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Clinical insights into the cross-link between mood disorders and type 2 diabetes: A review of longitudinal studies and Mendelian randomisation analyses

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ABSTRACT

Mood disorders and type 2 diabetes mellitus (T2DM) are prevalent conditions that often co-occur. We reviewed the available evidence from longitudinal and Mendelian randomisation (MR) studies on the relationship between major depressive disorder (MDD), bipolar disorder and T2DM. The clinical implications of this comorbidity on the course of either condition and the impact of antidepressants, mood stabilisers, and antidiabetic drugs were examined. Consistent evidence indicates a bidirectional association between mood disorders and T2DM. T2DM leads to more severe depression, whereas depression is associated with more complications and higher mortality in T2DM. MR studies demonstrated a causal effect of MDD on T2DM in Europeans, while a suggestive causal association in the opposite direction was found in East Asians. Antidepressants, but not lithium, were associated with a higher T2DM risk in the long-term, but confounders cannot be excluded. Some oral antidiabetics, such as pioglitazone and liraglutide, may be effective on depressive and cognitive symptoms. Studies in multi-ethnic populations, with a more careful assessment of confounders and appropriate power, would be important.

1. Introduction

Mood disorders and type 2 diabetes mellitus (T2DM) are among the top leading causes of disability worldwide, affecting around 4% and 6% of the population, respectively (Dattani et al., 2021; Khan et al., 2019; Vos et al., 2020). In addition to their high prevalence, epidemiological studies showed that mood disorders and T2DM often co-occur (Wimberley et al., 2022). Compared to the general population, people with major depressive disorder (MDD) or bipolar disorder (BD) have twice the chance of being diagnosed with T2DM (Wimberley et al., 2022). Likewise, the risk of developing MDD or BD is almost doubled after a diagnosis of T2DM (Anderson et al., 2001; Wang et al., 2019; Wimberley et al., 2022). This comorbidity results in high social costs, reduced quality of life, and increased mortality (Holt et al., 2014; Molosankwe et al., 2012).

Many biological and behavioural/environmental factors may contribute to this comorbidity. Patients with mood disorders frequently lead an unhealthy lifestyle, e.g., altered sleep patterns, sedentariness, poor diet, and tobacco/substance use, which may predispose to insulin resistance and T2DM (Fanelli and Serretti, 2022). Second-generation antipsychotics are often prescribed for mood disorders, and they can have significant metabolic side effects (Goncalves et al., 2015). In terms of biological mechanisms, genome-wide and locus-specific patterns of genetic overlap were found between MDD, BD and T2DM, suggesting co-heritability between these conditions, and pointing to the existence of common etiopathogenetic mechanisms (Fanelli et al., 2022a; 2022b), as illustrated in Fig. 1. These may include alterations in insulin signalling and inflammation, as well as hypothalamic-pituitary-adrenal (HPA) axis and gut microbiota dysregulations (Fanelli and Serretti, 2022). Insulin signalling plays a pivotal role in the brain, where it is involved in neuroprotection, neurogenesis, and synaptic plasticity (Nguyen et al., 2018). Of note, insulin from the periphery can cross the blood-brain barrier, but it is also centrally produced by the choroid plexus, and insulin receptors are present on both neurons and astrocytes (Lyra et al.,

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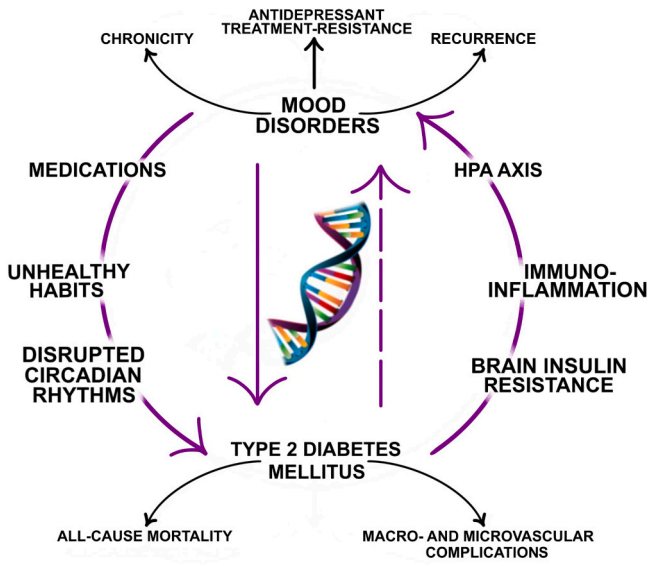

Fig. 1. Summary of the evidence from epidemiological and MR studies. Meta-analyses and cohort studies corroborated the hypothesis of a bidirectional relationship between mood disorders and T2DM. MDD predicts higher risk of subsequent T2DM, as confirmed by Mendelian randomization studies. Results of studies on T2DM predicting incident mood disorders are contrasting. Many biological and behavioural/environmental factors may contribute to this correlation. The co-occurrence of T2DM and mood disorders can lead to worse outcomes for both conditions. Abbreviations: HPA=Hypothalamic–pituitary–adrenal; MR=Mendelian randomisation; T2DM=type 2 diabetes mellitus.

2019). Brain insulin resistance may impact the dopaminergic-mesolimbic reward circuit and the expression of glutamatergic receptors in the hippocampus, with detrimental effects on cognition and hedonic perceptions (Fanelli and Serretti, 2022). Both depressive and manic episodes were linked to persistent low-grade inflammation and elevated levels of circulating pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor-α, which can lead to affective symptoms through HPA axis hyperactivity and changes in neurotransmission (Nguyen et al., 2018). A systemic inflammatory state, further induced by adipose tissue accumulation and a high-fat diet, may also disrupt insulin signalling, leading to the development of T2DM (Nguyen et al., 2018).

Given the considerable individual and socio-economic impact of the comorbidity between T2DM and mood disorders, and the steadily increasing prevalence of both these conditions in recent years (Holt et al., 2014; Molosankwe et al., 2012; World Health Organization, 2022), it is of paramount interest to clarify the presence of a possible causal link between them, to improve their prevention and treatment. To achieve this objective, we reviewed the literature on the association between mood disorders (MDD and BD) and T2DM. We specifically focused on longitudinal studies, as these are best suited to provide information about bidirectional and temporal relationships, and Mendelian randomisation (MR) studies, which use single-nucleotide polymorphisms (SNPs) associated with an exposure to examine whether an association between the exposure and an outcome is compatible with a causal effect (Davies et al., 2018). In addition, we provided a qualitative synthesis of longitudinal studies on the impact of co-occurring mood disorders and T2DM, in terms of clinical course of either condition. Finally, we evaluated the potential beneficial or detrimental effects of psychotropic treatments in T2DM, as well as of antidiabetic drugs in mood disorders.

2. Methods

An electronic search of the literature was conducted on PubMed looking for studies investigating the relationship between T2DM and mood disorders, namely MDD and BD, and published from inception until September 2022. We used search terms related to mood disorders and diabetes mellitus, as well as antidepressants, mood stabilisers, and antidiabetic medications. The search was restricted to published only studies, written in English, and conducted in human samples. The full search query used is available as Supplementary Methods. The final search was performed on October 3rd, 2022.

