Research Article

DISEASE-MODIFYING EFFECTS OF TYPE 2 DIABETES MELLITUS AND BIPOLAR DISORDER COMORBIDITY

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ARTICLE INFO	ABSTRACT
	Aim: The aim of this review was to better understand the risks and care issues associated with poorly managed type 2 diabetes mellitus, in relation to poor prognosis of bipolar disorder. **Methods:** A systematic review of the literature was conducted using combined terms "Type 2 diabetes" OR "Insulin Resistance" AND "Bipolar Disorder" AND "Outcome" AND "Course of illness" in a variety of databases. The publications were all filtered following pre-defined criteria. **Results:** Nine primary articles were selected. The analysis showed that in patients diagnosed with type 2 diabetes, there was association of higher uncontrolled bipolar symptoms period corresponding with the severity of the bipolar disorder. Individuals with bipolar disorder and diabetes mellitus experienced neurodegenerative disorders with more depressive symptoms. Additionally, higher rate of non-compliance was identified with the use of bipolar disorder medications. **Conclusions:** Overall results indicated an overlapping clinical pathophysiology relationship between both diabetes mellitus and neuropsychiatric disorders. There is a need for collaborative care among psychiatric and general medical providers.

INTRODUCTION

Background

The National Institute of Clinical Excellence (NICE) defines Bipolar Disorder (BD) as a lifelong, disabling condition which is categorised by episodes of mania and hypomania[1]. Mania consists of "abnormally elevated mood or irritability and related symptoms with severe functional impairment or psychotic symptoms", defined as bipolar I (BD-I). Hypomania is characterised by "periods of abnormally low mood which relate to symptoms with decreased or increased function for four days or more", this is defined as bipolar II (BD-II)[2]. Anderson, Haddad, and Scott conducted a worldwide survey, which found several countries had a median onset at the age of 25 and overall lifetime prevalence of 0.6% for BD-I, with 0.4% for BD-II[2]. Medical comorbidities are responsible for the early mortality rates in BD. The mortality rateis higher amongst patients diagnosed with manifestations of the metabolic syndrome (obesity and diabetes, cardiovascular illnesses). The highest risk factor is the onset of diabetes mellitus(DM); many studies identified approximately two-fold higher mortality rate in BD with multi-morbidity compared to the general population[3].

Growing evidence supports the existence of a link between BD and DM and suggests "shared risk factors and disease mechanisms"[4]. Type 2 diabetes mellitus (T2DM) isa chronic illness, which frequently goes undiagnosed for many years because the hyperglycaemia develops gradually. At early stages it is often not sufficiently severe for the patient to notice any of the classic symptoms of diabetes. It carries increased risks of a range of complications[5]. The prevalence of T2DM in people with schizophrenia or BD is two to three times higher than in the general population. Amongst patients with severe mental illness, 9.9% and 11.3% had T2DM. In addition, this was identified with causal relationships in overlapping functional disturbances affecting regions of the brain which contribute to manic episodes[6]. This suggests that the high prevalence amongst T2DM patients of BD has clinical implications for self-care and care for those working in diabetes and psychiatry services[7].

In recent literature reviews on this topic, Calkin *et al*.[8] and Charles, Lambert and Kerner[4] raisedthe possibility that these co-morbidities, imposed disease-modifying effects on each other, which appeared substantial, impacting both treatment response and outcome. However, they were unable to evaluate large-scale studies on the late onset of BD, and reported that available literature lacked large sample sizes and longitudinal data[4]. McIntyre *et al*. reviewed cross-sectional and longitudinal studies and based upon the outcomes, recommended a management plan with baseline observations at referral to provide a reference point[9]. Pendlebury and Holt (2010) made similar recommendations[7].

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Overall, these comorbidities appear associated with a severe course of the mental illness, reduced quality of life, and premature mortality[10]. This has led to recommendations that focused attention is required, to improve diagnosis, treatment, management, and outcome[4].

Aim

This systematic review explored recently published cross-sectional, observational and randomised controlled studies. The primary objective was to examine the risks associated with poorly managed T2DM, in relation to, association with, or causation of, BD. Secondly; to examine the long-term care provided for co-existing T2DM with BD. Consideration was also given to the identification of any strategies in place to manage the risk of worsening BD.

