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Review

Pharmacological management of diabetes in severe mental illness: A comprehensive clinical review of efficacy, safety and tolerability

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Abstract

Introduction: The increased prevalence of Type 2 diabetes mellitus (T2DM) in severe mental illness (SMI) contributes to increased cardiovascular morbidity and reduced life expectancy for people with SMI.

Areas covered: In the present clinical review, we summarize the efficacy, safety and tolerability of selected diabetic pharmacotherapy options in SMI and discuss the quality and strength of evidence.

Expert commentary: General principles for treating T2DM in SMI involve identifying treatments which promote weight loss and which have low or no risk of hypoglycemia. Patient engagement in decision making about treatment choices is an important factor to ensure adherence and successful use of the chosen therapy. The first line therapeutic option for T2DM in SMI for which there is most evidence is metformin. Based on general population data, second line treatment options in combination with metformin to achieve glycated haemoglobin treatment goals include GLP-1R agonists, DPP-4 inhibitors, sulphonylureas, SGLT2 inhibitors, pioglitazone and insulin, with most evidence for the use of GLP-1R agonists in SMI. Alongside efficacy and tolerability, treatment for T2DM in SMI should be considered on a patient-tailored basis.

Keywords: schizophrenia; psychosis; antipsychotics; metformin; GLP-1R agonists

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Introduction

Severe mental illnesses (SMIs) are associated with increased rates of cardiovascular disease and associated excess premature death [1,2], which translates to a 15 to 20 year shortened life expectancy for those with SMIs compared to the general population [3,4]. Higher rates of modifiable cardiovascular risk factors are seen in SMI, with 33-57% of patients with SMI (i.e. schizophrenia, schizoaffective disorder, bipolar affective disorder) meeting the criteria for metabolic syndrome throughout the course of the illness [5-7].

Most antipsychotics have the potential to cause weight gain, and increase the risk of type 2 diabetes mellitus (T2DM) [8]. Clozapine and olanzapine, which have the greatest affinity for 5-HT2C and Histamine (H)1 receptors[9], have the greatest weight gain potential, which can occur early in the course of treatment [10-12], before plateauing as treatment continues[13]. The most dramatic weight gain is seen in antipsychotic naïve patients over the first six weeks of treatment and the majority of those with initial weight gain do not lose that weight thereafter, even on switching to more weight neutral antipsychotics [10]. Second generation antipsychotics (SGAs) such as aripiprazole, amisulpride, lurasidone and asenapine, have a more neutral metabolic side effect profile [10,14,15].

People with schizophrenia and their families have a higher risk of T2DM than the general population, indicative of a genetic liability [16-19]. A comparative meta-analysis established that people with SMI (n=133,470) are significantly more likely to have T2DM than matched controls (n=5,622,664; relative risk=1.85; 95%CI=1.45-2.37) [14]. T2DM prevalence is consistently elevated in each of the three major diagnostic subgroups (schizophrenia, schizoaffective disorder and bipolar affective disorder) compared to matched controls [14], especially in males (RR=1.43; 95% CI=1.20 to 1.69, p<0.001). Antipsychotic medication (please see table 1), in particular certain SGAs, duration of antipsychotic use and polypharmacy all contribute to a heightened risk of T2DM [14,20,21]. Clozapine, in particular, has a rapid effect with 55% developing glucose dysregulation within 3 months of starting, independent of weight gain [22]. There is preclinical evidence of olanzapine having

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acute, direct effects on glucose homeostasis, with rapid onset of glucose intolerance and increased insulin resistance, which can be reversed by antidiabetic medications [23]. Meta-analysis of atypical antipsychotic trials in healthy volunteers provides evidence of decreased insulin sensitivity and associated increased insulin resistance occurring independent of SMI, and as a direct and early consequence of atypical antipsychotics[24]. For people with SMI who have an increased endogenous risk for glucose dysregulation, this is further exacerbated with the use of antipsychotic medication[25].

Four percent of patients with first episode psychosis (FEP) have T2DM, with rates of 2.9% seen in antipsychotic naïve FEP patients and 11% in established multi-episode psychotic disorders [14]. In a multi-episode psychosis cohort, 20% met criteria for T2DM, with a further 30% having evidence of glucose dysregulation [7]. In the meta-analysis of Vancampfort et al, all individual antipsychotics, except for aripiprazole and amisulpride, had significantly higher T2DM risk compared to antipsychotic-naïve participants [14].

Lifestyle factors such as increased prevalence of cigarette smoking[7,26], high levels of sedentary behaviour and physical inactivity [27-30], poor diet [31] and suboptimal vitamin D levels[32-34] in psychotic disorders further increase the risk of T2DM, cardiovascular disease and premature mortality [35,36]. Antipsychotic naïve patients have elevated levels of insulin resistance and hypertriglyceridaemia, prior to the use of antipsychotic medication [37,38], indicating that people with psychotic disorders carry an inherent increased risk for T2DM which is further exacerbated by the interplay with other risk factors. However, a recent GWAS study with Mendelian randomisation found no evidence of a causal relationship between schizophrenia and diabetes, indicating that lifestyle and environmental changes may be key [39]. The study findings adds to inconclusive GWAS findings in diabetes and schizophrenia[40] and contrasts with gene association studies identifying several shared genes between both disorder[41-43]. The inconsistency between epidemiological data and gene association studies which have indicated a shared genetic risk between T2DM and schizophrenia, and inconclusive GWAS findings will require additional research to account for the discrepancy.

INSERT table 1 here

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Patients on long term antipsychotics should receive regular monitoring of cardiometabolic parameters and evidenced based interventions for glucose dysregulation as well as for dyslipidemia and hypertension. However, studies continue to demonstrate the suboptimal use of pharmacotherapy for T2DM in SMI. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study identified that 30% of patients with schizophrenia and T2DM were not receiving treatment for T2DM[44]. A later cross sectional study found that only 60% of those with schizophrenia and T2DM received diabetic pharmacotherapy [45]. In a UK National Audit of 5091 people with SMI, only 53.5% were in receipt of treatment (defined in the broadest sense, advise on diet and exercise or prescription for diabetic medication) for “high glucose levels”[46]. The UK National Audit of Schizophrenia identified in a review of mental health case records that only 36% of patients with evidence of glucose dysregulation had received a lifestyle intervention or diabetic medication [47].