The records resulting from the search query were screened to find potentially relevant studies by inspecting titles and abstracts. The full text of the selected studies and those of uncertain relevance were retrieved and carefully examined to determine the pertinence of each study. Then the list of references in the included articles was screened to identify other potentially eligible studies not captured by the initial search. Studies whose samples consisted of patients with type 1 diabetes mellitus were excluded, as well as commentaries, letters and editorials. We only included longitudinal studies (i.e., observational studies and clinical trials), meta-analyses of longitudinal studies, and MR studies, as these are the best suited to study the temporality and direction of associations and possible causal effects.

The present review was narrative, as a quantitative synthesis and standardized quality assessment of the included articles were not within the scope of this work. The main reasons for this choice were the heterogeneity of the considered studies and the breadth of the research questions and methodologies. However, to provide a description of the results of our literature search, we synthesised the article selection process in Supplementary Figure 1.

3. Results

The initial literature search identified 2130 unique abstracts, out of which 232 full-text articles were evaluated to determine their eligibility. Ultimately, 84 papers were included in the review. The study selection process is summarised in Supplementary Figure 1.

3.1. Epidemiological studies

3.1.1. Mood disorders predicting incident T2DM

Previous meta-analyses of prospective studies supported the hypothesis of a link between depression and a subsequent diagnosis of T2DM (Supplementary Table 1). In detail, a meta-analysis of nine studies with a mean follow-up of 9.4 years and a total of 174,035 individuals, found a relative risk (RR) of T2DM of 1.37 in the group with depression (95% CI 1.14–1.63) (Knol et al., 2006). This result is similar to what was reported by a later meta-analysis (RR 1.60 [95% CI 1.37–1.88]) that extended the total sample size to 222,019 individuals from 13 studies, with the same average duration of follow-up (Mezuk et al., 2008). The inclusion of an almost doubled total sample size did not change the result in a following meta-analysis (Rotella and Mannucci, 2013).

Other longitudinal studies were published after the mentioned meta-analyses, and they overall confirmed that depression increases the risk of incident T2DM in samples with various ethnic origins and clinical characteristics. Two studies used insurance claims/national registries in Asian samples, extracting data referred to 11,670 and 461,213 individuals, respectively, referred to ~7 years (Chen et al., 2013; Meng et al., 2018). Other studies confirmed the finding, but they showed a smaller sample size and/or shorter duration of follow-up, and/or they were performed in samples with specific clinical characteristics. Specifically, a study in 2981 individuals found an increased risk of incident T2DM within two years in those with depression or anxiety, particularly in those with both conditions. However, this association was attenuated after adjusting for risk factors of T2DM, such as plasma triglyceride

levels and lifestyle (Atlantis et al., 2012). A study on a large cohort of 161,808 post-menopausal women reported consistent results, but it considered elevated depressive symptoms rather than a diagnosis of MDD, with a follow-up of 7.6 years (Ma et al., 2011). This limitation was balanced by the fact that the study evaluated the persistence of elevated depressive symptoms (baseline and year 3), which helped in distinguishing between transitory symptoms and probable MDD. Interestingly, only the group with persistently elevated depressive symptoms (probable MDD) had an increased risk of incident T2DM after adjusting for confounders.

Other consistent evidence from the literature highlighted the synergistic interaction between metabolic dysregulation/prediabetes and comorbid depressive symptoms on the risk of T2DM (Deschenes et al., 2016; Schmitz et al., 2016). However, it should be noted that a recent study on a total of 1766 individuals from a German nation-wide cohort, followed for 12 years, showed no increased risk of incident diabetes in the group with MDD (Nubel et al., 2022). The relatively small sample size of this study represents a limitation, but as discussed in the next section, longitudinal cohort studies are not free of potential limitations and risk of bias, therefore results (both positive and negative) should be interpreted carefully.

Although the cumulative evidence suggests a link between depression and incident T2DM, it is crucial to consider the influence of several confounding factors on the presented results. As mentioned before, adjusting for confounders reduced the effect size in studies that reported an association. The risk of bias coming from confounders is often not easy to evaluate, as the available studies were heterogeneous in terms of sample characteristics and covariates included.

Among potential confounders, undetected diabetes at baseline represents a relevant variable. Some studies relied on self-reported diabetes at baseline (e.g., (Chen et al., 2013; Ma et al., 2011), resulting in the risk of not controlling appropriately for this confounder. However, the exclusion of these studies did not change the pooled relative risk of T2DM compared to the overall estimate in an early meta-analysis (Knol et al., 2006). Other than undetected diabetes at baseline, there are risk factors for T2DM, such as overweight/obesity and lifestyle (e.g., physical activity and alcohol intake), that not all studies controlled for in an exhaustive way (Chen et al., 2013; Knol et al., 2006; Mezuk et al., 2008). Notably, many of these risk factors are shared between depression and T2DM (Milaneschi et al., 2020), therefore it is fundamental to adjust for them to avoid spurious or inflated results. Concomitant medications for depression are another important variable to take in account, as antidepressants and antipsychotics can have an impact on metabolic parameters (Goncalves et al., 2015; Rotella and Mannucci, 2013). However, most studies did not adjust for the prescription of these medications (Knol et al., 2006; Mezuk et al., 2008), and those that did adjust did not consider the specific medications but the class (e.g., (Ma et al., 2011). Interestingly, antidepressant prescription was associated with an increased risk of incident T2DM, independent of depressive symptom severity (Andersohn et al., 2009; Kivimaki et al., 2010; Rubin et al., 2010). However, not all studies that reported an effect of antidepressant prescription adjusted for psychopathology (Pan et al., 2012). With one exception (Wium-Andersen et al., 2021), previous studies did not adjust for the concomitant prescription of antipsychotics. Some antipsychotics are not rarely prescribed in depression and the prevalence of diabetes is ~ 12% among people taking antipsychotics (2–3 folds than the general population) (Holt and Mitchell, 2015), therefore this variable should be considered as covariate in future studies.

Other modulating factors have been investigated in relation to the effect of depression on the risk of incident T2DM. Several studies considered the severity of depression and reported higher risk in case of severe and persistent depressive symptoms (Carnethon et al., 2003; Engum, 2007; Golden et al., 2008; Golden et al., 2004; Ma et al., 2011; Meng et al., 2018; Windle and Windle, 2013). Data about sex-specific correlations are contrasting (higher risk in women (Carnethon et al., 2003; Demmer et al., 2015) or in men (Mezuk et al., 2008) or no effect of sex (Chen et al., 2013)). Age seems to be a modulating factor, consistent with a couple of studies that found that the risk of incident T2DM becomes lower as age increases (Chen et al., 2013; Mezuk et al., 2008). Regarding socio-demographic factors, a lower education level was associated with increased risk (Mezuk et al., 2008), while social support does not seem to modify the risk of incident diabetes (Laursen et al., 2017).