Study Question

Why do patients experience a different outcome for BD when diabetes mellitusis present?

METHODS

A systematic search was conducted using combined terms;"Type 2 diabetes" OR "Insulin resistance" AND "Bipolar Disorder" AND "Outcome" AND "Course of illness" in a variety of databases using ScienceDirect, PubMed and Cochrane library for papers published between January 2002 and December 2017. The search revealed a total of 3,127 articles, in which 40 publications were found in PubMed, 2,255 in Summons, 611 in ScienceDirect and 221 in Cochrane library. Potential articles were then screened by titles and abstracts and narrowed down to a total number of 76 publications after removal of replications. Articles were included if they were observational, cross-sectional or randomised, had a pre-defined sample size, participants were above the age of 16 years, had been diagnosed of T2DM, and diagnosed with a BD of any type using DSM VI or V and/or ICD-10. Articles were excluded if participants were diagnosed withtype-1 diabetes or if the article was published in language other than English language, was a systematic review or meta-analysis.A total of nine publications were identified to meet the relevant criteria, as well as strong supporting evidence to effectively meet the aim of the review.

RESULTS

The results from the review are summarised in (Table 1).The nine studies that were identified in this review consisted of three cohort studies, four cross-sectional studies and two randomised trials.

Insert table 1 here

Quality of selected studies

All studies reported information on the methodologies, and all used a quantitative approach. They had detailed thoroughly their methods and their discussion of the results was of high quality. These studies included within the review, followed a pattern, in the sampling methods used (Table 2).

Chronic course and Elevated episodes

In the recent cross-sectional study by Calkin (n=121)>50% of the participants had insulin resistance or T2DM[11]. Those patients with T2DM had 3-fold higher odds of a chronic course of BD and 3 fold higher odds of rapid cycling when compared to euglycemic patients. This was supported by another review which evaluated several cross-sectional and longitudinal studies associated with common underlying mechanisms between the disorders[9]. Ruzickova et al.compared several studies on the clinical features of BD with or without T2DMusing a cross-sectional design[12]. The study compared 26 patients with comorbidity of T2DM to 196 patients without T2DM; all patients were diagnosed with BD. It was suggested that disability with poor overall functioning was present in patients with T2DM. However, there were limitations to this study; there was an age difference between the participants with comorbid T2DM and those without. McIntyre et al. conducted an international retrospective study with a large sample size, which found an association of a more complex illness presentation and less favourable outcome within BD patients when comorbidity with T2DM is present[13].

Mansur et al. conducted a cross-sectional study, in patients with BD, to investigate the moderating effects of impaired glucose metabolism (IGM) on variables of illness and severity of BD[14].Their outcomes also suggested that patients with IGM had an earlier onset of BD, with longer duration of illness experienced and higher ratio of manic and hypomanic to depressive episodes. Overall the results suggested a possible accelerating disease course in the IGM subpopulation. The study consisted of 55 patients with BD, of which only 8 individuals had been diagnosed withT2DM, so is not readily generalised. A high proportion of women were recruited in the study of Sylvia et al. which could potentially indicate some link with biochemical differences in genders[14].In a 12.5-year observational study, it was again identified that patients with T2DM among patients with BD had a higher hospital mortality rate and experienced more complications[15]. Evidence from a recent review by Buoli, Serati and Altamura supported the association of rapid cycling BD with severe biological abnormalities and revealed that participants within the studies had signs of increased damage to DNA and presented with more endocrine dysregulation[16]. Although this review found potential and actual candidate biomarkers, most of the studies included, used wide inclusion criteria and open-label design which limited heterogeneity. Subsequently, they found rapid cycling to worsen the course of BD, however, the sample was limited, and obesity was high in this cohort of participants[17].Although obesity and impaired glucose tolerance is prevalent in patients with BD who currently take antipsychotics, it has been suggested that these factors are present within these individuals before taking these medications[6]. In support of this, it was discovered that the use of multiple drugs can affect the overall course of illness in BD[17].Furthermore, some recent studies evaluated biomarkers such as oxidative stress and adiponectin in patients diagnosed with both BD and IGM. It was shown that these disorders had a negative impact on the illness course with low values of these biomarkers signifying an increased number of episodes[18,19].

