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A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain*

Trisha Menon[1,2], Serene Lee[1,3], Xuan Yi Gong[1], Sabrina Wong[1,4,5], Gia Han Le[1,4,6], Angela T.H. Kwan[1,7], Kayla M. Teopiz[1], Roger Ho[8,9,10], Bing Cao[11], Taeho Greg Rhee[12,13], Yang Jing Zheng[1], Kyle Valentino[1], Kangguang Lin[14], Maj Vinberg[15], Heidi K.Y. Lo[16] and Roger S. McIntyre[17]

[1]Brain and Cognition Discovery Foundation, Toronto, Ontario, Canada; [2]Department of Psychology, University of Toronto, Toronto, Ontario, Canada; [3]Department of Health Sciences, Queen's University, Kingston, Ontario, Canada; [4]Mood Disorder and Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada; [5]Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada; [6]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; [7]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [8]Department of Psychological Medicine, Yong Loo Lin School of Medicine, Singapore; [9]Institute for Health Innovation and Technology (iHealthtech), National University of Singapore, Singapore; [10]Division of Life Science (LIFS), Hong Kong University of Science and Technology (HKUST), Clear Water Bay, Hong Kong, China; [11]Key Laboratory of Cognition and Personality, Faculty of Psychology, Ministry of Education, Southwest University, Chongqing, 400715, P. R. China; [12]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; [13]Department of Public Health Sciences, University of Connecticut School of Medicine, Farmington, CT, USA; [14]Department of Affective Disorder, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, Guangdong Province, China; [15]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [16]Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China and [17]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Abstract

Objective. Many psychotropic drugs are highly associated with related weight gain. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are established anti-obesity and glucose-lowering agents. Preliminary evidence also indicates they are fit for purpose in mitigating psychotropic drug-related weight gain (PDWG). This systematic review aims to synthesize the extant evidence from randomized controlled trials (RCTs) on the effects of GLP-1RAs on weight change in persons experiencing PDWG.

Methods. Online databases (ie, PubMed, OVID Medline, Google Scholar) were searched to identify relevant studies from inception to January 1, 2024. Articles were screened by title, abstract, and full-text by three independent reviewers against inclusion and exclusion criteria.

Results. We identified six studies with participants aged ≥18 (n=374) that were eligible for inclusion in our systematic review. Most studies reported a significant and clinically meaningful effect of GLP-1RAs on anthropometrics and/or metabolics. All RCTs replicated the finding of modest or greater effects of GLP-1RAs; the most studied agents were liraglutide and exenatide. There was insufficient literature to conduct a meta-analysis.

Conclusion. Evidence suggests that GLP-1RAs are effective in mitigating weight gain in persons prescribed psychiatric medication. It is hypothesized that GLP-1RAs may moderate weight change in persons prescribed psychiatric medication through direct effects on metabolism and cognitive processes implicated in hunger/satiety. Future studies should aim to explore the long-term safety, tolerability, and efficacy profiles of various GLP-1RAs in the treatment and prevention of abnormal weight and metabolic homeostasis in psychiatric populations.

Introduction

Psychotropic drug-related weight gain (PDWG) frequently occurs with the use of psychiatric drugs, such as antipsychotics, antidepressants, lithium, and anticonvulsants. The onset of PDWG is often associated with non-concordance with treatment recommendations and dissatisfaction with psychiatric drugs[1]. Notwithstanding, the risk of weight gain with the use of psychotropic drugs varies depending on the type of drug used. For example, weight gain associated with antipsychotic use, such as clozapine and olanzapine, tends to be relatively higher compared to other psychotropic drugs[2]. For individuals experiencing PDWG, common management strategies include the discontinuation of the psychotropic drug causing weight gain and switching to an alternative drug that has a lower risk of PDWG or attempting a behavioral or pharmacologic intervention to target weight gain[1].

Review

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Corresponding author:
Roger S. McIntyre;
Email: roger.mcintyre@bcdf.org

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PDWG is a clinically relevant issue and a priority therapeutic target[3,4], as levels of obesity and body mass index (BMI) in psychiatric populations are rising at a higher rate compared to the general population[5–7]. Greater levels of obesity are especially concerning, as obesity is associated with higher morbidity and mortality, impaired global functioning, overall quality of life, and potentially shortened lifespan and health span in psychiatric populations[1,8–10].

