concentrations are needed to elicit the primary mechanisms of action that affect weight (CNS-mediated reduction in appetite) compared with concentrations required to elicit glycaemic control (regulation of insulin and glucagon secretion; Fineman et al., 2011).

Compared with exenatide BD or liraglutide, exenatide LA is associated with improved adherence (Johnston et al., 2014), treatment satisfaction and weight-related quality of life in patients with T2D (Best et al., 2009). Given the poor adherence to hypoglycaemic regimens among individuals with schizophrenia

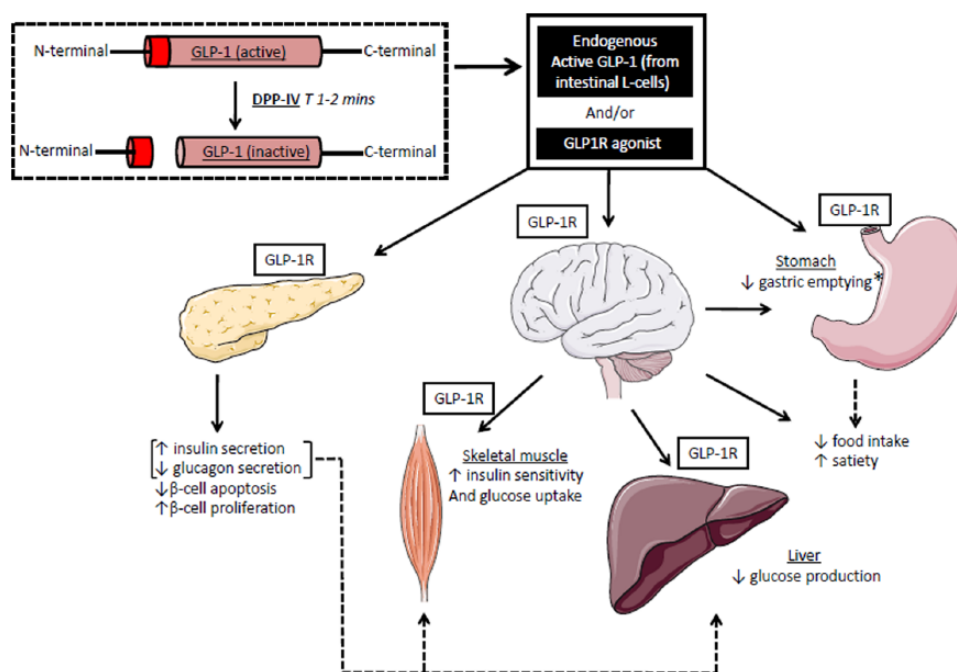


Figure 1. Glucagon-like peptide-1 (GLP-1) processing and tissue-specific effects to regulate glucose and energy metabolism. GLP-1 agents regulate satiety behaviour via efferent outflow from the central nervous system (CNS) by both direct activation of GLP-1 receptors (GLP-1Rs) in brain centres involved in feeding (via blood–brain barrier leaks) and indirectly via vagal afferents originating in the intestine. Through the effects of GLP-1R activation in the brain (particularly hypothalamic and brainstem nuclei), GLP-1 and its analogues reduce food intake, thereby causing weight loss. Glycaemic control by GLP-1 occurs through the combined contribution of all CNS dependent and independent pathways. Dashed arrows represent indirect effects of GLP-1 not mediated by direct interaction with GLP-1 receptors. *Effect is subject to rapid tachyphylaxis and is therefore transient. Figure adapted from Hoppner and Perez-Tilve (2015).

(Gorczyński et al., 2014), weekly dosing of exenatide LA arguably offers greatest practicality for psychiatric patients. Weekly injection of exenatide is particularly advantageous in this cohort of patients, as they are required to have a weekly blood test for the first 18 weeks of clozapine, and thus exenatide may be administered at the same time as the blood tests. This means patients unable or unwilling to self-inject can still be treated.

