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# BIPOLAR DISORDER AND DIABETES MELLITUS

## Clinical Features of Bipolar Disorder with and without Diabetes Mellitus

**Martina Růžičková, MD, FRCPC**
Third Faculty of Medicine, Charles University
Prague Psychiatric Center, Czech Republic

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PhD Thesis

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# BIPOLÁRNÍ PORUCHA A DIABETES MELLITUS

Klinické Koreláty Bipolární Poruchy s a bez Diabetes Mellitus

Discipline/Programme: Neuroscience

Board Chair: Prof. MUDr. Karel Šonka, DrSc.

Institute: Prague Psychiatric Center, Ústavní 91, 181 03, Praha

Author: MUDr. Martina Růžičková, FRCPC

Supervisor: Prof. MUDr. Cyril Höschl, DrSc.

**Declaration**

I hereby declare that this thesis is my own work and to the best of my knowledge and belief I have listed all sources of information used.

September 1, 2011 in Halifax
Martina Růžičková

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# Contents

**ABSTRACT**

Despite lots of research, the genetic and pathophysiological basis of bipolar disorder (BD) remains unclear. One of the possible reasons is that BD spectrum comprises a heterogeneous group of different subtypes of the illness sharing certain pathophysiological or genetic mechanisms. Patients with co-morbid diabetes mellitus (DM) may represent such a subgroup of BD with a distinct pathophysiology and possibly different clinical characteristics of BD. This thesis is aimed at investigating the possible link between BD and DM. Bipolar patients have about 3 times higher risk of DM (type 2 in particular). The first part of my thesis outlines the possible links between DM and BD, including medication, alterations in the hypothalamo-pituitary axis and signal transduction, and genetics. In the second part, I examined the possible differences in clinical characteristics between patients with (N=26) and without (N=196) co-morbid DM. Next, I examined the variables showing differences between groups, using logistic regression.

Patients were recruited via The Maritime Bipolar Registry. The prevalence of DM was 11.7%. Diabetic patients were significantly older than non-diabetic patients ($P < 0.001$), had higher rates of rapid cycling ($P = 0.02$), more chronic course of BD ($P = 0.006$), more disability ($P < 0.001$), lower scores on GAF ($P = 0.01$), higher BMI ($P < 0.001$) and more hypertension ($P = 0.003$). Treatment with antipsychotics was not significantly associated with a higher risk of DM ($P = 0.16$).

The findings suggest that the diagnosis of DM in BD has relevance for the clinical course, prognosis and outcome of BD. The clinical implications are discussed in the thesis. The findings support the assumption that patients with co-morbid DM represent a subgroup of BD with possibly distinct pathogenesis and clinical picture, and will be used for genetic research of BD at Dalhousie University.

**Key Words:** Bipolar disorder, diabetes mellitus, co-morbidity, clinical correlates, clinical course, pathophysiology, genetics, heterogeneity.

**ABSTRAKT**

Patofyziologický a genetický podklad bipolární poruchy (BP) je stále nejasný i přes množství výzkumu věnovaného tomuto onemocnění. Jedním z možných důvodů je, že spektrum BP obsahuje heterogenní skupinu podtypů BP definovaných určitými patofyziologickými a genetickými mechanismy. Pacienti s komorbidním diabetes mellitus (DM) mohou představovat takovou podskupinu BP charakterizovanou určitou patofyziologií a klinickým obrazem BP. Základem této disertační práce je studium vztahu mezi BP a DM. Pacienti s BP mají asi 3 krát vyšší prevalenci DM (zvláště 2. typu). V první části práce se zabývám možnými souvislostmi mezi BP a DM s ohledem na farmakoterapii, změny ve funkci hypotalamo-hypofyzární osy a v signální transdukci a možnou společnou genetickou predispozici. V druhé části práce jsem porovnala data bipolárních pacientů s (N=26) a bez (N=196) komorbidního DM rekrutovaných přes Maritime Bipolar Registry, abych zjistila, jestli se tyto dvě skupiny bipolárních pacientů liší v klinických charakteristikách. Charakteristiky, ve kterých se pacienti lišili, jsem dále použila v logistické regresi.

Prevalence DM u BP v bipolárním registru byla 11.7%. Věk pacientů s DM byl vyšší ($P < 0.001$), měli více rychlého cyklování ($P = 0.02$), chronického průběhu BP ($P = 0.006$), nižší skóre na GAF Scale ($P = 0.01$), více pracovní neschopnosti ($P < 0.001$), vyšší BMI ($P < 0.001$) a vyšší prevalenci hypertenze ($P = 0.003$). DM nebyl asociován s léčbou antipsychotiky ($P = 0.16$).