Given the cardiometabolic side effect burden, there is a need for awareness that all patients treated with antipsychotics require screening and monitoring for cardiometabolic risk, including T2DM and that they may benefit from both pharmacological and non-pharmacological interventions for weight loss. Prevention and pharmacotherapeutic interventions for T2DM is an important aspect of the treatment of psychotic disorders.

2. Aims

In this present clinical review, we aim to summarise the published efficacy and tolerability of pharmacotherapeutic interventions in T2DM in SMI, focusing on glucose lowering therapies. The use of other methods for glucose lowering such as antipsychotic switching and lifestyle modification [48,49] have been previously reviewed and will not be covered in our review

3. Management of type 2 diabetes mellitus (T2DM)

3.1 Treatment goals

Glycated haemoglobin, (HbA1c) offers the utility to assess, diagnose and monitor T2DM in patients with established SMI, negating the need for a fasting plasma

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sample, although fasting samples are preferred on initiation of antipsychotics because of the risk of an idiosyncratic rapid dysregulation of glucose metabolism[22]. Generally, the goal for diabetic therapy is to lower glucose levels to attain an HbA1c of <7.0% (48mmol/mol) [50,51] with no complications and a relatively long life expectancy. The use of less stringent HbA1c targets may be required for example in the elderly patient with significant cardiovascular morbidity, where hypoglycaemia may result in significant morbidity. Also, for the patient who does not adhere to the diabetic treatment regimen, where non-compliance with clinical care occurs- a strict HbA1c target may not be appropriate, it may be difficult to attain with standard

Box 1: **Laboratory diagnosis of diabetes**

A diagnosis of diabetes can be made on the basis of any of the following laboratory values

- Fasting blood glucose (on two separate days) ≥7 mmol/L (126 mg/dl)
- Random plasma glucose ≥ 11·1 mmol/L (200 mg/dl) + Symptoms
- Haemoglobin A1c≥6·5% (48mmol/mol)
- Oral glucose tolerance test ≥2 h plasma glucose ≥11·1 mmol/L (200 mg/dL)

approaches, and flexibility in defining HbA1c target thresholds is required. This is the status for some with SMI and a diagnosis of T2DM. The diagnostic criteria for T2DM are shown in box 1.

3.2 Treatment algorithms (see Figure 1)

If a person meets criteria for T2DM but with a HbA1c close within the target range (<7.0%), then lifestyle modification, with dietary and exercise advice is recommended, with a view to rechecking HbA1c in 3-6 months, before considering the need for diabetes pharmacotherapy [52,53]. A recent meta-analysis demonstrated that lifestyle interventions are effective in improving glycaemic control in people with diabetes and SMI[48].

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The first line pharmacological intervention is to treat with metformin monotherapy in addition to lifestyle modification. If HbA1c concentrations are poorly controlled for 3 months or longer, despite treatment with a single drug (usually considered to be a rise of HbA1c to 58 mmol/mol (7.5 %) or higher), drug treatment should be intensified, alongside reinforcement of advice regarding diet, lifestyle, and adherence to drug treatment.

For first line treatment with metformin, a target HbA1c concentration of 6.5 % (48 mmol/mol) is recommended by some T2DM treatment guidelines in SMI [54]. This mirrors general population guidelines [53,55]. However, it is important to consider target HbA1c levels at the patient level, and adjust as appropriate to less stringent thresholds, such as 7.0% (53mmol/mol) for those with significant comorbidities or who are at heightened risk of hypoglycaemia and complications from same [50]. For patients with SMI, who may have increased difficulties in applying and adhering with diabetes self-management, and appropriate glucose monitoring, then a sensible recommendation would be to follow the target HbA1c threshold <7.0% (53mmol/mol) as recommended by the American Diabetes Association (ADA) [50].

3.3 Optimising glycaemic control

In the general population second line therapy recommendations involve the combination of metformin with a Dipeptidyl peptidase-4 (DPP-4) inhibitor, metformin and a sulfonylurea, metformin and a Sodium glucose transporter 2 (SGLT2) inhibitor, metformin and a glucagon-like peptide-1 receptor (GLP1R)-agonist, or metformin and insulin, with ongoing support of the patient to aim for an HbA1c level of < 7.0% (53mmol/mol). Please see figure 1.
For combination /second line therapy, an HbA1c concentration target of 53 mmol/mol (7.0 %) is recommended. However, if this degree of glycaemic control is deemed to be inappropriate in a person with SMI, due to concerns regarding hypoglycaemia, then following multidisciplinary team discussion and consideration of capacity issues, a less stringent HbA1c threshold may be chosen. Less stringent HbA1c goals (such as <8% (64 mmol/mol)) may be appropriate for patients with a history of severe hypoglycemia, extensive comorbid conditions, or diabetes where the goal is difficult to achieve due to patient difficulties in applying and adhering with diabetes self-management, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agent.

Insert figure 1 here adapted from Inzucchi et al 2015 [56]

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4. Treatment of type 2 diabetes mellitus in severe mental illness

4.1 Pharmacotherapy for T2DM in SMI

The overriding emphasis is that people with SMI and comorbid T2DM should be managed in line with diabetes treatment guidelines used in the general population, as set forth by the ADA [50], International Diabetes Federation[57], American association of clinical endocrinologists [55] and the National Institute of Clinical Excellence [53]. The comprehensive care required to prevent microvascular and macrovascular complications of diabetes requires a combination of lifestyle interventions, education programs and pharmacological treatments delivered across the healthcare spectrum ranging from the individual, and his or her family to primary and secondary care delivery services. In this review we will discuss selected treatment strategies for glycemic control in T2DM in SMI. We will focus on pharmacological treatments used to manage T2DM in the general population, most of which have little trial exposure in SMI populations. Support for this approach is emphasized in a recent meta-analysis of 10 studies reporting data from 33,910 people with schizophrenia and T2DM which found that people with schizophrenia adhered to diabetic medication on 77.3% of days prescribed (n=32080, 95%CI=73.6-81%, I^2=99.2%,), and adhered on 4.6% more days per year than those without schizophrenia (p<0.01, 95%CI=2.4-6.7%, I^2=92.5%, schizophrenia n=19367, controls=170,853) [58].