GLP-1RAs are well tolerated, with the main side effects being mild-to-moderate transient gastrointestinal effects including nausea and vomiting occurring in up to 20% of patients and typically resolving within four to eight weeks (Harris and McCarty, 2015). Less frequently, patients describe headache, fatigue, reflux, dizziness and transient injection site redness, itchiness or haematoma; hypoglycaemia incidence is low due to the glucose-dependent insulinotropic effect (Shyangdan et al., 2010). Available agents differ slightly in their propensity to cause adverse events. Injection-site reactions appear more common with longer-acting agents, particularly exenatide weekly, while gastrointestinal disturbances are less common with exenatide weekly compared with exenatide twice daily or liraglutide (Trujillo et al., 2015). Notably, there are a small number of reported cases of pancreatitis with GLP-1RA treatment in patients with T2D. However, it is unclear whether this relationship is causal or coincidental, given the independent association between T2D and risk of acute pancreatitis (Monami et al., 2014). There are also safety concerns regarding thyroid C-cell tumours with GLP-1RAs, given increases in the incidence of tumours in rodent studies with clinically relevant GLP-1RA exposure (Ryan and Acosta, 2015). However, the human relevance of this effect

appears to be low, and there has been no association of human C-cell tumours with GLP-1RAs (Ryan and Acosta, 2015).

Clozapine-mediated disturbance to the GLP-1 system

The mechanisms underlying clozapine-induced metabolic deterioration are not completely understood, but the aetiology is likely multifactorial involving receptor, hormonal and genetic interactions. A body of evidence in rodent models has shown that clozapine and olanzapine (and to a lesser extent quetiapine and haloperidol) cause a hyperglycaemic state and rapid increase in both glucagon and insulin (Boyda et al., 2010; Houseknecht et al., 2007; Smith et al., 2008, 2009, 2014). These findings have been replicated in several clinical studies of healthy human subjects, showing significant elevations in glucose, insulin and glucagon with short-term olanzapine treatment (Sacher et al., 2008; Sowell et al., 2003; Teff et al., 2013). Although this clinical state is traditionally interpreted as analogous to insulin resistance (Houseknecht et al., 2007; Sacher et al., 2008), a series of mechanistic rodent studies by Smith et al. (2008, 2009, 2014) show insulin action in peripheral tissues is preserved after clozapine. Rather than metabolic derangements being a product of direct insulin resistance, clozapine acts via increasing glucagon secretion which subsequently increases hepatic glucose output (Smith et al., 2008, 2009). This is responsible for concurrent hyperinsulinemia and the phenotype mimicking insulin resistance (Smith et al., 2008). Simultaneously, clozapine induces a preference for

high-fat/high-sugar foods, shown in both rats (Smith et al., 2009) and humans (Henderson et al., 2010).

There is some evidence that clozapine's modulation of adrenergic, histaminergic and serotonergic systems as well as direct stimulation of glucagon from pancreatic islets may cause the observed abnormalities in glucose levels (Roerig et al., 2011; Smith et al., 2014). However, a 2009 rodent study by Smith et al. provided the first evidence that GLP-1 may play a key role. Clozapine and olanzapine caused rapid and reversible reductions in active GLP-1 levels which is likely to make a major contribution to the changes in food preference and the secretion of glucagon to levels high enough to overcome the counter-regulatory effects of insulin, leading to impaired glucose tolerance (Smith, 2011; Smith et al., 2009). Although not fully elucidated, a postulated mechanism through which clozapine inhibits GLP-1 secretion involves antagonism of muscarinic M1 and M2 receptors. Among all antipsychotics, clozapine has one of the highest antagonistic affinities for muscarinic receptors (Nasrallah, 2008), and GLP-1 secretion from intestinal L-cells is stimulated by muscarinic neurotransmission (Anini et al., 2002; Deacon, 2005).