Another relevant point to consider is the possible influence of unipolar vs bipolar depression on the risk of incident T2DM, as these disorders have largely different pathogenetic mechanisms (Johnston-Wilson et al., 2000). Unfortunately, there is much less literature on BD in this regard and no meta-analysis to the best of our knowledge. The available results are not univocal, and in most cases the potential effects of confounders do not seem appropriately accounted for. One of the available studies extracted insurance claims from a nation-wide database in Taiwan, to test the risk of initiation of antidiabetic medications within 10 years in people with MDD or BD at baseline vs matched controls (Bai et al., 2013). The authors reported an increased risk in BD but not in MDD; however, they did not control for prescription of psychotropic medications, body mass index (BMI), and other risk factors for T2DM, such as prediabetes at baseline. Further, the incidence of T2DM itself could have been underestimated, because the prescription of antidiabetic medications was the primary outcome, instead of T2DM diagnosis. Conversely, studies in the Danish registries found a similar increase in the risk of incident diabetes in both MDD and BD (Wimberley et al., 2022; Wium-Andersen et al., 2021). The results were confirmed when antidepressant/antipsychotic prescription and socio-demographic variables were considered (Wium-Andersen et al., 2021). However, these studies did not control for T2DM risk factors either, such as BMI, medical comorbidities, and lifestyle at baseline (Wimberley et al., 2022; Wium-Andersen et al., 2021). A smaller study with a 13-year follow-up included 475 patients with affective psychosis (bipolar or unipolar) and found no increased risk of incident T2DM after controlling for several confounders, including medications, BMI, cholesterol, and inflammation levels (Dieset et al., 2019). Finally, in a Swedish nation-wide cohort of 6,587,036 individuals, people with a diagnosis of BD were found to have a ~1.5 fold increased risk of developing diabetes within 7 years, but BMI, lifestyle and medications were not considered as potential confounders (Crump et al., 2013). Therefore, studies with positive findings were larger but did not correct appropriately for confounding factors, the only negative study was smaller but adjusted the analyses for confounding factors in a more complete manner.

In conclusion, there is quite robust evidence of an increased risk of incident T2DM in people with depression (at least MDD), but this effect may be largely explained by shared risk factors between depression and T2DM and concomitant medications. Overall, epidemiological studies were not able to determine if there are depression-specific mechanisms that may link depression to the subsequent development of diabetes.

3.1.2. *T2DM predicting incident mood disorders*

The hypothesis of an increased risk of depressive disorders in people with a primary diagnosis of diabetes is controversial (Supplementary Table 1), as available studies and meta-analyses reported small effect sizes and they suggested that medications for T2DM, characteristics of the disease and of individuals, lifestyle, and the modality used for diagnosis ascertainment could largely account for/modulate the observed (small) effects.

Two meta-analyses of longitudinal studies reported T2DM as a modest predictor of subsequent depression, with a pooled RR of 1.15 (95% CI 1.02–1.30) (Mezuk et al., 2008) and OR of 1.34 (95% CI 1.14–1.57) (Chireh et al., 2019). However, sensitivity analyses to test the robustness of findings showed that these results may be affected by confounders. Studies with clinical measures of depression indeed reported smaller effects than those using only self-reported data, and the exclusion of the latter group made the results no longer significant

(Mezuk et al., 2008), similar to results found when considering self-reported diabetes (Chireh et al., 2019). Further, the exclusion of samples that had short (≤5 years) follow-ups also made the results no longer significant, suggesting that depressive symptoms may have been undetected at baseline, at least in part of the studies (Mezuk et al., 2008).

Individual studies found sex-specific effects (higher risk of depression/higher severity of depressive symptoms in women vs men (Jacob and Kostev, 2016; Lloyd et al., 2020; Salinero-Fort et al., 2018; Trento et al., 2015), age-related effects (Chen et al., 2013; Trento et al., 2015) and effects of lifestyle, medical comorbidities, and diabetes medications, e.g., (Golden et al., 2008; Jacob and Kostev, 2016; Salinero-Fort et al., 2018), though without univocal evidence. This underlines the complexity of the relationship between depression and T2DM. For example, older age in patients with T2DM was found to have a negative impact on the severity of depressive symptoms (Trento et al., 2015), but older age is also associated with a longer duration of T2DM and a higher risk of having developed complications of the disease (e.g., retinopathy, neuropathy, coronary heart disease), which were associated with increased risk of depression (Jacob and Kostev, 2016; Lloyd et al., 2020). However, another study reported a higher risk of depression in younger patients (Chen et al., 2013). In this regard, it should be noted that the latter study considered new diagnoses of depression in patients with T2DM within a period of 7 years, while the previously mentioned work just assessed the severity of depressive symptoms at baseline and at follow-up (after 8 years) (Trento et al., 2015), therefore there is a substantial difference in study design.

Variables associated with T2DM severity were also suggested as modulators of the occurrence and the persistence of depressive symptomatology, such as worse glycaemic control (Fisher et al., 2008; Jacob and Kostev, 2016; Maraldi et al., 2007). Several lifestyle factors were also associated with a greater risk of depression, including physical inactivity (Lloyd et al., 2020; Salinero-Fort et al., 2018), higher BMI and unhealthy eating habits (Lloyd et al., 2020; Schmitz et al., 2013). Consistently with these findings, high levels of stress and reduced perceived health status were found to be markers of incident depression (Lloyd et al., 2020). The association with the risk of incident depression or depressive mood seems stronger in subjects with treated vs untreated diabetes, especially in the case of insulin therapy, which could be a sign of worst glycaemic control or more severe complications/comorbidities (Golden et al., 2008; Lloyd et al., 2020; Pan et al., 2010). In addition, the psychological burden linked to the management of a complex therapy may contribute to depressed mood (Golden et al., 2008). On the contrary, another study demonstrated that the prescription of insulin and oral antidiabetic drugs did not affect the risk of depression (Jacob and Kostev, 2016).

The literature is much scarcer for incident BD in T2DM. To the best of our knowledge, there are only two large studies in population-based cohorts. An earlier study in a Taiwanese population-based cohort (~800,000 individuals) reported a 2.62-fold higher risk of a mood disorder (both MDD and BD) in patients with diabetes not taking any oral antidiabetic medication, but not in those taking an antidiabetic medication (Wahlqvist et al., 2012). A more recent study in the Danish registries confirmed increased odds of BD in patients with previous T2DM (hazard ratio (HR)= 2.25, 95% CI 2.08–2.43), with an effect size comparable to that observed for incident MDD. The analyses were adjusted for sex, birth year, and family history of both mood disorders and T2DM, but they did not consider possible confounding and/or mediating effects of psychotropic medications and/or lifestyle (Wimberley et al., 2022).

Based on the discussed evidence, we can conclude that the relationship between T2DM and incident MDD and BD is complex and likely affected by multiple modulators. As discussed, a replicated finding was a higher risk of incident depression in women with T2DM compared to men. However, the most recent meta-analysis of incident depression in T2DM did not stratify the analyses by sex (Chireh et al., 2019), and a previous one did not identify sex effects (Mezuk et al., 2008), but it did not include the recent studies that highlighted the described higher risk in women (see above). This reflects the general difficulty in considering all the variables that modulate the link between T2DM and depression in epidemiological studies.