A recent clinical study on the metabolic syndrome and adverse clinical outcomes in patients with BD studied 143 stable outpatients aged 18-65 performing fasting biochemical assessments to investigate the prevalence of metabolic syndrome[20]. Bai et al. found that patients with BD and T2DM had more adverse clinical outcomes than those without; including more hospitalisations, poorer insight, poorer global function and more impaired executive functioning.

Table 1 Evidence for effects associated with type 2 diabetes mellitus (DM) prevalence and poor management in bipolar disorder (BD)

Author	Title	Type of study	Types of Bipolar Disorder	Types of Diabetes Mellitus	Method of evaluation	Participants Age (Years)	Population (n) of BD participants	Results for both BD and T2DM
Calkin *et al.* 2015	Insulin resistance and outcome in bipolar disorder	Cohort	Bipolar type 1 and 2	Type 2 diabetes mellitus and insulin resistance	Maritime bipolar registry	> 18	121	50% and 48.7% of BD patients with DM and IR had a chronic course of illness, 38.5% and 39.5% of DM and IR patients had higher rates of rapid-cycling than euglycemic, 36.8% and 36.7% of DM and IR patients more likely to be refractory to lithium
Hajek *et al.* 2014	Insulin resistance, diabetes mellitus and brain structure in bipolar disorder	Cross-sectional	Bipolar type 1 and 2	Type 2 diabetes mellitus and insulin resistance	Maritime bipolar registry	> 18	33 with insulin resistance, 26 without	Smaller hippocampal volume in BD patients with IR or T2DM
Ruzickova *et al.* 2003	Clinical features of bipolar disorder with and without comorbid diabetes mellitus	Prospective	Bipolar type 1 and 2 or other	Type 2 diabetes mellitus	Maritime bipolar registry	> 18 Average age = 52.5 with DM and BD	26 diabetics 196 non-diabetics	11.7% of DM prevalent in the population Higher rates of rapid cycling. The more chronic course of BD with DM, Patients scored lower on global assessment of functioning scale
Bai *et al.* 2016	Metabolic syndrome and adverse clinical outcomes in patients with bipolar disorder	Clinical cohort	Bipolar disorder type 1 and 2	Type 1 or 2 diabetes mellitus	Psychiatric outpatient in a university hospital	16-65	143	BD patients had 29.4% prevalence of a metabolic syndrome. Those who had a metabolic syndrome had more previous hospitalisations, poorer global function, and more impaired executive function
Mansur *et al.* 2016	Impaired glucose metabolism moderates the course of illness in bipolar disorder	Cross-sectional	Bipolar disorder any type	Impaired glucose metabolism or type 2 diabetes mellitus	Outpatient unit	> 18 Average age = 42.85 with DM and BD	55	IGM and DM patients had an earlier age of onset of BD, Longer illness duration and a higher ratio of manic/hypomanic to depressive episodes
Kemp *et al.* 2010	Medical comorbidity in bipolar disorder: the relationship between illnesses of the endocrine/metabolic system and treatment implications	Randomised double-blinded and open-label	Bipolar disorder type 1 and 2	Type 2 diabetes mellitus	University medical care center	18-65	225	Illness of the endocrine/metabolic system correlated with depressive symptoms. With A 1-unit increase in BMI, response decreased 7.5% to lithium and valproate
Sylvia *et al.* 2015	Medical burden in bipolar disorder: findings from the clinical and health outcomes initiative in comparative effectiveness for bipolar disorder study (Bipolar CHOICE)	Randomised	Bipolar disorder type 1 and 2	Type 1 and 2 diabetes mellitus	Medical database	18-68	482	Early age of onset of BD symptoms, lower chance of cardiometabolic conditions. Although more time spent depressed, longer duration of illness for DM patients, particularly females
Mansur *et al.* 2016	Brain-derived neurotrophic factor, impaired glucose metabolism, and bipolar disorder course	Open-label	Bipolar disorder type 1 and 2	Impaired glucose metabolism and type 2 diabetes mellitus	Outpatient unit	>18	83	In adjusted models for IGM and T2DM patients, lower levels of BDNF were found and more psychiatric hospitalisations, suicide attempts and number of previous mood episodes associated
Hajek *et al.* 2015	Type 2 diabetes mellitus: A potentially modifiable risk factor for neurochemical brain changes in bipolar disorder	Cross-sectional = 4.57, p=0.06	Bipolar disorder type 1 and 2	Type 2 diabetes mellitus	Maritime bipolar registry	>18	59	Levels of N-acetyl aspartate were lowest in DM patients compared to euglycemic