These data suggest that clozapine-induced GLP-1 hyposecretion and associated defects in glucose homeostasis may be a significant causative pathway in the diabetogenic effect of clozapine. It has previously been assumed that the pathogenesis of T2D is secondary to the obesity that develops with clozapine. However, these mechanistic studies provide evidence that clozapine can also cause impairment of glucose metabolism via direct molecular effects on the GLP-1 pathway, independent of weight gain (Newcomer, 2005). Indeed, glucose disturbance following antipsychotic administration in human subjects is seen in the acute phase before weight gain occurs, suggesting direct effects on mechanisms regulating glucose homeostasis (Teff et al., 2013; Vidarsdottir et al., 2010a). This is also consistent with clinical evidence showing rapid T2D development in clozapine-treated patients without an association with weight gain (Henderson et al., 2005; Lamberti et al., 2005). GLP-1 is also known to play an active role in macronutrient selection and regulating the intake of high-sugar foods (Peters et al., 2001; Shin et al., 2008). This is consistent with the hypothesis that clozapine-induced suppression of GLP-1 may be a key contributor to hyperphagia and weight gain associated with clozapine. A recent study has also shown the impact of genetic variation in GLP-1 signalling on antipsychotic-induced weight gain, further suggesting a role of the GLP-1 axis in mediating the obesogenic effects of clozapine (Brandl et al., 2014).

Ultimately, these early preclinical data support the possibility that clozapine-associated obesity and diabetes are mediated independently through a common causative pathway: GLP-1 hyposecretion. Therefore, GLP-1RAs represent a compelling and targeted therapeutic strategy for treating and preventing both T2D and obesity in clozapine-treated patients.

Evidence for GLP-1RA in antipsychotic-associated obesity and diabetes

While there is a broad clinical evidence base to support efficacy and safety of exenatide in non-psychiatric populations, there is a paucity of data specific to clozapine-associated obesity and diabetes. However, it is possible that the effects of GLP-1RAs could be even greater in clozapine-treated patients and superior to

current interventions, given that they directly target the GLP-1 signalling pathway involved in pathophysiology of clozapine-associated metabolic dysregulation. Unfortunately, supporting clinical data are currently limited to one case report of successful weight loss and HbA1c reduction with liraglutide in a 60-year-old patient with schizophrenia on clozapine who had obesity and dysregulated T2D (Ishøy et al., 2013). As a result, this area is receiving increased attention with three published protocols for currently ongoing placebo-controlled RCTs (Ishøy et al., 2014; Larsen et al., 2014; Mayfield et al., 2015). Consequently, to date, the impact of GLP-1RAs on antipsychotic-treated populations is based primarily on indirect and theoretical considerations, as well as data from four key preclinical studies.

Subsequent to finding that clozapine acutely reduces GLP-1 levels, Smith et al. (2009) investigated two strategies to restore GLP-1 signalling and counter the elevated glucagon: exendin-4 (the natural, structurally identical form of exenatide) and sitagliptin (a DPP-4 inhibitor). Single administration of exendin-4 before an oral glucose tolerance test normalised both glucose utilisation and glucagon levels in clozapine-treated rats. Sitagliptin only partially restored GLP-1 signalling, failing to overcome clozapine-induced defects in glucose metabolism. Similarly, in their 2014 study, Smith et al. showed Boc5 administration (a non-peptidic GLP-1RA) for 14 days overcame the deleterious effects of clozapine on glucose tolerance in rats. In support of this, Lykkegaard et al. (2008) and Sharma et al. (2014) also found that liraglutide treatment (14 days and 21 days, respectively) in olanzapine-treated rats reversed or significantly reduced the metabolic abnormalities associated with long-term olanzapine treatment (including increased food intake, body weight, cholesterol and glucose intolerance). These promising preclinical data provide the first evidence that GLP-1RA's beneficial effects on weight and glycaemia may be translated to antipsychotic-induced metabolic disorders.

However, these preclinical data must be interpreted in the context of several limitations regarding the use of rodent models. While animals represent a validated model for investigating glucose metabolism, the extent to which the findings of GLP-1 suppression following antipsychotic administration in animal models translates to human subjects is currently unknown. Animal models are associated with a number of considerations which reduces their validity as an approach to identifying mechanistically novel pathways. Notably, the cognitive blunting actions of antipsychotics, which potentially mask the effect on food intake and metabolism, are not addressed by animal models, and the reduction in delusions and hallucinations which may also have implications for energy metabolism in humans cannot be feasibly modelled by animal paradigms (Dunn et al., 1993). Additionally, given the non-specificity of antipsychotic drugs, particularly clozapine, which has a broad spectrum of receptor actions, the doses used in animals may be associated with significantly different pharmacodynamic properties compared with that in humans (Kapur et al., 2003). Dosing in animal models is also complicated by the differential time course of antipsychotic effects, with a four- to six-fold shorter half-life in rodents than in humans (Kapur et al., 2003). These factors may contribute to weak correspondence in the effect of antipsychotics on GLP-1 between animal models and humans. Indeed, the preclinical findings of GLP-1 suppression following atypical antipsychotic administration have yet to be replicated in clinical studies, although this area has not been studied in detail. Two available studies in healthy male subjects treated with short-term olanzapine report unchanged (Vidarsdottir