Treatment of PDWG includes lifestyle and behavioral modifications, which are similarly effective as weight-loss intervention in psychiatric populations as compared to the general population[11]. However, individuals with severe mental illness may face unique barriers to engaging in these aforementioned interventions including economic, healthcare access and availability and cognitive aspects intrinsic to mental illness affecting motivation and treatment implementation. Consequently, alternative pharmacologic interventions for the treatment and prevention of PDWG and related metabolic abnormalities are needed.[1,12]

Glucagon-like peptide-1 (GLP-1) is a peptide hormone produced by the intestine in response to meal ingestion, which stimulates the secretion of insulin, decreases gastric emptying and inhibits food intake[13,14]. GLP-1 receptor agonists (GLP-1RAs) mimic the functions of endogenous GLP-1, having beneficial effects on metabolic regulation and allowing for weight loss[15]. As a result, GLP-1RAs, such as exenatide and semaglutide are commonly administered as a treatment for obesity in type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome[16]. Similarly, GLP-1RAs have been used to treat PDWG[17–22]. In this systematic review, we aim to synthesize extant evidence from randomized controlled trials (RCTs) on the use of GLP-1RAs to mitigate PDWG.

Methods

Search and selection strategy

A systematic search was conducted on online databases, including PubMed, OVID Medline, and Google Scholar, from inception until January 1, 2024. Subsequent manual searches of the reference lists of any relevant articles were conducted. The databases PubMed, and OVID Medline were searched using the following Boolean search string: ((“depression” OR “schizophrenia” OR “bipolar disorder”) AND (“weight gain”) AND (“antipsychotic*” OR “psycho* drug”) AND (“GLP-1”)). A second search string was used to search for the efficacy of Food and Drug Administration (FDA)-approved GLP-1 agonists against the topic of interest in RCTs: ((“psycho* drug”) AND (“weight gain” OR “weight loss”) AND (“GLP-1” OR “glucagon-like peptide-1” OR “exenatide” OR “liraglutide” OR “dulaglutide” OR “lixisenatide” OR “insulin degludec” OR “insulin glargine” OR “semaglutide” OR “tirzepatide” AND “randomized controlled trial”)). Studies were limited to the language of publication (ie, English).

Three reviewers (SL, XYG, and TM) independently screened articles using the Covidence platform. After removing duplicated articles, identified studies were screened by titles, abstracts, and full-text against eligibility criteria. Any conflicts regarding article screening between reviewers were resolved through discussion.

Eligibility criteria

Eligible studies had enrolled participants who had previously or currently been prescribed a psychotropic drug (ie, antidepressants, antipsychotics) and experienced drug-related weight gain. The eligible population was limited to adults aged ≥18 who were clinically diagnosed as overweight/obese. Additionally, only studies developed as RCTs with GLP-1RA intervention groups and placebo-controlled groups were considered.

Studies were excluded if they: (i) were secondary research (eg, systematic reviews, meta-analyses of RCTs, narrative reviews, commentaries, etc.), (ii) were animal studies, and (iii) were not written in English.

Data extraction process

Extracted data were established a priori using a piloted data extraction table. Data extraction was conducted by three independent reviewers (TM, SL, and XYG). The extracted data included: i) authors and publication year, ii) study design, iii) sample size, iv) participant eligibility criteria, v) treatment allocation, vi) study duration, vii) treatment outcomes, and viii) significance operationalized by p-values indicating relationships between the control and experimental groups, where a p-value <.05 was considered significant in yielding weight loss benefits by GLP-1RAs. For papers that did not report a final p-value, the primary outcome measure defined by the authors was obtained.

Study of risk of bias assessment

Study quality was assessed by three independent reviewers (SL, XYG, and TM) using Cochrane’s revised risk-of-bias tool for randomized trials (Table 1)[23]. Each paper was assessed at least twice by two different reviewers.

The signaling questions in Table 10 of the risk-of-bias tool approached the potential biases of each selected study: bias due to outcome measurement, bias between intervention groups, bias from non-blind study design, bias due to knowledge of the intervention, and bias in outcome due to perceived knowledge[23].

Results

Study results and selection

The initial search generated 8945 publications from PubMed and OVID Medline databases, as seen on the PRISMA Flowchart (Figure 1). After removing study duplicates, 4566 papers remained for title and abstract screening, of which 70 were deemed eligible for full-text screening. From full-text screening, six eligible publications were included in the systematic review, the majority being excluded due to study design or wrong outcome (ie, the study’s final outcome was irrelevant to the research question).