Table 2 Summary of included reviews

Articles	Sampling	Dropouts	Age	Interview method and location
Hajek *et al.*, 2014	Purposive	Not reported	Reported	Not reported
Ruzickova *et al.*, 2003	Purposive	Not reported	Reported	Not reported
Bai *et al.*, 2016	Purposive	Not reported	Reported	Not reported
Mansur *et al.*, 2016b	Purposive	Not reported	Not reported	Not reported
Calkin *et al.*, 2015	Convenience	Reported	Reported	Not reported
Mansur *et al.*, 2016a	Convenience	Reported	Not reported	Not reported
Hajek *et al.*, 2015	Random	Not reported	Reported	Not reported
Sylvia *et al.*, 2015	Random	Reported	Reported	Not reported
Kemp *et al.*, 2010	Random	Reported	Reported	Not reported

However, alimitation was that only 10 individuals out of all participants had T2DM, which indicates a poor representation of the population in relation to the outcomes assessed. In addition the cognitive function and clinical examinations were assessed by the author. In comparison, Sylvia *et al.* conducted a randomised multi-site study of the medical burden in BD, for a comparative trial of lithium or quetiapine for six months[14]. The research conducted consisted of 482 participants with BD-I and BD-II.

Only 6.2% of the overall participants had T2DM, which supported evidence that hypertension is the most common manifestation of the metabolic syndrome found in patients diagnosed with BD[14,20]. Patients with T2DM along with common metabolic disorders had a higher prevalence in older ages but had less severe manic symptoms. This outcome could be related to a link between metabolic disorders and depression. The study indicated that those using lithium in comparison to quetiapine had lower overall rates of depression

and mania on average. The limitation of this study was that the information collected was assessed at a single time point.

Brain Abnormalities

Both type 1 and 2 DM are associated with a variety of central nervous system complications including distorted brain imaging, increased rates of cognitive decline, the risk of neurodegenerative diseases and depression. Although alterations in insulin signalling leads to complications, these are poorly recognised[21]. In T2DM, hyperglycaemia and hyperinsulinemia activate proteins involved in the insulin signalling pathways, facilitating insulin resistance[22]. A study by Liu *et al.* found that due to the protein content, insulin activity in the brain and signalling pathways are decreased in T2DM which leads to overactivation of GSK-3β and downregulation of insulin receptors in the brain, leading to neurodegeneration and impaired cognitive function in the long-term[23]. In a recent study, Mansur *et al.* measured and compared plasma levels of the biomarker Brain-Derived Neurotrophic Factor (BDNF) in individuals with BD and within healthy controls, to assess the moderating effect of IGM[24]. The study carried out was a randomised study, which consisted of 83 patients across both active and controls. They found that individuals with BD had lower levels of BDNF, which indicates that IGM may modify the relationship between the course of BD and the biomarker readings. Furthermore, the study found that the levels of BDNF were related to lifetime depressive episodes, psychiatric hospitalisations and suicide attempts. The sample size in this study was small and it used cross-sectional design. Fujinami *et al.* found similar results suggesting that aging is a factor that influences serum BDNF levels[25].

Hajek *et al.* conducted a cross-sectional study, on 59 BD patients[26]. They found that T2DM damages the hippocampus, causing atrophy; however, this was identified as being preventable. The methodology of the study included interviews, performed by clinicians and was reviewed in a blinded fashion. It was found that the group of BD patients with T2DM had a smaller hippocampal volume. The results provided evidence that diabetes care amongst BD patients can be improved. In a similar study, Hajek also attempted to understand the brain structure changes with IGM and T2DM. In their later observational study, readings indicated that BD patients had the lowest N-acetyl aspartate levels and total creatine, providing evidence of neurochemical alterations, indicating poorer functioning and clinical outcome in patients with these co-morbidities[27]. Once again, on average BD patients with co-morbid T2DM experienced more hospitalisations, longer duration of illness and higher history of psychotic symptoms, but overall, a lower number of illnesses over the study period compared to other BD patients. It was found that the association with elevated neurochemical alterations originated from IGM changing to T2DM. There were several limitations to both studies; the cross-sectional design limited associations being made between T2DM and brain structure. There were also some strengths; the biochemical evaluation, which assessed both T2DM and BD together with other clinical information allowing control for potential confounders.