et al., 2010b) or elevated postprandial GLP-1 levels following olanzapine administration (Teff et al., 2013). Another clinical study by Ebdrup et al. (2014) also reported no influence of antipsychotics on GLP-1 in antipsychotic-treated male patients with schizophrenia spectrum disorder. However, the majority of patients were receiving metabolically neutral antipsychotic agents rather than clozapine or olanzapine. Notably, these clinical studies do not report the use of inhibitors to protect the active form of GLP-1(7–36) amide which does not persist very long in the circulation due to cleavage of the two N-terminal amino acids by DPP-4 to produce inactive GLP-1(9–36). These clinical studies either measure total plasma GLP-1 concentration or have unclear reporting on the use of active or total GLP-1, whereas only active GLP-1 capable of signalling to the pancreas was measured in the rodent model which demonstrated attenuated levels following clozapine (Smith et al., 2009). Furthermore, the Vidarsdottir et al. (2010b) study measured total glucagon hormone which incorporates active glucagon hormone as well as oxyntomodulin and glicentin, rather than solely measuring active glucagon hormone secreted from pancreatic α cells as was performed in animal studies. These factors may underlie the lack of consistency between animal and human studies, and therefore the lack of standardised blood collection and analysis methods introduces difficulty in reconciling rodent and human data. Interestingly, Vidarsdottir et al. (2010a) had previously reported that active glucagon levels did rise in humans exposed to olanzapine, which provides good supporting evidence of the mechanism proposed in preclinical models. However, given the lack of human data to date, the relevance of preclinical findings regarding beneficial effects of GLP-1RAs remains uncertain.

Nevertheless, despite the current limitations in the consistency of evidence, available preclinical findings demonstrate a mechanistic link between GLP-1 and antipsychotic-associated metabolic dysregulation, which is in agreement with the only available case report in this area (Ishøy et al., 2013). This supports the possibility that GLP-1RAs may represent a potentially effective method of ameliorating the negative metabolic effects in patients receiving atypical antipsychotics, especially those with a high metabolic burden such as clozapine. This area requires further high-quality clinical evidence in human subjects to support this notion and further evaluate if the GLP-1 effects observed preclinically translate to patients with schizophrenia.

GLP-1RA's clinical use in T2D and obesity in non-psychiatric populations

The efficacy of GLP-1RAs as agents for treating T2D is well established. GLP-1RAs now also have a broad evidence base as agents for obesity, and their place in T2D treatment as second- or third-line agents is also changing, as clinical data surrounding extraglycaemic benefit continue to emerge (Gunton et al., 2014; Nathan et al., 2009).

Exenatide BD, liraglutide and exenatide LA are effective in reducing HbA1c and other glycaemic parameters (fasting and postprandial blood glucose) as both monotherapy and when combined with first- and second-line agents in T2D (Iepsen et al., 2014). This has been consistently demonstrated across major large phase III clinical trial programs for each GLP-1RA:

AMIGO ($n=1446$), LEAD ($n=4408$) and DURATION ($n=3569$) trial programs, respectively. Meta-analyses of comparator-controlled RCTs showed GLP-1RAs reduced HbA1c by approximately 1% relative to placebo and produced equivalent or superior improvements compared to insulin, sitagliptin, rosiglitazone, pioglitazone and sulphonylureas (Gross et al., 2011; Shyangdan et al., 2010). However, differences in the pharmacokinetics of different GLP-1RAs lead to variation in their effect on basal versus postprandial glycaemia, as demonstrated through DURATION-1,-5,-6 and LEAD-6 head-to-head clinical trials (Trujillo et al., 2015).