Table 1. Risk of Bias Assessment

Study	1	2	3	4	5	Risk of bias judgments
Ishoy et al. (2016)	N	N	N	N/A	N/A	Low
Maagensen et al. (2021)	PN	N	Y	N	N/A	Low
Siskind et al. (2020)	N	Y	N	PN	N	Low
Larsen et al. (2017)	N	N	N	N	N	Low
McElroy et al. (2024)	N	N	N	N/A	N/A	Low
Whicher et al. (2020)	N	N	N	N/A	N/A	Low

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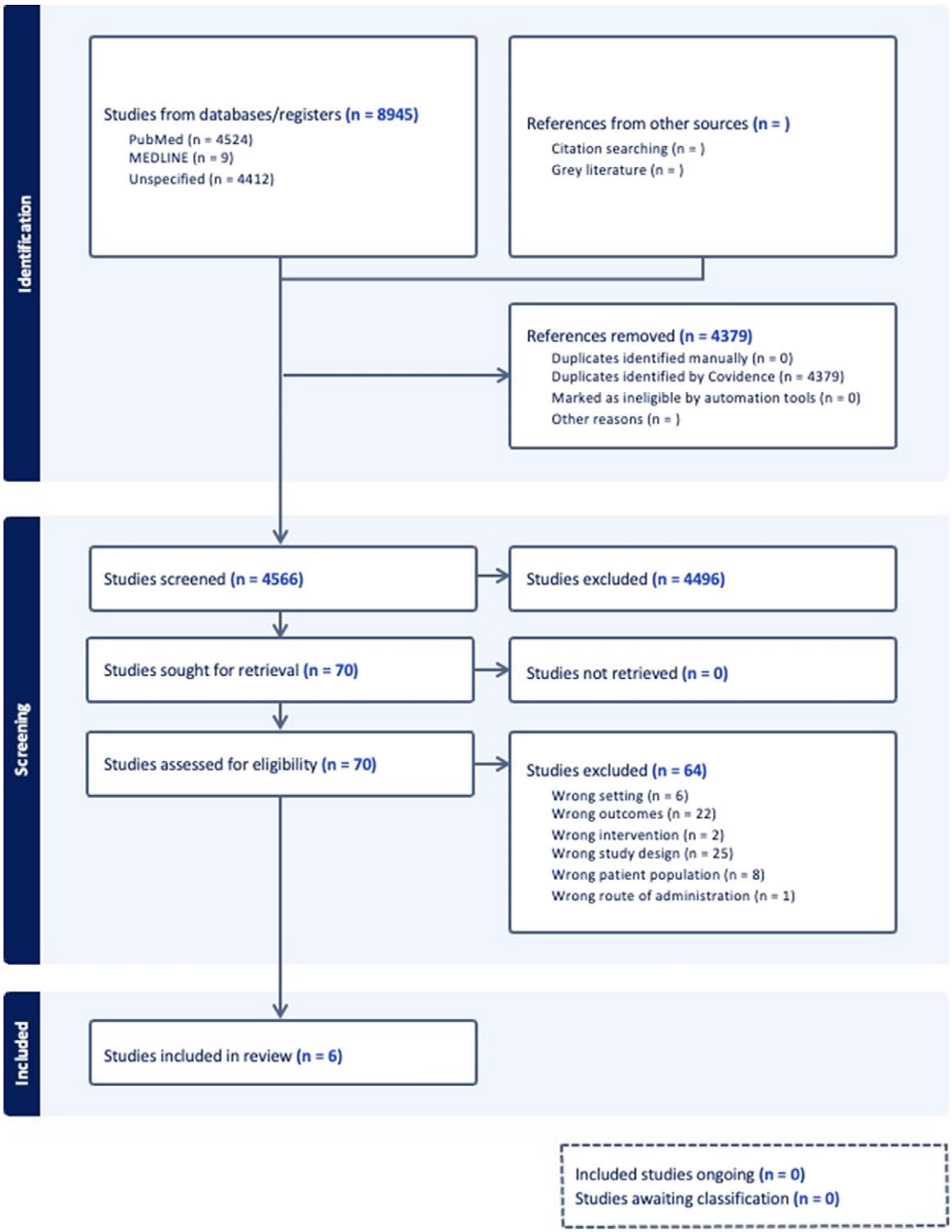
Figure 1. PRISMA Flow Diagram



Synthesis

A summary of the characteristics and results of the six included RCTs is displayed in Table 2 and Table 3. All participants undergoing treatment were either obese, prediabetic, or diagnosed with diabetes mellitus (DM). Additionally, the participants were either diagnosed with a schizophrenia spectrum disorder or bipolar disorder.