Song found that a group of patients with metabolic syndrome showed a significant reduction in mean cortical thickness and volume in both brain hemispheres compared with control studies indicating that neurodegenerative processes, due to

metabolic syndrome, are present even in the preclinical stage when compared to patients with BD[28].Yates *et al.*, reviewed several studies and identified a correlation between these metabolic disorders and brain function[29]. Although within these studies, differences in the population demographics, ages and gender explained lack of consistency throughout their findings.

It was identified that in the older patient, cognitive impairment may interfere with psychosocial functioning in BD patients compared to younger patients[30]. In support, Schouws *et al.*, conducted a study to examine the neuropsychological functioning in a group of 119 elderly patients with early and late onset BD compared to a control group of 78 patients without BD[31]. The findings included BD patients scoring the lowest on almost all the cognitive measures used. The limitations were that the actual age of participants and the medications they used were not indicated. The late-onset participants were more impaired in psychomotor performances than the early-onset patients. Conversely, Beavers found no relationship between decline in cognitive function and high HbA1c readings. In agreement[32] Musenreviewed the previous literature and found no group effects on brain structure or cognition decline with T2DM alone[33].

Treatment Refractory

An association between poor treatment response and outcome was noted in patients with BD and metabolic disorders. Calkin *et al.*, observed 80 BD patients receiving a trial of lithium for 6-months, to assess for a response to treatment using the Alda scale[11]. The study found patients with Insulin Resistance (IR) and T2DMwere refractory to lithium treatment. However, the 6-month period of assessment was too short to confirm the validity of this finding. Similarly, Kemp *et al.* examined,in an open-label study, the relationship between the medical burden of BD in 225 patients taking lithium and valproate for rapid-cycling presentations of BD[34]. The results showed that in patients who were receiving lithium and valproate, individualswithT2DM, had a greater risk of depression and poorer treatment outcomes. It was hypothesised that a possible mechanism in insulin resistance and T2DM, is that patients experience chronic peripheral hyperinsulinemia, which has been linked to down regulation of insulin receptors within the blood-brain barrier, to restrict the insulin channel to the brain[35].

Kemp *et al.* (2010) identified "that for every 1 unit increase in BMI over 23, the chances of response to treatment is decreased by 7.3%"[34].The limitations of this study, was that rapid-cycling BD was only treated with lithium and valproate in combination and was not compared to another comparative drug.

Unsatisfactory Diabetes Care

It is suggested that only a fraction of individuals with BD seek treatment[15]and this the lack of treatment is known to lead to a chronic, difficult to treat condition and poor quality of life[10]. In addition, easier admission to private hospitals was shown to increase the BD patients'admission rate when compared to general hospitals and primary care trusts[15].This was supported by Sullivan,*et al.* in a database retrospective study; the authors found that out of 4,275 visits byT2DM patients hospitals across America, only 136 visits were made by persons with comorbid psychotic disorders. In those 136 patients, a direct

link was found in relation to poor self-management due to psychiatric disorders and need for emergency care[36].

Winkley *et al*. found poor attendance at diabetes education sessions amongst mental health patients (20%)[37]. Goldberg *et al*. found poorly documented access to medical care by those who had mental illnesses due to social and environmental factors[38]. In support, it was found that patients with severe mental illnesses may have poor access to general healthcare, with fewer opportunities for cardiovascular risk screening and poor prevention schemes available, in comparison to non-psychiatric groups[39].

An earlier study by Dixon *et al*. compared HbA$_1$c levels in 200 patients with T2DM and schizophrenia with major mood disorders, to a control group of 100 patients with severe mental illness[40]. The results were surprising, as findings suggested that patients with severe mental illnesses across the three groups had lower HbA$_1$c levels in comparison to those without mental illnesses, however there was no data specific to BD patients.