4.2 Meta-analysis of treatment of T2DM in SMI

A recent meta-analysis of the clinical effectiveness of pharmacological (and non-pharmacological interventions) for improving glycaemic control in people with SMI identified that pharmacological interventions (mean difference (MD), -0.11mmol/L; 95% confidence interval (CI), [-0.19, -0.02], p = 0.02, n = 2536) were effective in lowering fasting glucose, but not HbA1c (pharmacological MD, -0.03%; 95% CI, [-0.12, 0.06], p = 0.52, n = 1515 compared with usual care or placebo[48]. In a subgroup analysis, only sufficient studies to assess the effectiveness of metformin and antipsychotic switching were available, with both strategies found to improve HbA1c (metformin: MD = -0.08; 95% CI, [-0.14, -0.03]; p = 0.004; I^2 = 0% ;antipsychotic switching: MD = -0.11%; 95% CI, [-0.18, -0.05]; p = 0.001; I^2 = 0%), and metformin alone: MD = -0.15mmol/L; 95% CI, [-0.29, -0.01]; p = 0.04; I^2 = 51%) and with metformin alone improving fasting glucose levels(MD = -0.15mmol/L; 95%

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CI, [-0.29, -0.01]; p = 0.04; I2 = 51%), compared to placebo or control, though with modest effect sizes [48]. This replicated previous meta-analysis supporting the effectiveness of metformin in improving glycaemic control in SMI, with statistically significant improvements in fasting glucose for metformin (MD = -0.18mmol/L; 95% CI, [-0.35, 0.00]; n = 9 studies; I^2 = 73%); and in HbA_{1c} (MD = -0.08%; 95% CI, [-0.13, -0.03]; n = 3 studies; I^2 = 0%)[59]. This meta-analysis also identified improvements in HbA1c with adjunctive aripiprazole (MD = -0.65%; 95% CI, [-1.25, -0.06]; n = 2 studies; I^2 = 89%). Both reviews identified only modest improvements in reported HbA1c and fasting glucose with individual pharmacological interventions.

4.3 Antidiabetic medication selection in SMI

General principles for treating T2DM in SMI involve identifying treatments which promote weight loss and which have low or no risk of hypoglycemia. Patient engagement in decision making about treatment choices is important to help with adherence and the success of the chosen therapy.

Obesity is common in people with SMI, with rates of 50% identified, and 83% with central obesity (327/396), with a particular high rate in females (95% (160/169)) [7], so choosing medications which aid weight loss or are weight neutral is preferable. These include metformin, incretins such as glucagon-like peptide-1 receptor (GLP-1R) agonists, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) agents [52,60]. Sulfonylureas, thiazolidinediones and insulin based therapies are associated with increased weight gain [60] compared to other diabetic pharmacotherapies, and logically, although not subjected to meta-analysis, may not be ideal choices for early use in this population.

In SMI, the selection of medications should also be guided by risk for hypoglycaemia. For people with psychotic illnesses, several factors place them at increased risk of complications due to hypoglycaemia. The interplay of active psychotic symptoms, cognitive deficits, mood episodes and social factors all may increase the risk to the person if hypoglycaemic episodes were to occur, or may reduce their ability to identify early hypoglycaemic signs. Hence, agents with a low risk for hypoglycaemia such as GLP-1R agonists, DPP-4 inhibitors and the newest SGLT2 inhibitors are preferred choices for second line therapies in SMI. Sulfonylureas and insulin are associated with an increased risk of hypoglycaemia, and increased need for more frequent glucose monitoring, potentially reducing utility and acceptability.

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5. Diabetic medications

The recommended doses of diabetic medication are shown in table 2.

Insert table 2 here

5.1 Metformin

Metformin is a biguanide which increases insulin sensitivity, reduces hepatic synthesis and release of glucose, and increases glucose uptake by muscles. Metformin reduces both basal and post prandial glucose levels. Metformin is recommended as the first line treatment for T2DM in all national and international guidelines.

Metformin is generally well tolerated. If persistent hyperglycaemia, metformin may be titrated over 2-3 weeks to reduce the risk of nausea and vomiting (affecting approximately 10-20%). If poorly tolerated, then the long acting formulation may be considered to reduce the occurrence of nausea and vomiting, though this is rarely used in clinical practice. Metformin is typically commenced at 500 mg bd and titrated every 8-12 weeks to a dose of 1000mg twice daily, based on glycaemic control. Periods of 2 months [50] and 3-6 months[53] have been recommended to assess the effect of metformin in improving glycaemic control . Please see table 2 for recommended medication doses in T2DM.

In those at risk of diabetes in the general population, a meta-analysis showed that metformin was associated with a 40% reduction in the risk of developing T2DM over a mean follow up period of 1.8 years [61]. In T2DM in the general population, metformin use is associated with lower risk for cardiovascular mortality compared with sulfonylureas [60].

5.2 Adverse events

Metformin was first introduced into clinical practice in Europe in the 1950s, but only obtained a licence for use in USA in 1995. Historically, the use of metformin was somewhat limited due to concerns regarding the development of lactic acidosis,

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though recent evidence from a systematic review of observational studies has shown that the risk is not increased with metformin use in those with mild or moderate renal impairment, compared to those with T2DM and not treated with metformin [62]. Metformin is contraindicated in those with severe renal impairment (estimated glomerular filtration rate <30 ml/min/1.73m^2), hepatic failure and heart failure due to the risk of lactic acidosis. For SMI patients with mild (eGFR 45-59 ml/min/1.73m^2) or moderate (eGFR 30-44 ml/min/1.73m^2) renal impairment , a more gradual dose titration and possible use of a lower maximum dose might increase safety in these patients [62] A baseline renal function assessment is recommended, and 6 monthly or annual renal function measures can be taken with cardiometabolic blood markers. The long-term use of metformin has been associated with 2.45 increased odds ratio of developing vitamin B12 deficiency compared to non-metformin treated comparators [63]. Vitamin B12 deficiency secondary to metformin use is associated with neuropathy [64], and should be treated with supplementation.