3.2. Mendelian randomisation studies

Several MR studies tested the two-way causal association between MDD and T2DM (Supplementary Table 2), but none between BD and T2DM. A causal effect of MDD on T2DM was found by two well-powered two-sample MR studies, using summary statistics of genome-wide associations studies, including only subjects of European ancestry and a random-effect inverse-variance weighted (IVW) method (OR=1.22, 95% CI 1.09–1.36, and OR=1.26, 95% CI 1.10–1.43) (Tang et al., 2020; Tao et al., 2022). This effect was robust to sensitivity analyses that excluded possible horizontal pleiotropic effects, except for the less efficient Egger-MR – it frequently produces less precise estimates and suffers from a significant loss of power -, where the direction of the effect was nevertheless maintained. No causal association was shown in the opposite direction (T2DM → MDD) by the same studies (Tang et al., 2020; Tao et al., 2022). This negative finding is in line with an MR study using population-based individual-level data from a Scottish sample (N = 19,858) (Clarke et al., 2017). To the best of our knowledge, only one MR study reported a causal association of T2DM with MDD, using individual-level data from East-Asian ancestry subjects (N = 11,506) (Xuan et al., 2018). The results showed a probable causal effect of T2DM on MDD (OR=1.83, 95% CI 1.25 – 2.70, and OR=1.57, 95% CI 1.04–2.37, derived using the Wald-type estimator with unweighted and weighted genetic scores for T2DM, respectively). The findings were confirmed by excluding pleiotropic variants and using the IVW method but not the Egger-MR, where the association was found to be non-significant and in the opposite direction (Xuan et al., 2018).

Overall, there is robust evidence of a causal effect of MDD on the risk of T2DM in European populations, while a causal effect in the opposite direction was found only by one study in East-Asian subjects, and it needs replication by more powerful studies. Further studies on ethnically diverse samples would be important.

3.3. Effects of mood disorders/type 2 diabetes comorbidity on the course of either condition

Given the chronic/relapsing nature of both mood disorders and T2DM, it is intriguing to better understand whether their co-occurrence may worsen the course of either condition.

Many prospective studies have explored depression trajectories in the context of T2DM, with the general conclusion that T2DM leads to a greater chronicity of depression, and worse depressive symptoms over time (Supplementary Table 1). In this regard, an 8-year follow-up study found that patients with T2DM on insulin treatment experienced a mild but significant worsening of depressive symptomatology over time (Trento et al., 2015). This was corroborated by a 5-year study, showing that most patients with T2DM had low and persistent depressive symptoms, with a gradual worsening in 7.5% of cases (Whitworth et al., 2017). A lifetime history of MDD, followed by female sex, higher BMI, and younger age, were the strongest predictors for persistent depressive symptoms in T2DM (Whitworth et al., 2017). A number of social and clinical factors were also associated with the recurrence or relapse of depressive symptomatology in T2DM; for example, lack of home ownership, diabetes treatment complexity or dissatisfaction with antidepressant medications (de Groot et al., 2015), as well as poor control of glycaemic parameters (Ell et al., 2012; Maraldi et al., 2007). A recent study indicated that MDD occurring either before or after the diagnosis of T2DM may significantly increase the risk of dying by suicide (Huang et al., 2022).

No longitudinal studies investigated the relationship between T2DM and the clinical course and treatment outcomes of BD. Only one study

conducted in the population-based Danish registries showed that women but not men with treatment-resistant depression (TRD) had a higher prevalence of a previous diabetes diagnosis than those without TRD. The risk of subsequent diabetes instead was increased for both sexes in individuals with TRD, after adjusting for the age at first antidepressant prescription and the number of other medical comorbidities (Madsen et al., 2021). However, there is still no longitudinal research investigating whether the presence of T2DM in BD or MDD may impact on treatment effects or may be related to specific symptom patterns.

Considering the consequences of depression on diabetes, many studies found that it may be associated with worse medical outcomes, e.g., more severe cardiovascular complications, and higher all-cause mortality (Supplementary Table 1). This association may be at least partly mediated by poorer glycaemic control, which effect, despite small, may increase the risk of complications. An association between depressive symptoms and increased glycated haemoglobin (Hb1Ac) values was indeed observed in elderly patients at risk of depression or having depression, in a longitudinal 1-year study (Sirirak et al., 2022). A sex-specific effect of MDD on glycaemic changes in T2DM was also suggested, with females but not males being less likely to return to normal glycaemic values (Nubel et al., 2022). However, studies on larger samples found no association between mood symptoms or lifetime MDD/BD and worse glycaemic control in T2DM (Aikens et al., 2009; Ismail et al., 2017; Speerforck et al., 2019; Whitworth et al., 2017).

As discussed, the effect of depression on glycaemic control seems negligible, but it may still considerably increase the risk of complications. In a cohort of elderly Mexican Americans, diabetes with comorbid depression predicted a greater risk of vascular complications, higher disability and mortality, as well as an earlier occurrence of these negative outcomes (Black et al., 2003). The risk of adverse outcomes increased with the severity of depression (Black et al., 2003). A number of other studies replicated these findings and showed that MDD in T2DM may increase the risk of advanced macrovascular complications, such as stroke, myocardial infarction, and heart failure (Ismail et al., 2017; Lin et al., 2010; Novak et al., 2016; Scherrer et al., 2011a), as well as microvascular complications, such as proliferative retinopathy and end-stage renal disease, compared to non-depressed patients with T2DM or patients with either diagnosis (Lin et al., 2010; Novak et al., 2016). Not surprisingly, in a 12-year follow-up study, baseline diabetes mellitus and lifetime moderate MDD were associated with an intensified antidiabetic treatment at follow-up (Speerforck et al., 2019). This was not found in diabetic patients with lifetime mild or severe MDD or lifetime BD (Speerforck et al., 2019). Most importantly, several studies confirmed a synergistic effect of comorbid depression and T2DM on increased mortality, even after controlling for sociodemographic, other health, and lifestyle variables (Huang et al., 2022; Jung et al., 2021; Naicker et al., 2017; Novak et al., 2016; Prigge et al., 2022; Sullivan et al., 2012; Zhang et al., 2005). The increased mortality in the presence of this comorbidity exceeded the sum of the risk associated with diabetes and depression alone (Prigge et al., 2022). Likewise, longitudinal studies focusing on BD and comorbid T2DM have corroborated these findings. In a 7-year follow-up study, subjects with BD had a higher risk of dying by a diabetes-specific cause than the general population, particularly in females (Crump et al., 2013). Additionally, there was an association between BD and premature mortality for diabetes mellitus (Crump et al., 2013). A more than 60% increase in the RR of mortality was also shown in patients with newly diagnosed BD and previous diabetes mellitus during a 3-year follow-up (Pan et al., 2016).

3.4. Do antidepressants and mood stabilisers impact on incident T2DM risk?

Many population-based studies found that individuals taking antidepressants have an increased risk of incident T2DM, especially in the long-term, as confirmed by a meta-analysis including studies with a mean follow-up of 5.8 years (OR 1.31, 95% CI 1.18–1.45) (Ma et al., 2011; Pan et al., 2010; Rotella and Mannucci, 2013). The association was stronger for selective serotonin reuptake inhibitors (SSRI) and multiple antidepressant users, while non-significant for other classes of antidepressants (mainly tricyclic antidepressants (TCAs)) in a study on middle-aged women followed for ~10 years; however, this could be due to the higher frequency of SSRIs prescription vs other classes (Pan et al., 2010). Another long follow-up study including individuals of both sexes found that those taking antidepressants were more likely to develop T2DM, regardless of the antidepressant class/molecule; participants were free of diabetes and cardiovascular diseases at baseline (Pan et al., 2012). However, the association was attenuated after adjusting for cardio-metabolic risk factors and BMI (Pan et al., 2012). The link between long-term use of antidepressants and increased diabetes risk was confirmed for both TCAs and SSRIs in other studies (Andersohn et al., 2009; Kivimaki et al., 2010; Rubin et al., 2010). Depressed patients on moderate-to-high daily doses of antidepressants for more than 24 months showed a nearly doubled risk of diabetes vs non-users, and this effect was independent of depression severity (Andersohn et al., 2009). In an 18-year study including ~6000 middle-aged individuals, antidepressant use was associated with incident diabetes defined as use of antidiabetics or self-reported diagnosis, but not with diabetes detected during screenings of blood biomarkers or with increased glucose levels over time (Kivimaki et al., 2011). The analyses were adjusted for socio-demographic variables, other cardiovascular risk factors and medication use. These findings suggest that the association between antidepressant use and incident T2DM may be at least partly explained by the more frequent healthcare service use in patients with depression (Tusa et al., 2019), which increases the probability that T2DM is early diagnosed. This observation, together with the difficulty in adjusting for all the factors associated with long-term antidepressant use (e.g., lifestyle) suggests caution in concluding there may be an association with incident T2DM risk.