A group of T2DM patients with mental illnesses was recruited from number of mental health centres, and compared to a group recruited from primary care trusts, regarding their ability to self-care. HbA$_1$c and knowledge about diabetes were poorer in patients treated in mental health centres than in those in primary care[41]. Nevertheless, the study did not control other health-related features, such as the use of medications, which can adversely affect outcomes. This study was not randomised.

Considering that BD has elements of depressive mood, the findings of Shin *et al*.[42] and Lunghi *et al*.[43] may be applicable. Shin reported that individuals with different types of depression had impaired problem-solving abilities which may have accounted for poor self-management[42].This was supported by Lunghi *et al*. looking at medication adherence in patients taking anti-diabetics within two groups of patients; one included patients diagnosed with depression and the other patients without a depression diagnosis. Within the study, 52% participants in the first group experienced non-adherence to the drugs compared to 49% of participants in the second group[43]. This suggests that depression was an independent risk factor for anti-diabetic non-adherence. Similar findings came from a study by Gonzalez, which found low adherence to dietary intakes such as fruits and vegetables, and poor exercise and foot care[44].

Integrated Care

It is suggested that a "stronger integration of medical and psychiatric care could help prevent the negative effects of these co-occurring disorders on the long-term outcome of patients with BD"[4]. Supporting this, Coventry *et al*. conducted a cluster-randomised trial to test the effectiveness of an integrated collaborative care model for patients with long-term mental and physical comorbidities. They concluded that the integration of low-intensity psychological treatment with primary care can improve self-management in the short term but required the practitioners to be trained to deliver the integrated service[45]. Similarly, Chwastiak *et al*. demonstrated the probability of successful implementation of a collaborative care program for poorly controlled T2DM patients in the urban community within primary care clinics using a retrospective cohort design[46]. A total of 151 patients with mental disorders including BD, using the program, had a decrease of 0.9mmol/molin HbA1c levels vs. a 0.2 mmol/moldrop in 483

patients who did not attend the program. This suggested that integration of collaborative healthcare is a promising strategy for chronic disease management. It was acknowledged that poor assessment of patients with mental illnesses such as BD causes challenges such as patients not being able to recall the hypo – or hyperglycaemia episodes they experienced. Often, symptoms are mistaken for other psychiatric illnesses leading to misdiagnosis[47].

In respect of care for BD, Kilbourne *et al*. conducted a randomised controlled trial to examine a psychological care model in comparison with medical care model[48]. Fifty eight participants were recruited of whom, 27 received BD care based on the psychological model and the rest received care based on the medical model. There was a significant difference in physical health, with evidence of a decline in quality of life in the psychological model group after 6-months compared to those treated under the medical model where improvements were shown. When using the medical model of care, specific care goals were set, including recognition of the mania and depressive episodes and changeovers, identification of triggers and improvement of coping strategies such as setting diet and exercise goals. Additional aspects were considered in depressive episodes such as suicide prevention and follow up on treatment adherence[48].

Pharmacological Management

Bennett *et al*. focused on identifying the benefits and harms of antidiabetic medications such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists; as mono- and combined therapies in T2DM adults[49]. The results from this study showed that all the anti-diabetic medications used had broadly similar efficacy, in reducing levels of HbA$_1$c by 1 percent over the course of the study as a monotherapy. In comparison, Metformin had a higher percentage of HbA$_1$c reductions. In support, Wahlqvist *et al*. evaluated whether anti-diabetic medications were a pre-cursor for affective disorders including BD[50]. Follow-up studies followed a large-scale cohort (n= 800,000) of Taiwanese subjects over 50 years of age. The results identified that the combination of both sulfonylureas and metformin reduced the risk of worsening BD in T2DM, regardless of gender. The use of a large cohort study was considered as study strength, however, the study did not factor for the severity of diabetes within the individuals as they were recruited from a database.