5.3 Metformin in SMI

Metformin should be considered as the first line treatment for T2DM in SMI, as it is well tolerated, inexpensive and HbA1c reductions of 1% to 2% can be expected with monotherapy [50]. In perhaps the best designed study of metformin use to treat T2DM in SMI, a double blind study of 148 overweight (BMI ≥27kg/m^2) people with SMI showed that metformin titrated to 1000mg daily was associated with mild mean reduction in HbA1c levels (-0.07%; 95% CI=-0.14 to -0.004), and a mean reduction in weight of -2.0 kg (95% CI=-3.4 to -0.6) compared to placebo over a 16 week trial period [65].

Additionally, metformin has been shown to attenuate weight gain in antipsychotic treated patients [59,65-68], with an approximate weight loss of 3kg compared to placebo [54]. In T2DM in the general population, metformin has been shown to reduce the transition from pre diabetes (defined as a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/l or an HbA1c level of 6.0-6.4% (42– 47 mmol/mol) [69]) to T2DM [70,71]. Metformin is used in clinical practice to delay or prevent the progression to T2DM in those with pre diabetes and SMI (especially in those treated with clozapine and olanzapine, both antipsychotics with an increased risk of glucose dysregulation)-though as of yet, this recommendation is based on trial data in the general population [69,70]. There is no placebo controlled trial data of metformin use in SMI to prevent or delay the onset of T2DM in patients with pre diabetes.

5.4 Combination therapies

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For those who fail to have adequate glycaemic control with metformin, the next step in SMI may be the use of either incretin-based therapy glucagon-like peptide 1 receptor (GLP1-R) agonists or dipeptidyl peptidase 4 (DPP4) inhibitors, sulphonylureas or sodium glucose transporter 2 (SGLT2) inhibition agents. The approach to consider GLP-1R agonists as a second line diabetic treatment is recommended by the American Association of Clinical Endocrinologists in the general population [72].

5.5 Incretins

These include injectable GLP1-R agonists and DPP4 inhibitors. GLP1-R agonists increase glucose-dependent insulin secretion and have a low risk of hypoglycemia, and are associated with weight loss. GLP is a gut produced incretin hormone which is secreted in response to food intake [73]. It stimulates the release of insulin, reduces glucagon release and delays gastric emptying. DPP4 is an enzyme which breaks down GLP, thus limiting its action[73].

5.6 GLP-1R agonists

GLP-1R agonists (exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide) act by increasing insulin secretion in response to glucose loads, decreasing glucagon secretion and delaying gastric emptying and increasing satiety. The GLP-1R agonists are administered as subcutaneous injections and are available in short acting or extend release formulations (e.g. Exenatide weekly administration), potentially improving adherence and patient acceptability[74]. Exenatide exists in two formulations: twice daily (Byetta®) and once weekly (Bydureon®, Eli Lilly and Company, Indianapolis, Indiana, USA). Liraglutide (Victoza®, Novo Nordisk A/S, Bagsvaerd, Denmark) is administered once daily. Dulaglutide (Trulicity®) is administered as a once weekly subcutaneous injection.

GLP-1R agonists are recommended as second line therapies in the general population by the American Diabetes Association (ADA) [50] and the American Association of Clinical Endocrinologists [55,72] . In the UK, they are recommended to be “used in patients with a BMI $\geq$ 35 kg/m^2 and with specific psychological or medical problems associated with obesity; **or** for those who have a BMI lower than 35 kg/m^2 but for whom insulin therapy would have significant occupational implications **or** if the weight loss associated with glucagon-like peptide-1 receptor agonists would benefit other significant obesity-related comorbidities”[75,76]. This

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specific restriction on their use relates to the higher costs, and cost effectiveness of GLP-1R agonists compared to other antidiabetic agents[76]. This analysis was based on their being more cost effective in comparison with insulin glargine in patients with BMI > 33 or 35 kg/m^2 , wherein they have an association with a higher degree of weight loss compared to insulin[77,78]. In SMI, this needs to be weighed against their ability to improve glycaemic control, with little risk of hypoglycaemia, and to reduce weight. Further, their administration technique and dose scheduling may improve adherence and acceptability, making them applicable for consideration in SMI as second line treatments.

5.7 GLP-1R agonists, administration and benefits in SMI

The potential for weight loss (average weight loss of 3 to 4.5 kg) and low risk of hypoglycaemia seen in general population samples with the use of GLP-1R agonists such as exenatide and liraglutide make them attractive options for the treatment of T2DM in SMI[73,79-81].

Exenatide is administered twice daily within one hour of morning and evening meals, while the extended release formulation is administered once weekly (2mg dose weekly). Liraglutide is administered subcutaneously once daily, and due to its intermediate half-life and delayed time to effect compared to exenatide, can be administered at any time. Liraglutide and exenatide are associated with mean reductions in HbA1c of 0.8%-1.8% [79,82-86]. Extended release exenatide is a once weekly subcutaneous injection, and has been associated with mean reductions in HbA1c of 1.0%-1.8%[86]. In comparator studies, extended release exenatide has been associated with significantly increased reductions in mean HbA1c compared to immediate release twice daily exenatide and once daily liraglutide [86,87]. Exenatide, luraglutide and other GLP-1R agonists are associated with weight loss[88]. Liraglutide has demonstrated dose dependent reductions in body weight, 6.0% (6.4 kg) with liraglutide (3.0-mg dose), 4.7% (5.0 kg) with liraglutide (1.8-mg dose), and 2.0% (2.2 kg) with placebo (estimated difference for liraglutide [3.0 mg] vs placebo, -4.00% [95% CI, -5.10% to -2.90%]; liraglutide [1.8 mg] vs placebo, -2.71% [95% CI, -4.00% to -1.42%]; P < .001 for both), though with increased gastrointestinal side effects with the 3.0mg dose compared 1.8mg and placebo[89].