The evidence is scarcer regarding the use of lithium or valproate and the risk of incident T2DM. Existing studies do not show an increased risk of diabetes in patients taking lithium vs other mood stabilisers, taken individually or in combination, but the evidence is limited by a short duration of treatment or follow-up and the lack of a treatment-free/placebo control group (not feasible due to ethical reasons). In an early study, 460 patients with BD in long-term treatment with lithium were followed for a period between 6 months and 6 years; there was no increase in diabetes mellitus risk, as observed by fasting blood glucose measurement, although weight gain was observed (Vestergaard and Schou, 1987). More recently, in a cohort of ~7000 patients with BD, those receiving lithium showed no difference in the rate of T2DM compared to those treated with valproate, olanzapine, or quetiapine (Hayes et al., 2016). However, the median treatment duration was 1.48 years, which was a relevant limitation as T2DM develops typically in the longer term (Hayes et al., 2016). Lithium in combination with antipsychotics or anticonvulsants showed no evidence of increased cardiometabolic risk in patients with BD (Kohler-Forsberg et al., 2022); however, also this study had a relatively short follow-up (24 weeks).

3.5. Positive effects of treatments for depression and diabetes on either condition

The identification of effective treatment strategies for both mood disorders and T2DM is pivotal given the high comorbidity between the two conditions, as well as the common risk factors and etiopathogenetic mechanisms (Fanelli and Serretti, 2022). Early studies investigated which drugs among those approved for MDD or BD had the best efficacy in patients with T2DM (e.g., (Gulseren et al., 2005). More recently, precision medicine and the development of a systemic vision of psychiatric disorders have become highly important. For example, several studies investigated the repurposing of antidiabetic drugs for treating mood disorders, as many of them cross the blood-brain barrier (Heneka et al., 2005; Kastin et al., 2002; Labuzek et al., 2010). An overview of

studies on this topic is described in Supplementary Table 3.

3.6. Antidepressants and mood-stabilisers

As expected, treatment with antidepressants showed an effect on depressive symptoms in samples of depressed patients with comorbid T2DM or altered glycaemic status (Supplementary Table 3). The available clinical trials did not find differences in the decrease of depressive symptoms within 12 weeks when comparing an SSRI vs another SSRI (Gulseren et al., 2005; Khazaie et al., 2011). Two trials reported a higher benefit of agomelatine over an SSRI (sertraline or paroxetine) on depression scores after 12–16 weeks of treatment (Kang et al., 2015; Karaiskos et al., 2013). However, these studies did not provide an estimation of power to support sample size choice, and the statistical significance of the difference between the considered drugs seems doubtful. Other studies compared an antidepressant (SSRI or nortriptyline) vs placebo, and confirmed the benefit of the active treatment on depressive symptoms (Lustman et al., 2000; Lustman et al., 1997), despite one negative 6-month study on a small sample treated with sertraline (Echeverry et al., 2009). A couple of studies investigated the potential benefits of paroxetine in patients with T2DM and subthreshold-mild depressive symptoms, finding no benefits on quality of life in the short term (10 weeks) or after 6 months (Paile-Hyvarinen et al., 2003; Paile-Hyvarinen et al., 2007). A recent network meta-analysis found that escitalopram, agomelatine and paroxetine have evidence of higher benefit on depression severity in patients with T2DM vs placebo, with escitalopram raking first; on the other hand, nortriptyline had a large but non-significant effect (Srisurapanont et al., 2022).

Data about antidepressant efficacy on glycaemic control (HbA1c) are conflicting. Although long-term antidepressant use was suggested to increase incident T2DM risk (see the previous paragraph), SSRIs may improve glycaemic control after 12 weeks, with similar benefits of citalopram and fluoxetine (Khazaie et al., 2011) and higher effect of sertraline over placebo at month 6 (Echeverry et al., 2009). However, no benefits over placebo were reported for citalopram (Nicolau et al., 2013), or no improvement in patients receiving fluoxetine or paroxetine (Gulseren et al., 2005). The results of a recent meta-analysis are helpful to interpret these conflicting results (Srisurapanont et al., 2022). The paper found that vortioxetine, escitalopram, agomelatine, sertraline, fluoxetine, and paroxetine reduced HbA1c significantly more than placebo, with vortioxetine ranking first, followed by escitalopram and agomelatine. The meta-analysis also reported that the hypoglycaemic benefits of agomelatine and vortioxetine were drawn from two trials with a moderate risk of bias. Interestingly, an open-label trial conducted in 93 patients with comorbid T2DM and MDD demonstrated that bupropion hydrochloride improved glycaemic control, BMI, as well as diabetes self-care in the acute phase (10 weeks), and this effect persisted during the maintenance phase (24 weeks) (Lustman et al., 2007). The improvement in glycaemic control in both the short- and medium-term was suggested to be potentially mediated by improvements in mood, although the findings must be interpreted with caution given the lack of a control arm and randomisation, as well as the small sample size (Lustman et al., 2007). Of note, in a large cohort of 93,653 individuals with depression, SSRIs, TCAs and other antidepressants prescribed for at least 12 weeks reduced the risk of incident myocardial infarction within a period of 8 years, with HRs ranging from 0.50 to 0.66 (Scherrer et al., 2011b).

To summarise, the available evidence suggests that antidepressants are effective in treating depression in patients with T2DM, and some antidepressants may have positive effects on glycaemic control, in the short term. Escitalopram seems to have good support for both depressive symptoms and glycaemic control. The positive impact of effectively treating depression in the long term should also be considered. Unfortunately, the studies that investigated the potential effects of mood stabilisers on HbA1c levels and T2DM complications are much scarcer. In patients with BD, mood stabilisers (including lithium) and antidepressants, in monotherapy or combination, were associated with a decrease in HbA1c levels vs no psychotropic medication, independent from having a diagnosis of diabetes (Castilla-Puentes, 2007). On the contrary, antipsychotics in monotherapy or in combination with a mood stabiliser are known to have a negative effect on glycaemic control, while lithium monotherapy may be slightly better than lithium combination with another mood stabiliser (Castilla-Puentes, 2007; Kohler-Forsberg et al., 2022; Kuperberg et al., 2022).