Additionally, GLP-1RAs consistently caused clinically meaningful weight loss across the AMIGO, LEAD and DURATION trials (Iepsen et al., 2014). A recent systematic review of 51 studies (mean duration 31 weeks) reports dose-dependent weight loss ranging from 1.22 to 3.31 kg in T2D patients treated with exenatide or liraglutide (Sun et al., 2015). The improvements in glycaemic control and body weight were sustained over three years of treatment (Klonoff et al., 2008; MacConell et al., 2013).

In addition to causing weight loss in diabetic patients, a growing evidence base supports that GLP-1RAs also cause progressive and sustained weight loss in non-diabetic obese patients via reduced appetite and food intake (Van Can et al., 2014). A recent meta-analysis of eight studies 12–56 weeks in duration has demonstrated that GLP-1RA treatment causes dose-dependent, clinically significant weight loss (mean -2.85 kg; Zhang et al., 2015). Weight loss in non-diabetic obese patients is of greater magnitude than that in diabetic patients (VilSBoll et al., 2012). The recent approval of liraglutide 3 mg for chronic weight management in obese or overweight (with co-morbidities) patients without diabetes makes it the first diabetic agent with dual approval (Ryan and Acosta, 2015).

The large phase III SCALE (Satiety and Clinical Adiposity–Liraglutide Evidence in Nondiabetic and Diabetic adults) clinical trial program, consisting of four RCTs involving >5000 overweight or obese non-diabetic patients, was pivotal in supporting liraglutide approval. A key SCALE study ($n=3731$) reported a 56-week double-blind, placebo-controlled trial of liraglutide (3 mg) adjunctive to lifestyle counselling for weight reduction (Pi-Sunyer et al., 2015). Liraglutide was associated with significant and sustained improvements in body weight compared with placebo (-8.4 kg vs. -2.8 kg). The 56-week SCALE Maintenance trial ($n=422$) also showed liraglutide could convincingly maintain prior weight loss (Wadden et al., 2015). SCALE trials also reported significant improvements in secondary glycaemic outcomes, cardiometabolic risk factors and quality-of-life measures. These findings are consistent with an earlier phase II double-blind, placebo-controlled, 20-week RCT ($n=564$) of non-diabetic obese patients which showed that liraglutide (1.2–3 mg) caused a significant dose-dependent weight loss (-7.2 kg for 3 mg vs. -2.8 kg for placebo) that was sustained in a two-year open-label extension (Astrup et al., 2009, 2012). Nevertheless, there remains a lack of long-term safety and efficacy data beyond two years while results are awaited from SCALE extension studies.

Although exenatide has been less extensively studied and remains unlicensed for obesity indications, there is some, albeit less robust, evidence for exenatide BD for weight loss in obese non-diabetic adults. Data are limited to four small-scale ($n=41–152$) randomised comparator-controlled studies of short duration

(12–24 weeks) where total mean weight loss from baseline ranges from 2.5 to 5.1 kg (Dushay et al., 2012; Elkind-Hirsch et al., 2008; Kelly et al., 2012; Rosenstock et al., 2010).

GLP-1RA may also improve glucose tolerance in the pre-diabetic state and delay the onset of diabetes. Three trials report reduced prevalence of prediabetes where GLP-1RA treatment was associated with 84% (Astrup et al., 2009), 70% (Pi-Sunyer et al., 2015) and 77% (Rosenstock et al., 2010) of pre-diabetic participants attaining normal glucose tolerance.

Therefore, GLP-1RA induction and maintenance of glycaemic control and weight loss in diabetic and non-diabetic subjects, coupled with significantly improved obesity-related risk factors, emphasise GLP-1RAs' attractive pharmacological potential as agents for clozapine-associated obesity and diabetes – conditions which commonly coexist.