Dulaglutide is administered as a weekly subcutaneous injection at 0.75 mg (recommended dose as monotherapy) or 1.5 mg (as an add-on therapy). It is the third once weekly GLP-1R formulation, providing improvements in HbA1c of 0.7% to

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1.5%, with 55%–78% of patients attaining HbA1c≤7% and weight loss of 1.3-3.0kg [90]. Dulaglutide monotherapy was more efficacious than metformin in attaining improved glycaemic control (mean difference in HbA1c: Dulaglutide 1.5mg vs metformin -0.22% (-2.4 mmol/mol) and Dulaglutide 0.75mg vs metformin--0.15% (-1.6 mmol/mol) ($p < 0.025$, both comparisons))[91]. Dulaglutide in combination with metformin (0.75mg and 1.5mg weekly) has demonstrated increased efficacy in reducing HbA1c compared to sitagliptin combined with metformin at one year follow up (mean HbA1c changes: Dulaglutide 1.5mg: -1.10 +/- 0.06% (-12.0 +/- 0.7 mmol/mol), Dulaglutide 0.75mg: -0.87 +/- 0.06% (9.5 +/- 0.7 mmol/mol), and Sitagliptin: -0.39 +/- 0.06% (4.3 +/- 0.7 mmol/mol) ($p < 0.001$, both comparisons), with greater weight loss for both doses too in comparison with sitagliptin (dulaglutide 1.5 mg (-3.03 +/- 0.22 kg), dulaglutide 0.75 mg (-2.60 +/- 0.23 kg) compared with sitagliptin (-1.53 +/- 0.22 kg) ($p < 0.001$, both comparisons) [92]. Dulaglutide has shown to lead to greater reductions in HbA1c (1.5mg: -1.51 ± 0.06% (-16.5 ± 0.7 mmol/mol),0.75mg: -1.30 ± 0.06% (-14.2 ± 0.7 mmol/mol), compared to exenatide 10 µg (-0.99 ± 0.06% (-10.8 ± 0.7 mmol/mol) and placebo -0.46 ± 0.08% (-5.0 ± 0.9 mmol/mol) ($p<0.001$) (all treatments in combination with metformin or pioglitazone), at 52 weeks, with lower incidence hypoglycaemia in patients receiving dulaglutide 1.5 mg than in those receiving exenatide [93]. In the AWARD-6 study, at 26 weeks of treatment with liraglutide and dulaglutide there was no significant difference in reductions in HbA1c between the medications [83].

5.8 Adverse events with GLP-1R agonists

They can be associated with nausea and vomiting (in 10-20% of patients) which can last for up to 3 months after initiation [73] and patients should be informed of this side effect. The weight loss effects, and reduced cardiovascular mortality associated with some agents in this class (liraglutide) [94,95] make them attractive options for the treatment of T2DM in SMI. Exenatide requires a dose reduction in severe renal impairment, and though no dose change is required for liraglutide and other GLP-1R agonists, they should be used with caution and with close monitoring of renal function [96,97].

The GLP-1R agonists and DPP4 inhibitors have been reported to be associated with the occurrence of pancreatitis in a small number of patients in clinical trials and post marketing data. However, the results are far from conclusive, with a large meta-analysis of over 1.3 million people finding that observational data does not support the link between GLP-1R agonists and DPP4 inhibitors and pancreatitis [98]. There

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have been mixed reports of associations between exenatide and liraglutide use and pancreatic cancer, though analysis of data by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) indicated that there was insufficient evidence to suggest a causal association between incretin therapies and pancreatic cancer (or pancreatitis)[99]. Animal studies have identified a potential increased risk of thyroid C-cell neoplasms with GLP1 receptor agonists [100], though no association has been identified in trial data [89,101]. The use of GLP1 receptor agonists is contraindicated in those with a personal or family history of medullary thyroid carcinomas or multiple endocrine neoplasia syndrome type 2 [75].

5.9 Evidence base for the use of GLP-1R agonists in SMI

GLP-1R agonists were first shown to reduce clozapine induced weight gain and improve glycaemic control in a schizophrenia patient in a 2013 case report [102].Two randomised controlled trials(RCTs) have published findings on the use of GLP-1R agonists for antipsychotic-associated obesity and glucose tolerance in obese, non-diabetic patients[103,104], and there is one RCT investigating GLP-1R agonists in clozapine-treated patients with either diabetes or obesity[105,106].

The first RCT of antipsychotic-treated, obese, non-diabetic, schizophrenia spectrum patients, comparing once-weekly subcutaneous exenatide 2mg (n = 23) or placebo (n = 22) injections for 3 months identified significant weight loss in both groups [104]. However, there was no significant difference in weight loss between the exenatide (2.24 +/-3.3kg) and placebo groups (2.23+/- 4.4 kg) after 3 months of treatment [104]. This was a naturalistic study cohort of a small number of people with SMIs who were treated with a wide range of antipsychotic medications and some with antipsychotic polypharmacy. The study authors hypothesise that as antipsychotic medications all have dopamine 2 antagonism as a common pharmacodynamic effect, that the weight reducing effects of GLP-1R agonists may be related to dopaminergic signalling, and thus raising the possibility that the benefits of exenatide in SMI may be better matched to patients treated with antipsychotics with relatively low dopaminergic affinity (eg quetiapine, olanzapine or clozapine) [104].

A recent Danish randomized clinical double-blind trial of 214 overweight or obese people with a schizophrenia spectrum disorder treated with olanzapine or clozapine investigated the use of liraglutide to improve cardiometabolic parameters over a 16 week period[103]. The trial findings for 103 people randomized to once-daily subcutaneous injection of liraglutide (upward titration from 0.6mg to 1.8mg

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(maintenance dose) daily) or placebo, demonstrated compelling evidence to support the efficacy of liraglutide versus placebo in improving glucose levels (HbA1c−0.2 (0.04)% vs 0.06 (0.04)%;), reducing prediabetic status (−n=13 (85.7% of liraglutide treated patients with pre-existing prediabetes) vs −6 (40.0% of placebo treated patients,) body weight (decreased by −5.3 kg; 95% CI, −7.0 to −3.7 kg) and low density lipoprotein (LDL) (−15.4 mg/dL; 95% CI, −23.2 to −7.7 mg/dL)[103]. This important study provides fresh impetus to consider the use of GLP-1R agonists as a second line treatment for T2DM in SMI, and potentially as a weight loss agent and in preventing the transition from prediabetes to T2DM in those treated with clozapine or olanzapine.