3.7. Antidiabetic medications

3.7.1. Insulin

Insulin receptor knockout mice have depressive-like behaviours, and both depression and cognitive symptoms were associated with low insulin-like growth factor-1 in the elderly (Mueller et al., 2018). Therefore, it was hypothesised that insulin may have effects on both depressive and cognitive symptoms, particularly in the elderly. A previous study tested this hypothesis in type 2 diabetic elderly patients with poor glycaemic control, by randomising them to continuing oral medication, switching to insulin twice-a-day or basal insulin (Hendra and Taylor, 2004). The group that switched to basal insulin showed a decrease in depressive symptoms at months 1 and 3, though not at month 6; however, the study included only 19 patients per arm and the clinical significance and reproducibility of results seem doubtful. Another small study in elderly patients with poorly controlled T2DM adopted a similar design (though not randomised), with one group continuing oral medication and another switching to insulin. This study reported benefits on well-being and mood in the group that switched to insulin, however, as outlined, the study had relevant limitations (Reza et al., 2002).

Other studies tested intranasal insulin effects on mood and cognitive function in healthy individuals (Benedict et al., 2004), in euthymic BD (Mcintyre et al., 2012) or in treatment-resistant depression (TRD) (Cha et al., 2017). These studies were also limited by small sample sizes. The first study reported an improvement in mood and memory after 8 weeks (vs placebo) in healthy individuals, consistently with the results of the second, which found an improvement in executive functioning in BD patients at week 8. On the contrary, the latter study did not find benefits on mood or neurocognitive functioning in TRD.

In conclusion, there is currently poor evidence in support of a possible effect of insulin on mood and neurocognitive functioning, since the results come from small and heterogeneous samples (Supplementary Table 3).

3.7.2. Metformin

Metformin, a biguanide compound, is a commonly prescribed hypoglycaemic agent. Two recent meta-analyses of randomised clinical trials (RCTs) found metformin to have a neutral effect on mood symptomatology compared to placebo and inferior to active controls (Moulton et al., 2018; Nibber et al., 2022). Among the RCTs included in these meta-analyses, only one found metformin to be effective on depressive symptomatology, mainly by improving cognition (Guo et al., 2014). This result is in line with the meta-analytic finding that metformin was superior to placebo in improving cognitive function in patients with cognitive impairment (Nibber et al., 2022).

A recent randomised placebo-controlled study not included in the cited meta-analyses tested adjunctive metformin in a group of non-diabetic patients with treatment-resistant BD and insulin resistance (Calkin et al., 2022). The study reported a significant improvement in depression and anxiety, as well as in insulin resistance, although gastro-intestinal side effects were common.

In conclusion, metformin does not show consistent benefits on depressive symptoms (Supplementary Table 3), and a relevant point for future research would be to test if it may improve specific depressive symptoms (e.g., cognitive symptoms) rather than the whole depressive spectrum. Another hypothesis worth further study is the possible

preventing effects of oral antidiabetics on the development of mood disorders. This was suggested by a population-based study showing that the combination of metformin and sulfonylurea may reduce the risk of mood disorders in patients with T2DM, despite metformin alone did not show a protective role (Wahlqvist et al., 2012).

3.7.3. Thiazolidinediones

Thiazolidinediones, also known as peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, are oral hypoglycaemic agents that ameliorate insulin sensitivity by enhancing fatty acids storage and adipocytes differentiation (Raymond et al., 2014). A first meta-analysis included four RCTs and tested pioglitazone in MDD or BD, showing benefits vs control treatments, on both remission (OR 3.3, 95% CI 1.4–7.8) and symptom improvement (mean difference=2.8, 95% CI 1.4–4.3) (Colle et al., 2017). The benefit of pioglitazone on depressive symptomatology either alone or as an add-on treatment was confirmed by a following larger meta-analysis (Moulton et al., 2018). Interestingly, the improvement in depressive symptoms was predicted by female sex, but not by the severity of depressive symptoms or by glycaemic control at baseline (Moulton et al., 2018). A significant reduction of depressive symptoms was also reported in three open-label studies, two testing pioglitazone and one rosiglitazone (Kemp et al., 2012; Kemp et al., 2014; Rasgon et al., 2010). However, a double-blind placebo-controlled RCT (not included in the cited meta-analyses) failed to demonstrate antidepressant effects of pioglitazone in 38 outpatients with bipolar depression, but it was limited by lack of power and the concurrent use of other psychotropic medications (Aftab et al., 2019).

Overall, there is suggestive evidence for a positive effect of pioglitazone on depressive symptomatology, regardless of a mood disorder diagnosis (Supplementary Table 3). However, previous meta-analyses suffer from high heterogeneity, and future studies should include more homogeneous populations, particularly in terms of psychiatric diagnosis.

3.7.4. Glucagon-like peptide-1 receptor agonists (GLP-1Ras)

Most studies on the neuropsychiatric effects of glucagon-like peptide (GLP-1) receptor agonists (GLP-1Ras) were conducted on animal models (e.g., Chaves Filho et al., 2020). A previous meta-analysis considered the effect of GLP-1Ras on depression rating scales and found GLP-1Ras to be superior in reducing depression compared to control treatments, meta-analysing data that included both depressed and non-depressed patients with diabetes (Pozzi et al., 2019). Limitations of these results are the small number of included studies, the possibility of severe bias found for some studies, and the high heterogeneity.

As outlined for other anti-diabetic treatments, cognitive dysfunction represents a possible target symptom for GLP-1Ras as well. A four-week open-label trial tested the effectiveness of liraglutide on a sample of 19 non-diabetic patients with MDD or BD and below-average cognitive performance (Mansur et al., 2017). The results are clearly preliminary, but it is encouraging that a significant improvement in depressive symptoms and executive functions was observed, with no correlation with levels of glycaemia or insulin resistance (Supplementary Table 3).

3.7.5. Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of oral antidiabetics, also known as gliptins, which act by blocking the degradation of the incretin hormones (Kasina and Baradhi, 2022). These hormones regulate glycaemic homeostasis after food intake by increasing insulin secretion (Kasina and Baradhi, 2022). DPP-4 inhibitors also have anti-apoptotic, anti-inflammatory, and immunomodulatory actions on multiple tissues (Kasina and Baradhi, 2022). These mechanisms seem very promising in terms of a possible antidepressant effect; however, all the available studies provided negative results. An RCT in 44 middle-aged patients with T2DM assessed the effect of sitagliptin, a DPP-4 inhibitor, and found it was inferior to placebo in alleviating depressive symptoms at week 12 (Moulton et al., 2021). The RCT had, however, several limitations, including an inadequate sample size, the exclusion of patients with very poor glycaemic control, and the use of a self-reported measure of depressive symptoms (Moulton et al., 2021). An observational study in 10 elderly patients with T2DM evaluated the effect of the DPP-4 inhibitor vildagliptin, as an add-on to metformin, with no evidence of benefits on depressive or cognitive symptoms at month 11 vs baseline (Tasci et al., 2013). Another RCT compared the DPP-4 inhibitor linagliptin to glimepiride, a hypoglycaemic drug of the sulphonylurea class, and found no differences on cognition, in 3163 middle-aged patients with T2DM, over a median of ~6 years of follow-up (Biessels et al., 2021).

Overall, there is currently no evidence to support the use of DPP-4 inhibitors for the treatment of depressive and cognitive symptoms (Supplementary Table 3); however, there are only three available studies, two of them showed a small sample size, and each of them had a different design.