Beneficial effects of GLP-1 beyond glucoregulation and weight loss

There is increasing preclinical and clinical evidence that GLP-1RAs mediate a wider spectrum of beneficial effects (reviewed in Ryan and Acosta, 2015). For example, GLP-1RAs appear to have trophic and protective effects on β -cells, providing substantial clinical benefit in T2D and pre-diabetes by potentially preserving or restoring functional β -cell mass and counteracting an underlying cause of T2D progression (Shyangdan et al., 2010). GLP-1RAs also appear to have cardioprotective effects, and several emerging lines of evidence support improvement in cardiovascular risk markers, including blood pressure and lipid profiles (Ryan and Acosta, 2015). Two studies (Dixit et al., 2013; Sharma et al., 2014) have recently described antipsychotic-like and antidepressant-like effects of GLP-1RAs in rodent models for psychosis and depression, demonstrating particular value in psychiatric patients suffering co-morbid metabolic disturbance. These pleiotropic effects, yet to be fully elucidated, may provide multifactorial benefits to enhance clinical outcomes and global functioning among patients with schizophrenia.

Additionally, GLP-1RAs have a number of favourable central effects which suggest their therapeutic utility in a multitude of conditions. Widespread distribution of GLP-1Rs in the brain and evidence for pro-cognitive and neuroprotective effects of GLP-1RAs suggest therapeutic potential in the treatment of neurodegenerative disorders. Several studies of GLP-1RAs in animal models of Alzheimer's disease have demonstrated benefit on memory impairment, amyloid plaque formation and hippocampal synaptic loss and plasticity (Gengler et al., 2012; McClean et al., 2011) while also demonstrating neuroprotective properties and improvement in motor deficits in models of Parkinson's disease (Bertilsson et al., 2008) and Huntington's disease (Martin et al., 2009). Although the clinical benefits are yet to be determined, there are several clinical trials currently testing the role of GLP-1 in neurodegenerative disorders, particularly Alzheimer's disease (Edison and Bouanane, 2015; Kapogiannis and Zukley, 2015) and Parkinson's disease (Foltynie, 2015; Unger, 2015). The mesolimbic brain structures and mechanisms of GLP-1 to control food reward are also common to the rewarding properties of drugs of abuse (Ebdrup et al., 2012). This suggests a role of enhancing central GLP-1R signalling, via either GLP-1RAs or DPP-4 inhibition, in treating substance abuse disorders. Several

lines of evidence have shown that GLP-1 attenuates cocaine and amphetamine reward (Egecioglu et al., 2013a; Graham et al., 2013). Additionally, GLP-1RA and DPP-4 inhibitors reduce the reinforcing properties of alcohol and alcohol-seeking behaviour (Egecioglu et al., 2013b) while inhibiting tolerance to alcohol's anti-anxiety effect and preventing withdrawal-induced anxiety (Sharma et al., 2015a, 2015b). Collectively, these data support a role of GLP-1 in drug-induced reward regulation and may justify investigation of GLP-1-based treatments as novel treatments for substance misuse (Gaiser, 2015). This is relevant to our population because of the high rates of co-morbid substance misuse in schizophrenia. Therefore, the spectrum of central effects of GLP-1 supports alternate and potential therapeutic application for GLP-1RAs across a broad range of disease states, independent of their actions in metabolic control. These areas of research have a rapidly evolving evidence base, as benefits of GLP-1-based therapy, and their clinical relevance, continue to be investigated.

Conclusion

Clozapine has a high propensity to cause metabolic side effects, contributing to cardiometabolic risk, impaired quality of life and premature cardiovascular morbidity and mortality. This represents a major and unresolved clinical challenge. Clozapine's obesogenic and diabetogenic effects can be independent, with each potentially mediated, at least in part, by GLP-1 hyposecretion. Current data showing benefit of GLP-1RAs in rodents treated with antipsychotics, coupled with their recognised weight loss and glycaemic effects, converge towards GLP-1RAs as an attractive therapeutic avenue to counterbalance metabolic abnormalities from clozapine. This is a rapidly evolving area, and ongoing long-term clinical studies are still required in this patient population to confirm an acceptable risk–benefit ratio. Nevertheless, there is a growing body of evidence suggesting that this novel treatment may be a new weapon in the therapeutic arsenal for treating clozapine-associated obesity and diabetes, and its underlying pathophysiology.

Declaration of Conflicting Interests

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