Literature findings

Weight change

There were convergent results across six studies reporting significant weight reduction with GLP-1RA treatment in persons with PDWG. Patients administered GLP-1RAs experienced average weight losses ranging from 3.0 to 5.3 kg, highlighting the potential of these agents to counteract the weight gain typically induced by

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Table 2. Included Study Characteristics and Results

Primary study	Subjects	Patient criteria	Medication	Duration	Treatment outcome	Significance
Ishøy et al.	Treatment (n=20) Placebo control (n=20)	Antipsychotic-treated, obese, nondiabetic, schizophrenia-spectrum patients	Exenatide 2 mg subcutaneous injection once weekly	3 mo	Body weight reduction following intervention was 2.2 ± 3.3 kg for the treatment group and 2.2 ± 4.4 kg for the placebo group	No significant difference in body weight reduction between the treatment and control groups
Maagensen et al.	Treatment (n=35) Placebo control (n=37)	Patients with schizophrenia or psychosis treated with clozapine or olanzapine, having prediabetes and a body mass index above 27 kg/m^2	Liraglutide (up-titrated by 0.6 mg per week to a daily dose of 1.8 mg)	16 wk	No specific data regarding weight loss is provided	No significant difference in body weight for individuals treated with liraglutide
Siskind et al.	Treatment (n=14) Usual care control (n=14)	A clinical diagnosis of schizophrenia or schizoaffective disorder; taking oral clozapine for >18 wk; stable body weight (<5 kg change in weight over the 3 mo before inclusion); BMI between 30 and 45 kg/m^2. Arm A: people with stable T2DM; Arm B: no T2DM.	Weekly subcutaneous injection of 2 mg exenatide	24 wk	By week 24, the mean body weight change of −5.29 kg in the treatment group and −1.12 kg in the usual care group	Participants using exenatide had a higher rate of weight loss and greater absolute weight loss than the usual care group; weight loss was clinically significant
Larsen et al.	Treatment (n=47) Placebo control (n=50)	Patients with schizophrenia spectrum disorders treated with clozapine or olanzapine; had prediabetes	Subcutaneous injection of once-daily subcutaneous liraglutide up-titrated to 1.8 mg	16 wk	At week 16, the mean weight loss for the treatment group was −4.7 kg for the treatment group, and −0.5 kg for the placebo group	Significantly more weight loss for the treatment group compared to the placebo group
McElroy et al.	Treatment (n=29) Placebo control (n=31)	Patients with stable bipolar disorder who were obese	Daily subcutaneous liraglutide (up to 3.0 mg)	40 wk	The overall mean change in body weight for the treatment group was −3.7 kg for the treatment and 0.0 kg for the placebo group	Participants receiving liraglutide had a significantly greater reduction in body weight than those receiving placebo
Whicher et al.	Treatment (n=15) Placebo control (n=19)	Adults with schizophrenia or first-episode psychosis prescribed antipsychotic medication who were overweight or obese	Once-daily subcutaneous liraglutide titrated to 3.0 mg	6 mo	From baseline to 6 mo, the mean change in body weight was −5.7 ± 7.9 for the treatment group and 0.3 ± 5.7 for the placebo group	Significant body weight reduction for participants in the treatment group

antipsychotic medications[6,19–22]. Wang et al. (2023) reported that participants administered subcutaneous exenatide reported an overall mean change in body weight of −5.29 kg[16]. In addition, the mean weight loss of participants taking subcutaneous liraglutide was found to be 5.3 kg more than those in the placebo group[20]. Similarly, McElroy et al. (2024) reported that persons administered subcutaneous liraglutide demonstrated a −3.7 kg mean change in body weight. Moreover, in a separate study by Whicher et al. (2021), it was observed that 53% of participants administered liraglutide experienced an overall weight change of ≥ 5% ($p = 0.015$).