3.7.6. Non-pharmacological interventions

A Cochrane meta-analysis found a non-significant effect of psychological interventions vs usual care (including pharmacological treatment when indicated) on glycaemic control in individuals with both depression and diabetes, in the short-, medium- and long-term (Baumeister et al., 2012). This meta-analysis also outlined that the quality of the available evidence was low, and it was not possible to evaluate the impact of psychological interventions on the risk of diabetes complications.

When looking at individual studies, the evidence is heterogeneous. Psychotherapy (in particular cognitive-behavioural therapy (CBT)), combined with pharmacological treatment and/or lifestyle modifications, was associated with a higher rate of response in terms of depressive symptomatology, both in the short- (10–12 weeks) and medium-term (6–12 months) (de Groot et al., 2019, Huang et al., 2016, Lustman et al., 1998, Piette et al., 2011, Safren et al., 2014). Only a part of these studies also showed a benefit of the intervention on glycaemic control (de Groot et al., 2019, Huang et al., 2016, Safren et al., 2014). However, these studies were generally limited in sample size (<100 participants in most cases) and were heterogeneous in terms of inclusion criteria, type of intervention and type of control. For example, some studies compared CBT with diabetes self-management training (Lustman et al., 1998), or other forms of enhanced usual care (e.g., educational and self-help material (Piette et al., 2011)), while others used just usual care as control (e.g. Huang et al., 2016).

On the other hand, psychoeducation or behavioural activation vs treatment as usual or other forms of enhanced treatment (e.g., physical exercise) does not seem to provide benefits in diabetic patients with subthreshold depression or depression, according to previous studies in small samples (Pibernik-Okanovic et al., 2009; Pibernik-Okanovic et al., 2015; Schneider et al., 2016).

A recent meta-analysis (32 RCTs, including a total of 3543 patients) contributed to clarify the cumulative evidence (van der Feltz-Cornelis et al., 2021). The results supported the efficacy of group-based therapy, psychotherapy, and collaborative care on glycaemic control in patients with diabetes and depressive symptomatology, with moderate heterogeneity among studies. High baseline depression and high baseline HbA1c were associated with a greater reduction in HbA1c. However, the meta-analysis also outlined that most studies had some risk of bias, mostly unclear reporting about randomization and blinding. Moreover, the control group considered in each study was variable (e.g., waiting list, usual care). Another limitation of this and the meta-analysis discussed above (Baumeister et al., 2012) was the inclusion of RCTs of both type 1 and T2DM, despite the fact that these have different pathogenesis and treatment.

4. Discussion

4.1. Summary of findings

Meta-analyses and cohort studies corroborated the hypothesis of a bidirectional relationship between mood disorders and T2DM (Fig. 1). MDD predicts a higher risk of subsequent T2DM, as confirmed by Mendelian randomisation studies, and this appears the finding with the strongest support emerging from this review. Evidence is scarcer for BD predicting the risk of incident T2DM, and the risk of confounding effects could not be excluded. Studies on T2DM predicting subsequent mood disorders outline a possible association, but show conflicting results, and further investigations are needed, particularly in patients with BD.

Independently from possible causal links, the available studies clearly demonstrated that the co-occurrence of T2DM and MDD can lead to worse outcomes for both conditions. T2DM leads to greater depression treatment resistance, chronicity, and more severe symptoms, while MDD leads to worse medical outcomes and higher mortality in T2DM. Both T2DM and mood disorders are associated with detrimental consequences on cognitive functioning and an increased risk of dementia (Fanelli et al., 2022c; Jorm, 2000). Therefore, the promotion of a healthy lifestyle represents a clinical priority, with the Mediterranean diet and physical exercise having strong support for the prevention of both conditions (Strasser and Fuchs, 2015). The early detection and treatment of impaired glucose tolerance in patients with mood disorders are of similar importance, as well as of anxiety, depressed/irritable mood, or sleep alterations in patients with T2DM (Benasi et al., 2021).

Psychopharmacological treatments may contribute to an increased risk of developing T2DM in patients with mood disorders, particularly in the long term, and it is advisable to avoid combination therapies. However, certain antidepressants and mood stabilizers showed efficacy in treating mood symptoms in patients with T2DM, and they may also have beneficial effects on glycaemic control, at least in the short term. Interestingly, promising results from clinical trials showed potential antidepressant benefits of hypoglycaemic drugs.

4.2. Modulators of the bidirectional association between mood disorders and T2DM

There are multiple confounders that should be taken into account when considering the bidirectional association between mood disorders and T2DM. As noted, these include cardiometabolic risk factors, such as cigarette smoking, which is frequent in mood disorders (Otte et al., 2016). MDD, particularly the atypical subtype, is often characterised by sedentary behaviour and increased appetite, leading to overweight/-obesity (Otte et al., 2016). Patients with BD have disrupted circadian rhythms and a high rate of alcohol and substance consumption (Hunt et al., 2016). Several medical comorbidities may affect mood and increase the risk of T2DM, such as obesity, Cushing's disease, polycystic ovary syndrome, and hypothyroidism (Diez and Iglesias, 2012; Golden, 2007; Kolhe et al., 2022). Further, mood disorders are characterised by low adherence to pharmacological and non-pharmacological medical prescriptions, which may increase the likelihood of incident T2DM (Grenard et al., 2011). On the other hand, the prescription of some medications for mood disorders can increase the risk of metabolic alterations. Long-term treatment with antipsychotics, especially second-generation ones, increases the risk of T2DM (Burghardt et al., 2018; Vancampfort et al., 2016). Almost all the included studies considered some of the discussed confounders and provided adjusted analyses that substantially confirmed the initial results. However, as previously discussed, we noticed a high heterogeneity in the factors each study adjusted for.

Given the metabolic effects of some psychotropic drugs, another significant topic discussed in this review was the possible effect of antidepressant prescriptions in modulating the link between mood disorders and T2DM. The prescription of more than one antidepressant and for a longer period was associated with a higher risk of T2DM (Pan et al., 2010), corroborating the importance of preferring monotherapy when possible. On the other hand, antidepressant combinations prescribed over a long period could indicate a more severe form of depression, e.g., with chronicity and recurrence, which are predictors of T2DM (Andersohn et al., 2009; Rubin et al., 2010). Another issue that suggests the complexity of the illustrated relationship is the finding that antidepressant users may seek medical attention more frequently than untreated or non-depressed people, increasing the likelihood of being diagnosed with medical conditions, including T2DM (Kivimaki et al., 2010). As previously stated, it is necessary to consider all the potential confounders and be cautious in stating that antidepressants may have a role in increasing the risk of diabetes.

4.3. Possible therapeutic effects of medications for mood disorders and T2DM on the other condition

Previous studies hypothesised that antidepressant prescription in patients with T2DM may ameliorate not only depression but also glycaemic control, despite conflicting data. Unfortunately, most antidepressant clinical trials excluded patients with T2DM, while those designed for comorbid mood disorders and T2DM are only a few and had small sample sizes. According to a meta-analysis of observational and cross-sectional studies in patients with T2DM and depression, individual characteristics may influence the probability of receiving an antidepressant prescription, such as sex, ethnicity, concurrent medications and comorbidities (Jeffery et al., 2021). Keeping in mind these limitations and modulating factors, the available evidence suggests that some SSRIs (particularly escitalopram), agomelatine, vortioxetine, and bupropion may have a positive impact on glycaemic control and in the prevention of cardiovascular complications, at least in the short-term (Lustman et al., 2007; Srisurapanont et al., 2022) (Fig. 2).