Z výsledků této studie vyplývá, že komorbidní DM má vliv na prognózu a průběh BP. V disertační práci shrnuji možné využití výsledků v klinické praxi. Výsledky podporují hypotézu, že pacienti s DM představují podskupinu BP s určitou patogenezí a klinickým obrazem a budou použity pro genetický výzkum BP, který probíhá na Dalhousie University v Halifaxu.

**Klíčová slova:** bipolární porucha, diabetes mellitus, komorbidita, klinický průběh, klinické koreláty, patofyziologie, heterogenita, genetika

## LIST OF TABLES



## LIST OF FIGURES

## PREFACE

Bipolar disorder (BD), also called manic – depressive disorder, is a complex psychiatric illness. The lifetime prevalence is approximately 1%. It is characterized by recurrent episodes of depression and mania or hypomania. The quality of life of bipolar patients is significantly affected by its life-long character.

BD represents one of the major health problems due to a high rate of disability and mortality. In 2000, the World Health Organization identified BD as the fifth leading cause of disability for the age group of 15 to 44 years (The World Health Report 2001) (1) (see Appendix A1).

The increased mortality in bipolar patients is not only due to suicide as would be expected in a psychiatric disorder with up to 20% risk of suicide. This population has increased rates of deaths due to cardiovascular reasons, when compared with the general population, as well (2). From this point of view, the fact that BD has been associated with a high prevalence of conditions considered to be risk factors for cardiovascular disease, such as diabetes mellitus or obesity is of particular interest (3-6).

Despite the amount of research devoted to BD, the etiological, genetic and pathophysiological basis of this illness remains unclear. One of the possible reasons is that bipolar spectrum disorders might represent a heterogeneous group of different subtypes/subgroups of this illness sharing the clinical feature of bimodal changes in mood. These subgroups might be characterized by distinct genetics, alterations in signal transduction, distinct clinical course or co-morbidities. Identification of such alternative phenotypes would help to unravel the pathophysiological basis and genetics of BD and facilitate the search for targeted treatments.

As mentioned above, bipolar patients have a higher risk of diabetes mellitus (DM) than the general population. The link underlying the increased co-morbidity between BD and DM is yet unknown. However, it is possible that BD with co-morbid DM share some common mechanisms predisposing them towards both, DM and BD.

Patients with BD and co-morbid DM might then represent a subtype/subgroup within the heterogeneous spectrum of bipolar disorders.

My thesis is devoted to investigating the possible link between BD and DM (non-insulin dependent diabetes mellitus in particular) and search for clinical characteristics shared by this subgroup of bipolar patients.

In the first part of my thesis, the Introduction, I will outline the literature suggesting a higher risk of DM in BD, the possible causes that might increase the risk of DM in BD, and the mechanisms that these disorders may have in common as intrinsic factors predisposing bipolar patients towards developing DM and *vice versa*. In the clinical part of my thesis, I will investigate whether bipolar patients with co-morbid DM differ from bipolar patients without co-morbid DM in clinical characteristics. The results of this study might lead to a better phenotypic characterization for future research. Depending on the results, this research might be the first in a series of studies that would use this co-morbidity in a search for genes involved in BD and for investigating the link between BD and DM.

# 1 Introduction

The association between manic - depressive illness and abnormalities in glucose metabolism had already been pointed out by several authors at the beginning of the last century (7;8). Since the second half of the last century, several researchers have investigated abnormalities in glucose metabolism among patients with manic depression, either in relation to the effects of lithium (9-11) or with respect to alterations in glucose metabolism during and outside of mood episodes (12;13). These studies were based mostly on the evidence of changes in glucose metabolism following lithium administration or on previously reported disturbances in glucose metabolism observed in the psychiatric population. Despite initial evidence, the first study that systematically examined the prevalence of DM in patients with manic depression appeared only in 1980 (5); it was followed by 2 additional papers in subsequent years (3;6). All 3 studies used the chart review method, and all found increased rates of DM in BD patients. In particular, Lilliker (1980) found the prevalence of DM to be 10% in 203 patients with manic depression, while the expected prevalence for the sample was 2% (5). Cassidy et al.(1999) reported a DM prevalence of 9.9% in a sample of 345 BD patients, compared with a prevalence of 3.4% expected for the general population (3). In a small sample of 53 patients, Regenold et al. (2002) found DM in 26% of BD I patients, while the expected rate was 13% (6). The mean age of subjects in this study was higher than in the studies of Lilliker et al. (1980) and Cassidy et al. (1999), which accounts for the higher observed (as well as expected) DM rates.

The reverse relation - a higher frequency of BD in subjects with DM - has been shown as well. Lustman et al. (1986) found a prevalence of 5.3% for mania and atypical BD in patients with DM type 2 (14). This is significantly higher than the lifetime prevalence of BD in the general population, which is usually estimated at 1%.