A smaller randomised, controlled, open-label, pilot trial of 28 clozapine treated patients were treated with once weekly extended release exenatide 2mg or treatment as usual. Compared to usual care those treated with once weekly exenatide had significant reductions in mean weight (-5.29kg vs -1.12kg, p=0.015), BMI (-1.78 vs -0.39 p=0.019), and fasting glucose (-0.34 vs 0.39, p=0.036) and HbA1c (-0.21 vs 0.03, p=0.004) [106]. These early promising findings in SMI will require further trial, and prospective observational data for confirmation and to address the evidence gap on their efficacy, tolerability and acceptability to people with SMI.

No trials of the use of dulaglutide in SMI have yet been conducted, though its once weekly administration and efficacy in improving glycaemic control and aiding weight loss make it a further attractive option for use in SMI.

5.10 Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 inhibitors (e.g. alogliptin, linagliptin, sitagliptin, saxagliptin, and vildagliptin,) maintain endogenous GLP1 concentrations, promoting lower glucose levels, by preventing the DPP4 enzymatic breakdown of GLP[107]. DPP-4 inhibitors have a low risk of hypoglycaemia and are weight neutral. They can be administered once daily, simplifying a patient's medication regimen. They are generally well tolerated and are not associated with gastrointestinal side effects [56].

Trial data with DPP-4 inhibitors in SMI is lacking to date, and efficacy data is extrapolated from general population study data. When combined with metformin they have been associated with reductions in HbA1c of 0.4%-0.8% [108-111].Dose reduction is recommended for DPP4 inhibitors in moderate to severe renal impairment, with the exception of linagliptin for which no dose change is required

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[97]. Saxagliptin has been associated with increased risk of hospitalisation due to heart failure compared to placebo [112], with the risk clustered in the first year of follow up, but not thereafter [113]. Subsequent observational studies have not found evidence of an increased risk of hospitalization for heart failure with DPP-4 inhibitors, including saxagliptin [114,115].

5.11 Sulphonylureas

The use of sulphonylureas is based on trial data in general population samples with T2DM, as trial data is lacking in SMI. Previously, the next step to optimise glycaemic control after an inadequate response to metformin, would be the addition of a sulfonylurea (gliclazide (most commonly used in clinical practice), glibenclamide, glimepiride, glipizide, tolbutamide) to metformin. However, this approach while still valid in terms of effectiveness in reducing fasting glucose levels, may not a preferred option in SMI, due to the risk of hypoglycaemia and weight gain with sulphonylureas [60]. Sulphonylureas as monotherapy and in combination with metformin are associated with an increased risk of hypoglycaemia, though for the non-obese patient with SMI, and with awareness of the risk of hypoglycaemia and diabetes self-monitoring, they may still be considered.

5.12 Sodium glucose transporter 2 (SGLT-2) inhibitors

SGLT-2 inhibitors (e.g. canagliflozin, dapagliflozin, and empagliflozin) are the newest diabetic medications. SGLT-2 inhibitors act via a relatively novel insulin independent mechanism, though inhibition of SGLT2 receptors in the proximal renal tubules to reduce glucose reabsorption by sodium glucose transporter 2 receptors, preventing reabsorption of glucose, and promoting glycosuria. This results in reduction of serum glucose, without the risk of hypoglycaemia [116]. SGLT-2 inhibitors have been associated with average reductions of HbA1C of 0.6%-0.9%[116] and weight loss of approximately 2-3kg in T2DM [117,118]. Empagliflozin reduces the risk of heart failure and improves cardiovascular outcomes [119]. The most frequent adverse effects with SGLT-2 inhibitors relate to their actions in the kidneys and to glycosuria, including polyuria, volume depletion with postural hypotension, and urinary and genital tract infections [60,117,120].There have been no trial or implementation studies of SGLT-2 inhibitors in SMI.

5.13 Insulin therapy

For those who have sustained HbA1c levels of > 9% (75 mmol/mol) despite

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combination therapy, the use of insulin can be considered. Basal insulin can be combined with oral antidiabetic medications (metformin, sulphonylureas, GLP-1R agonists and SGLT-2 inhibitors). Insulin may be administered as a once a day long acting formulation, twice a day mixed insulin or as a basal bolus regimen. This allows for enhanced glycaemic control.

In combination with oral antidiabetic medications in the general population, insulin has shown effectiveness in glycaemic control with a low risk of hypoglycaemia. Basal insulin is recommended to be commenced at a low dose at night time (e.g. 10 units) and titrated as per glucose control, generally aiming for 30-50 units to achieve target glucose levels and HbA1c.

Those with significantly elevated HbA1c (>10% (86 mmol/mol)), severe hyperglycaemia (>16.7 mmol/L (300 mg/dL) or clinical symptoms may be candidates for immediate insulin therapy (with or without additional medications) [50]. For those who fail to gain a HbA1c < 9.0% (75 mmol/mol), consideration of the use of insulin may be a more effective option, though its use needs to be balanced against the risk of hypoglycaemia.

As complexity increases with increased insulin dosing frequency, the risk of complications increases and careful selection of patients which would achieve significant benefit over risk is required. Insulin maintenance treatment in patients with SMI with sustained elevations of HbA1c despite combination therapy should only be selected if patient education allows for patients to understand the treatment, and for those with a record of medication adherence who can adhere to the treatment and medical follow up.