In addition, notable improvements in metabolic parameters, such as fasting plasma glucose levels dropping by up to 1.2 mmol/L and HbA1c decreasing by approximately 0.6% was reported in studies focused on prediabetic persons[17,20]. More specifically, these metabolic benefits are especially critical for patients at an increased

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Table 3. Additional study characteristics

Primary study	Country	Exclude persons with DM or not	Concurrent psychotropic medications	Post-intervention follow-up period	Dropout rate	Reasons for dropout
Ishøy et al.	Denmark	Exclude DM	Mostly atypical psychotropic medications, only one typical psychotropic in each group	0	Tx group: three dropouts Control group: two dropouts	Two due to GI side effects in the tx group (2/20) One due to dissatisfaction of GI effect
Maagensen et al.	Denmark	With prediabetes	Clozapine and/or olanzapine	0	N/A	N/A
Siskind et al.	Australia	Not specified	Clozapine	12 mo following the completion of trial	N/A Only 1 lost in follow-up	Due to discharge from health service
Larsen et al.	Denmark	With prediabetes	Clozapine or olanzapine	0	Seven patients (6.85)	One participant, a man in his 60s with a long duration of schizophrenia, died unexpectedly after 3 d of acute illness. No causal relationship to treatment with liraglutide.
McElroy et al.	US	Not specified	Antipsychotic, antidepressant, mood stabilizer	1 wk	More placebo recipients (n=11) than liraglutide (n=3) stopped the study medication for an adverse effect (p=0.02)	For the tx group, liraglutide stopped because of gastrointestinal issues (n=1), mood dysregulation (n=1), and suicidal ideation (n=1).
Whicher et al.	UK	Not specified	Mixed, mostly antipsychotic	0	Two participants in the intervention arm were unable to titrate to the maximum dose of liraglutide. One reached a max. tolerated dose of 1.2 mg daily and the other 2.4 mg daily.	

risk of diabetes and cardiovascular diseases. Only one study reported a post-intervention follow-up period of the weight effect over a 12-month period upon completion of the trial[19]. The other studies did not include the post-intervention follow-up periods so we are unable to conclude on the sustained effects of GLP-1 use on weight on PDWG.

Comparison of exenatide and liraglutide in treating PDWG

All studies reported on the effects of exenatide or liraglutide on PDWG, and both have demonstrated significant efficacy in promoting weight loss. However, their effectiveness and application vary across different populations, presenting distinct clinical implications. The specific evaluation of the use of exenatide in obese adults with schizophrenia treated with olanzapine and/or clozapine found an average weight loss of 5.29 kg, significantly more than the 1.12 kg loss in the usual care group[19]. This is a substantial reduction in BMI by 1.78 kg/m² and improvements in fasting glucose levels and HbA1c. These findings underscore exenatide's specific utility in mitigating the challenging metabolic side effects of antipsychotic medications in patients with schizophrenia who are treated with olanzapine and/or clozapine.

In contrast, investigations of daily liraglutide 3.0 mg in a broader population of overweight and obese individuals demonstrated a higher average weight loss of around 8–10% of initial body weight[22]. Liraglutide demonstrated sustained efficacy over 6 months, with significant reductions in BMI and improvements in lipid profiles, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, while increasing high-density lipoprotein (HDL) cholesterol levels. This broader applicability suggests liraglutide may offer more pronounced weight reduction benefits compared to exenatide, particularly in patients with generalized obesity and associated cardiovascular risks. For instance, an obese patient without psychiatric comorbidities but with a high cardiovascular risk profile might find liraglutide's comprehensive metabolic benefits more advantageous.

Effect on metabolic parameters

In addition to mitigating and weight-lowering effects of GLP-1 RAs, beneficial effects on metabolic parameters have also been reported. For example, a mean reduction of 3.2 cm in waist circumference and a reduction in BMI of 1.4 kg/m² was reported in one of the included studies. Improvements in lipid profiles were also noted, with reductions in total cholesterol, LDL cholesterol, and triglycerides, alongside increases in HDL cholesterol levels. Specifically, a reduction in total cholesterol by 0.5 mmol/L, LDL cholesterol by 0.4 mmol/L, and triglycerides by 0.6 mmol/L, coupled with an HDL increase of 0.3 mmol/L[20]. All studies demonstrated similar findings, showing comparable lipid profile

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improvements, thus suggesting that GLP-1RAs facilitate weight loss and contribute to broader cardiovascular health, which is particularly relevant for patients susceptible to metabolic syndrome. These findings are in accordance with the studies conducted in nonpsychiatric populations, for example, non-insulin-dependent DM.

Safety and tolerability

Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were the most common adverse events, generally mild to moderate in severity and diminishing over time[22]. Importantly, no severe adverse events were linked to GLP-1RAs, and the dropout rates were similar between the treatment and placebo groups (see Table 3). In addition to the aforementioned treatment-emergent profile, there is no evidence that GLP-1RAs engender or amplify any dimension of psychopathology. Reports of suicidality associated with GLP-1RAs have been thoroughly evaluated, and no cause and effect has been established[16,24]. In addition, preliminary findings suggest that GLP-1RAs may prevent and treat aspects of psychopathology, including cognitive impairment and mood-related symptoms[25,26,27].