The recent a 6-week randomised double-blinded trial by Zeinoddini *et al*. which evaluated safety and efficacy of pioglitazone in patients diagnosed with T2DM or metabolic syndrome with BD comorbidity; found that patients who took pioglitazone experienced an improvement in their depressive symptoms[51]. However, no physical assessment was undertaken, and accordingly it was difficult to determine if the drug was reliable in treating the diabetes to establish relationship between the improvement of diabetes control and the improvement of depressive symptoms. Oliveira *et al*., found that there was a significant improvement in depressive symptoms and physical functioning with the use of insulin leading to a reduction in HbA1c, however, there were few significant differences found in BMI and disease complications[52].In addition, a systematic review described how anti-diabetic medication had neurophysiological benefits, helping with both T2DM and long-term BD outcomes. The

author stated that specifically, thiazolidinediones were more effective in comparison tometformin[53].

Non-Pharmacological Management

McIntyre *et al*., specified that a complete evaluation of patients with BD should be carried out, as well as an assessment of both behavioural and medical factors[9]. These assessments include eating disorders; tobacco use, illicit drugs use or alcohol consumption, thyroid dysfunctions, T2DM (HbA$_1$c) and obesity (baseline body weight). In support, a randomised trial was recently conducted on 5,145 patients diagnosed with T2DM and BD, over 10 years. It examined the effects of intensive lifestyle intervention in comparison to medications alone. A considerable reduction in frequency was found for mild or more severe depressive symptoms (Beck Depression Inventory score ≥10) within these patients, in comparison to medications alone. A limitation found in this study was that quality of life was not assessed, which could have adversely affected the outcome of results[54].The daily intake of fruits, vegetables, whole grains and unsaturated fatty acids was found to be beneficial[55].

Evidence has found that regular physical exercise allows the body to reduce plasma glucose levels, by increasing the uptake of glucose into skeletal cells[55]. Kuyci *et al*. conducted a recent review of studies on the enhancement of treatment outcomes in patients with BD by incorporating aerobic exercise[56]. The results showed an array of links between effects on neurocognitive functions, neurotransmitter systems and insulin sensitivity across diverse ages, gender and populations. However, the intensity of exercises and the risk of precipitating a manic episode vs the benefit in depressive episode was not studied. Similarly, Sylvia, Ametrano and Nierenberg identified that those healthy individuals who participated in regular exercise interventions, had an association with increases in BDNF[57]. In addition, Conn *et al*. (2014) found through a meta-analysisa moderate improvement in HbA$_1$c levels[58].

A study by Ng, Dodd and Berk, investigated the effectiveness of a walking programme in acute BD, it was found that small changes in stress- and depression-related scores were identified from participants compared to non-participants[59]. This provided support for a therapeutic indication for mild physical activity in the acute treatment of BD

In support, it was discussed by Wright *et al*.,that it is important for clinicians to ensure patients are aware of positives and negatives that may arise during physical exercise interventions[60]. In contrast, it was concluded within a recent study by Sorkin *et al*. that clinicians should accentuate the importance of identifying and treating mental health issues to guide in prescribing appropriately in patients with T2DM[61].

LIMITATIONS OF THE REVIEW

A common limitation found across the studies was the use of cross-sectional design; this limited the significance, as it contributed to a higher level of bias, since associations between the intervention and control groups could not be established. Using perspective or observational designs would provide a better approach towards detecting associations, and can be used as an alternative to interpreting data as causal relationships. The publication dates of literature analysed covered a 15-year span and a number of countries. These factors allowed for disparities amongst the findings, as the

healthcare systems, screening equipment, and techniques, as well as the diagnostic criteria, were different. The medications being used within the studies may have affected the results observed; in addition, high rates of depression were identified across several studies which were represented as an intervention group in comparison to bipolar disorder as there was limited literature available. This may not have beena suitable representation of patients in this population.

CONCLUSION

In conclusion, due to the considerable burden associated with BD, the need for integrated care has been highlighted. Positive outcomes can be achieved. The optimal use of anti-diabetes medications, good diet and mild physical activity can improve both disorders. Overall, a suggestion for the use of future closer monitoring within this population is appropriate to recognise early signs and prevent the onset of T2DM in BD patients. However, it is clear that further longitudinal studies are required, focussing on assessing future therapeutic approaches in the population with BD and T2DM comorbidity to improve their health outcomes.

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