5.14 Thiazolidinediones

Thiazolidinediones (e.g. Pioglitazone, Rosiglitazone) work to improve insulin effectiveness by increasing insulin sensitivity and regulating glucose metabolism. Trial data for the use of rosiglitazone exists in antipsychotic treated patients with schizophrenia. Double blind trial data supporting reductions in glucose levels in patients treated with olanzapine and rosiglitazone (4-8 mg daily) compared to placebo and in those treated with rosiglitazone[121]. Non-significant reductions in insulin sensitivity index (SI- increases in ‘net fractional glucose clearance rate per unit change in serum insulin concentration after an intravenous glucose load’[122]) and glucose utilization (SG- the net fractional glucose clearance rate secondary to

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increased glucose independent of increase in circulating insulin concentrations) in clozapine patients with insulin resistance, treated with rosiglitazone (4mg daily) compared to placebo [122]. These findings suggested that rosiglitazone improved insulin sensitivity and glucose utilization in clozapine treated patients, perhaps mediated by rosiglitazone's direct and indirect effects on glucose transporter activity [123]. Subsequent to these trials, rosiglitazone was withdrawn from the UK market in 2010, due to increased risk of myocardial infarction. Pioglitazone is still available as an antidiabetic medication. However, due to concerns regarding the risk of cardiovascular disease and heart failure with their use [60], along with their propensity to cause weight gain, they are not preferred choices in SMI.

6. Expert commentary

There are a number of general principles involved in the pharmacotherapeutic management of T2DM in SMI which include: defining a glucose level or HbA1c goal, using metformin as first line treatment, the use of combination treatments if required to achieve HbA1c goals, the use of agents which may promote weight loss (GLP-1R agonists) or are weight neutral (DPP-4 inhibitors or SGLT2 inhibitors) and which avoid the occurrence of hypoglycaemic episodes [124].

Emerging evidence from pivotal RCTs for the treatment of diabetes in the general population report a significant risk reduction in cardiovascular morbidity and mortality for patients treated with SGLT-2 inhibitors [119] and GLP-1R agonists [95]. There is a critical clinical need to determine the therapeutic benefit of these medications in people with SMI and incipient or established diabetes mellitus, and to assess the impact on cardiovascular disease risk reduction in SMI.

When choosing an antidiabetic medication to use both efficacy and tolerability are important, not only because adverse effects can reduce subjective well-being and adherence, but also because they can adversely affect treatment outcomes. Notwithstanding the fact that differences in efficacy among antidiabetic medications are relatively small, the need to tailor treatment choice to individual patients is key, and shared treatment decisions should be a cornerstone in the management of T2DM in SMI. The use of strategies which may increase individual patient adherence is recommended. The use of once weekly exenatide or dulaglutide could be administered by community mental health nurses, and incorporated into weekly patient scheduled contacts or patients could be educated to self-administer the injection. The NICE guideline restrictions for the use of GLP-1R agonists in the UK

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based on cost effectiveness analysis[76], are not mirrored in other international guidelines[72]. Further, the restriction for their use in people with a BMI > >35 kg/m^2 is not fully merited based on the key trial data for the use of exenatide and liraglutide in which people had mean BMIs of 34.0 kg/m^2 and 31.9 kg/m^2 [125]respectively, and in basing their use on weight loss effectiveness rather than glycaemic efficacy, thereby limiting their use in people with refractory T2DM[126].

In this clinical review, we have summarised the available evidence and provided a clear rationale to guide treatment of T2DM in SMI, along with a treatment algorithm for the use of antidiabetic medication in SMI, extrapolated from data derived from studies of people with diabetes in general population study samples.

7. Five-year view

Trial data in relation to the use of antidiabetic medications (except for metformin) in SMI is limited. Prospective observational and implementation studies, and RCTs in the use of metformin in combination with GLP-1R agonists, DPP-4 inhibitors, sulphonylureas, pioglitazone and SGLT2 inhibitors are needed to address the evidence gap on the efficacy, tolerability and acceptability of antidiabetic medications in people with SMI.

While a lack of screening for, and identification of T2DM remains a problem in SMI, the major concern is the lack of treatment implementation for T2DM when it is identified, and the suboptimal treatment of T2DM, which should be rectified with the appropriate implementation of pharmacotherapeutic interventions. The comprehensive care required to prevent microvascular and macrovascular complications of diabetes will require a combination of lifestyle interventions, education programs and pharmacological treatments delivered across the healthcare spectrum with the involvement of the patient, their family members and collaborative approaches from primary and secondary care (mental health and endocrinology) services. Meta-analysis has shown that 56% of people with schizophrenia (n=33680) are "adherent" to diabetes medication, which was significantly higher than those without schizophrenia, indicating that diabetic medication programs can be successfully implemented in this population [58]. We believe that future clinical trials that investigate treatment efficacy and switching strategies in T2DM patients in SMI will increase our knowledge, familiarity and confidence in using these agents and lead to increased treatment implementation for T2DM in this population.

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8. Conclusion

In summary, metformin is the recommended first line treatment for T2DM in SMI, with emerging data in SMI to support the use of GLP-1R agonists. The use of DPP-4 inhibitors, sulphonylureas and SGLT2 inhibitors in combination with metformin to achieve HbA1C treatment goals are recommended approaches, but trial data in SMI is lacking.

A patient tailored approach to the selection of antidiabetic medications is required regarding the comparative effects and tolerability of treatments and patient preference. In ensuring this approach, a diagnosis of SMI or active psychotic symptoms should not be an obstacle to the initiation of diabetes medication in this patient population. The implementation of treatment protocols for T2DM in SMI and studies of their effectiveness and long term clinical outcomes are required. However, the paucity of trial data should not impede the appropriate initiation of treatments for T2DM in SMI.

9. Key issues

- There is increasing evidence that people with severe mental illness (SMI) have considerably worse physical health than the general population
- Type 2 diabetes mellitus (T2DM) is more common in people with severe mental illnesses with up to 20% meeting criteria for T2DM, and 30% having evidence of glucose dysregulation
- People with SMI and comorbid T2DM receive suboptimal treatment for diabetes
- Treatment with metformin is of proven benefit in this population and is the first line medication for the treatment of T2DM in SMI
- Metformin, and GLP1R- agonists are the only currently available diabetic medications investigated in trials of people with SMI and T2DM studies
- In the management of hyperglycaemia in patients with SMI and T2DM, glucagon-like peptide-1 receptor (GLP1R)-agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, sulfonylureas, sodium glucose transporter 2 (SGLT2) inhibitors, pioglitazone and insulin may be considered as combination therapy

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with metformin if the HbA1c target is not achieved after 3 months of metformin monotherapy at maximum tolerated doses