Lithium is another medication that may have a positive effect in

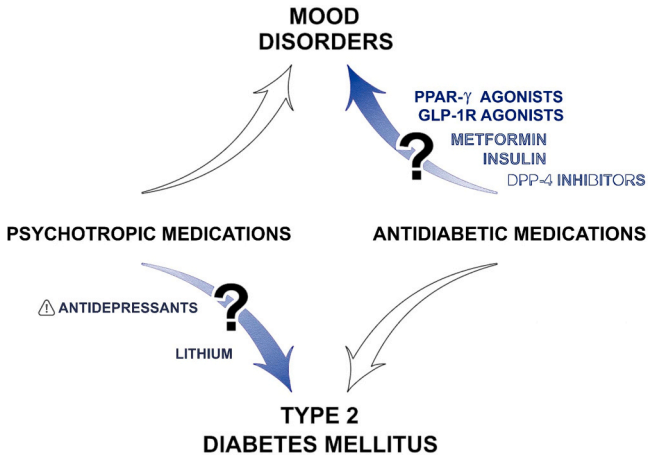

Fig. 2. Effects of treatments for depression and diabetes on either condition. Antidepressants, namely escitalopram, agomelatine, vortioxetine, and bupropion, may have a positive impact on glycaemic control, at least in the short-term, but the prescription of more than one antidepressant and for a long period may increase the risk of T2DM. Suggestive evidence indicates that lithium may improve glycaemic control, possibly by directly acting on the insulin signalling pathway. As shown at the top right of this figure, it has been hypothesised that drugs commonly prescribed for T2DM also exert effects on the brain. GLP1-R agonists and PPAR-γ agonists, such as liraglutide and pioglitazone, have shown promise in relation to their possible antidepressant effects. There is little evidence to support a possible effect of insulin and metformin on mood and neurocognitive functioning. No evidence supported the use of DPP-4 inhibitors for the treatment of depressive and cognitive symptoms. Abbreviations: PPAR-γ = peroxisome proliferator-activated receptor-γ; GLP1-R=glucagon-like peptide-1 receptor; DPP-4 =dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus.

patients with mood disorders at risk of T2DM (Fig. 2). Lithium acts on several molecular intracellular effectors of insulin signalling (Campbell et al., 2022). Indeed, lithium decreases the signalling of the phosphatidylinositol 3-kinase/Protein Kinase B (PI3K/Akt) pathway, by inhibiting the phosphatidylinositol cycle (PI-cycle) upstream and glycogen synthase kinase-3β (GSK3β) downstream (Campbell et al., 2022). Insulin resistance and related hyperinsulinemia lead to chronic GSK3β overactivation, which negatively impacts on glycidic metabolism and energy production at the mitochondrial level (Campbell et al., 2022). Lithium could therefore be considered an insulin sensitiser for cells, as suggested also by animal studies (Lee and Kim, 2007; Rossetti, 1989). Markers of insulin resistance should be considered as possible predictors of lithium response in future studies.

Insulin signalling plays a critical role in the energy metabolism of both neurons and glia, in brain areas involved in mood regulation and cognition (Lyra et al., 2019), therefore antidiabetic medications may exert effects also in the brain (Fig. 2). While insulin does not seem to improve mood, a procognitive action was hypothesised. Metformin was broadly tested for preventing or reducing the metabolic side effects of antipsychotics (Vancampfort et al., 2019) and it may modulate the blood-brain barrier function with neuroprotective benefits (Takata et al., 2013). Nevertheless, clinical studies do not provide conclusive results on possible antidepressant or procognitive effects. On the other hand, encouraging evidence is available for PPAR-γ receptor agonists. Thiazolidinediones' activation of central PPAR-γ receptors protects neurons from oxidative stress and apoptosis, and it enhances mitochondrial energy generation (Hauner, 2002; Villapol, 2018). GLP-1RAs enhance neurogenesis via the 5' adenosine monophosphate-activated protein kinase (AMPK)-pathway and have very preliminary evidence of antidepressant benefits (Andreozzi et al., 2016). Intriguingly, thiazolidinediones and GLP-1RAs exhibit anti-inflammatory effects, attributed to a downregulation of pro-inflammatory genes (Kothari et al., 2016).

4.4. Limitations of the available studies

This review aimed to provide a comprehensive overview on the topic of interest; however, the reviewed studies showed several limitations that should be considered. Longer follow-ups would have been useful to intercept all cases of incident T2DM, which have typically an insidious onset, to better analyse the course of these chronic/relapsing conditions, and to detect the effects of medications on depressive and metabolic symptoms. The heterogeneous presentations of both mood disorders and T2DM should be better considered, to reduce the risk of stratification, and to disentangle possible differences due to disease subtypes (e.g., MDD with atypical vs melancholic features, BD type 1 vs 2), various disease stages (e.g., acute or remission phases, depressive or manic phases, earlier or later stages of T2DM), presence or absence of complications and/or other comorbidities. Another issue that came up as a possible limitation was the use of self-reported questionnaires for the diagnosis of depression in many studies, and the prescription of antidepressants as a proxy for depression in a few studies (e.g., (Ismail et al., 2017; Ma et al., 2011). Likewise, in several studies T2DM was self-reported or assessed using records of antidiabetic treatments (e.g., (Atlantis et al., 2010; Bai et al., 2013), which could result in an underestimation of the incidence of diabetes. Some studies did not differentiate between type 1 and type 2 diabetes. However, $>95\%$ of all diagnosed cases of diabetes are T2DM (World Health Organization, 2022). Finally, as previously outlined, common confounding variables, such as lifestyle and medication use, were not systematically considered in previous research, and some important topics were only marginally or not investigated. It is worth noting that, despite the evidence of brain insulin resistance being involved in BD etiopathology (Mansur et al., 2021), there are no or few studies in BD for all the areas considered in this review. The paucity of studies could be explained by the lower prevalence of BD than MDD (Dattani et al., 2021), and the common use of screening and self-reported questionnaires in population studies, which have low positive predictive values for BD (Smith et al., 2011). Since cross-sectional studies have found that people with comorbid T2DM are more likely to experience a chronic course of BD, as well as rapid cycling, and are less prone to respond to lithium (Calkin et al., 2022; Calkin et al., 2015), future prospective studies should aim to elucidate the complex relationship between T2DM and BD, and to treat more effectively these disabling forms of BD.

5. Conclusion

Epidemiological studies and meta-analyses suggested an increased risk of incident T2DM in mood disorders and vice versa, with possible sex-specific effects. However, the evidence was less strong for the effect of T2DM on incident depression, and these associations may be subject to undetected confounders. T2DM leads to greater treatment resistance, chronicity and more severe symptoms of depression, and depression leads to worse medical outcomes, micro- and macrovascular complications, and higher mortality in T2DM. Some antidepressants may improve glycaemic control in the short term; however, they may be associated with metabolic alterations in the long-term. Lithium may have protective effects on metabolic parameters vs other treatment options, but long-term studies are lacking. The use of some oral antidiabetics, such as thiazolidinediones and GLP-1 receptor agonists, may be beneficial in treating depressive and cognitive symptoms in mood disorders.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105298.

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