Discussion

Taken together, the results of our analysis indicate that GLP-1RAs can meaningfully improve anthropometric and metabolic measures in persons experiencing PDWG. The outcome measures of interest are replicated, robust, and clinically meaningful, providing preliminary empirical support for these agents in the treatment and prevention of PDWG. Persons with mental disorders are differentially affected by obesity and metabolic comorbidity, which would provide separate and independent justification for the use of these agents[3,4]. Considering the heightened risk of obesity and metabolic comorbidities among those with mental disorders, there is a compelling, independent justification for employing these agents where indicated to primarily target obesity and/or comorbid T2DM. Although our primary focus has been on weight gain, a more systematic evaluation of GLP-1RAs would be beneficial, not only concerning body weight but also in addressing related conditions like metabolic syndrome, dyslipidemia, diabetes, nonalcoholic fatty liver disease, and cardiovascular disease. This broader perspective could provide a more comprehensive understanding of the therapeutic potential of GLP-1RAs.

The results of our analysis need to be interpreted with several limitations with respect to the methodology and extant literature. First, it is important to note that although the data generally suggest that the use of GLP-1RAs is beneficial in mitigating PDWG, the current data are mixed, and a portion of the studies are not placebo-controlled. Overall, three of the reviewed studies where patients were blinded to their treatment and one study without blinding showed a benefit of using GLP-1RAs to mitigate PDWG[19–22]. Conversely, two studies reported no significant benefit of using GLP-1RAs for body weight reduction[17,18]. Additionally, significant heterogeneity across the studies concerning patient demographics, illness characteristics, comorbidities, and treatment regimens presents a challenge. For instance, variations in baseline anthropometric and metabolic status and the presence of other health conditions could have influenced the outcomes, affecting the generalizability of the findings. The psychotropic medications prescribed in the extant studies included were also not uniform and the results reported may not apply to other psychotropic regimens. Moreover, within class (eg, antipsychotics), there is a gradient of liability for weight change; hence, no statements regarding specific mitigating capability can be made with GLP-1RAs for any particular agent. Additionally, the duration of the studies varied considerably, with some extending several months in duration, limiting the observation of long-term effects and potential side effects of GLP-1RAs. Only one study had a post-intervention follow-up, which allows the observation of the sustained effect of GLP-1[19]. Another critical limitation is the diversity in the types of GLP-1RAs used and the dosages administered, which may affect both efficacy and safety findings with GLP-1RAs in the psychiatric population.

Although the studies generally reported favorable tolerability profiles for GLP-1RAs, they primarily focused on short-term adverse events, such as gastrointestinal symptoms, with inadequate characterization of long-term tolerability. Although reports appear of an association between GLP-1RAs and suicidality, reports from the US FDA and European Medicines Agency have concluded that no causality exists[10,28,29].

With respect to clinical translation, an initial strategy for a person experiencing PDWG for consideration would be switching to medications with a lower propensity for weight gain. In addition to behavioral modification and dietary change, the use of adjunctive metformin can be considered. Evidence indicates that metformin has a larger effect size for weight mitigation when used in a primary prevention paradigm when compared to a secondary prevention paradigm[1]. GLP-1RAs should be considered in any person wherein the use would be indicated insofar as they have obesity and/or T2DM. More narrowly, GLP-1RAs could also be considered as potential treatment avenues in persons experiencing PDWG. It is separately noted that GLP-1RAs benefit other comorbidities known to differentially affect persons with serious mental illness (eg, cardiovascular disease, metabolic dysfunction associated with steatotic liver disease)[1]. Future research vistas include but are not limited to ascertaining whether GLP-1RAs also benefit dimensions of psychopathology, including cognitive impairment, reward behaviour and mood dysregulation[27,30].

Conclusion

Our results indicate that substantial and clinically meaningful effects of GLP-1RAs on weight and associated metabolic parameters is observed in persons with mental disorders receiving these agents either specifically to mitigate PDWG and/or contemporaneous therapeutic targeting of obesity as well as metabolic parameters. In addition to their benefit across weight and metabolic parameters, these agents are well-tolerated and safe with no identified serious safety concerns. Future research vistas include adequate well-controlled studies with GLP-1RAs in psychiatric populations evaluating obesity, metabolic and safety outcomes (e.g., suicidality)[31,24].

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