- Agents with a low risk for hypoglycaemia and which may mediate weight loss, such as GLP-1R agonists, DPP-4 inhibitors and the newest SGLT2 inhibitors are preferred choices for second line therapies in SMI.
- Patient engagement in decision making about treatment choices is important to help with adherence and the success of the chosen therapy.
- GLP1-R agonists, exenatide, liraglutide and dulaglutide are associated with improved glycaemic control and weight loss.
- Exenatide and liraglutide have shown improvements in glycaemic control in SMI, with liraglutide showing evidence for preventing the transition from prediabetes to T2DM in olanzapine and clozapine treated patients
- Exenatide and dulaglutide are available as once weekly subcutaneous injections, potentially improving adherence and acceptability
- Consider the use of GLP-1R agonists as a second line treatment for T2DM in SMI, and potentially as a weight loss agent and in preventing the transition from prediabetes to T2DM
- The major concern remains the lack of appropriate treatment intervention for T2DM, and the suboptimal treatment of T2DM in SMI.
- A relevant question is if earlier treatment with metformin or other agents during prediabetes might be beneficial in preventing the transition to T2DM in SMI.
- Prospective observational and implementation studies, and in the use of metformin in combination with GLP-1R agonists, DPP-4 inhibitors, sulphonylureas, pioglitazone and SGLT2 inhibitors are needed to address the evidence gap on the efficacy, tolerability and acceptability of diabetic medications in people with SMI.

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Table 1: Risk of weight gain and incident diabetes among second generation antipsychotic medications (Kessing *et al.*, 2010, Nielsen *et al.*, 2010, Rummel-Kluge *et al.*, 2010, Vancampfort *et al.*, 2016, Zhang *et al.*, 2017)

Second-generation antipsychotics and associations with T2DM
Lowest risk
Aripiprazole, amisulpride, lurasidone, and ziprasidone
Moderate risk
Asenapine, paliperidone, quetiapine, and risperidone
Highest risk
Clozapine and olanzapine

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Table 2: Medications to treat hyperglycaemia in T2DM and SMI

Medications	Starting Dose	Maximum Dose
Biguanides		
Metformin	500 mg BD	1000 mg TID
Sulphonylurea		
Glicalazide MR	30 mg OD	120 mg OD
DPP4i		
Sitagliptin	100 mg OD	100 mg OD
Linagliptin	5 mg OD	5 mg OD
Vildagliptin	50 mg BD	50 mg BD
GLP-1RA		
Liraglutide	0.6 mg OD	1.8 mg OD
Exenatide	5 mcg BD	10 mcg BD
Exenatide LAR	2 mg x1/week	2 mg x1/week
Dulaglutide	0.75 mg x/1/week	1.5 mg x1/week
SGLT2i		
Empagliflozin	10 mg OD	25 mg OD
Dapagliflozin	10 mg OD	10 mg OD
Canagliflozin	100 mg OD	300 mg OD
Thiazolidinedione		
Pioglitazone	15mg OD	45 mg OD

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Insulin		
Basal Glargine/Detemir/Degludec	N/A	N/A
Bolus Asparte/Glulisine/Lispro	N/A	N/A
Mix Asparte +p rotamine crystsallised insulin	N/A	N/A

Medications may require adjustment and discontinuation with renal failure. Refer to BNF or equivalent medical formulary for further information.

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Figure 1. Suggested Algorithm for Management of Hyperglycaemia in patients with Diabetes and SMI

Monotherapy

Lifestyle (Diet and Exercise)

Metformin Initially 500 mg BD, Increase to 1000 mg BD,

↓

If not achieving target HbA1c after 3-6 months, Add Second Agent

Dual Therapy~

Normal Weight* **BMI 18.5 -24.9**	**Overweight** **BMI 25-29.9**	**Obese** **BMI > 30**	**Underweight*** **BMI < 18.5**	**Osmotic Symptoms***
DPP4i	GLP-1RA	GLP-1RA	Sulphonylurea	Insulin
Sulphonulurea	SGLT2i	SGLT2i	DPP4i	Sulphonylurea
TZD	DPP4i	DPP4i	Insulin	
SGLT2i			TZD	

Lifestyle (Diet and Exercise)

↓

If not achieving target HbA1c after 3-6 months, Add Third Agent

Triple Therapy~

Normal Weight*	**Overweight**	**Obese**	**Underweight***	**Osmotic Symptoms***
DPP4i	GLP-1RA**	GLP-1RA**	Sulphonylurea	Insulin
Sulphonylurea***	SGLT2i	SGLT2i	DPP4i	Sulphonylurea
TZD***	DPP4i**	DPP4i**	Insulin	
Insulin***	TZD***	TZD***	TZD	
SGLT2i	Sulphonylurea***	Sulphonylurea***		
	Insulin***	Insulin***		

Lifestyle (Diet and Exercise)

↓

If not achieving target HbA1c after 3-6 months, Add Insulin Therapy

Insulin Therapy**

Basal Insulin
Premixed Insulin
Basal Bolus Insulin
Consider GLP-1RA

*If HbA1c > 10% (86 mmol/mol) or blood glucose > 300 mg/dl (16.6 mmol/L) and significant osmotic symptoms of polyuria, polydipsia and weight loss, assess for ketonaemia, ketonuria, consider T1DM, insulin administration and referral to an endocrinology service.

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**Do not combine GLP1-RA and DPP4i therapy

***Medications which typically result in weight gain.

****Consider rationalising oral antidiabetic medication, (e.g. < 3) when commencing insulin, and referral to endocrinology service if not already under review

~ Certain Combination treatments are more costly than others and healthcare systems may dictate which combinations are possible based on monetary resources.

Shared Decision making between the patient and healthcare practitioner is required to agree on treatment, ensuring an individual care plan. The patient must be informed of the potential side-effects of medication.

DPP4i=DPP-4 inhibitor; GLP-1 RA= GLP-1 receptor agonist; SGLT2-i, SGLT2 inhibitor; TZD, thiazolidinedione

Adapted from: American Diabetes Association Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., Peters, A. L., Tsapas, A., Wender, R. & Matthews, D. R. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 38, 140-9. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

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