Several possible mechanisms can play a role in the increased co-morbidity of the two disorders. An alteration in glucose metabolism due to effects of medication is one of them. Relatively recently, the co-morbidity of DM and BD has been emphasized in

the context of increasing evidence of the link between treatment with antipsychotic drugs and new onset DM (15-17). Some studies, however, have suggested that treatment with antipsychotics alone could not account for the entire risk of developing DM in bipolar patients (6). Moreover, changes in glucose metabolism in BD were documented in the literature already before the era of atypical antipsychotics (7). The effect of medications commonly used for treatment of BD on glucose metabolism is outlined in the next part of this thesis.

In addition to the effect of medication, there are many other possible links between BD and DM including lifestyle, hypothalamo-pituitary-adrenocortical axis (HPA) dysfunction and alterations on signal transduction level; mechanisms that are possibly based on genetic factors. The literature search revealed more details with regards to the above mentioned putative links. These links are outlined in this thesis in more detail as a theoretical basis for this study, which is the first study investigating differences in various clinical characteristics of bipolar patients with and without co-morbid DM.

## 1.1 Treatment for bipolar disorder as a cause of diabetes mellitus?

The management of BD includes treatment of depressive, manic, hypomanic or mixed episodes and prophylactic treatment aimed at preventing future episodes.

### 1.1.1 Does lithium treatment cause diabetes mellitus?

Having been used for more than half a century, lithium remains the gold standard in treatment of BD. It prevents recurrence of affective episodes in the maintenance phase of BD and is effective for treatment of acute depression and mania.

Lithium administration has been associated mostly with increased glucose uptake or increased glucose tolerance in animal, human and *in vitro* studies (9;18-22). Several observations of lithium induced hyperglycemia or acute-onset IDDM (insulin dependent diabetes mellitus) have been published in the form of case reports or animal research (23-25).

The majority of evidence so far suggests that lithium has a positive effect on glucose tolerance. In terms of short term effects of lithium treatment, Van der Velde and Gordon (1969) were among the first to examine glucose tolerance of lithium patients and found that the intake of lithium carbonate was followed by an increase in glucose tolerance. The improvement in glucose tolerance was reversed after discontinuation of lithium (9). Hu et al. (1997) showed significantly decreased fasting plasma glucose (FPG) and 1-h postprandial blood glucose after short-term lithium treatment in patients with diabetes treated with oral hypoglycemic agents or insulin. Thus, suggested an assisting hypoglycemic effect of lithium on antidiabetic treatment (26). Considering long-term lithium treatment, another study found a significant lowering of FPG after one year of lithium treatment followed by a rise to normal levels after three years (27). Agbayewa (1982) hypothesized that longer lithium treatment would lead to a further rise of FPG, thereby putting users at risk of developing impaired glucose tolerance (IGT) or DM. A follow-up study, however, failed to find any further effect of lithium treatment on glycosylated hemoglobin which reflects glycemic control over the previous 2 – 3 months (28). Finally, Vestergaard and Schou (1987) carried out a six-year prospective study of fasting blood sugar levels in patients on lithium. They examined 460 patients before lithium treatment, 226 patients after 6 months of treatment with lithium, and then decreasing numbers of patients on lithium for up to 6 years. They found no significant changes in their mean fasting blood sugar levels. Only one patient, a 56 year old man, manifested diabetes (11) .

Scattered case reports of hyperglycemia or acute onset of DM on lithium were published as well (23-25). The reports, however, are not in conflict with the fact that lithium possesses insulin-like effect. These patients seemed to suffer from other preexisting endocrinological issues, and one case was associated with lithium toxicity and bronchopneumonia (24).

Finally, in healthy volunteers, short-term administration of lithium did not result in any significant changes in insulin sensitivity (29).

With regards to animal research, Rossetti (1989) studied the effects of lithium in rats. In his study, lithium improved insulin mediated glucose uptake in both diabetic and healthy rats. The plasma level of lithium was within a range that, in humans, is considered therapeutic. These results were consistent with findings of some other studies looking at effects of lithium treatment in animals (30).

It is interesting that lithium did not have any effect on insulin sensitivity in healthy subjects as reported by Grof et al. (1984) (29) while it affected glucose tolerance in bipolar patients (9). This suggests that lithium might target a mechanism that plays a role in both BD and DM. So far, the literature suggests that treatment with lithium is not likely to blame for the increased risk of DM in bipolar patients.

### 1.1.2 Do other treatments used in bipolar disorder affect glucose metabolism?

#### 1.1.2.1 Anticonvulsants

Anticonvulsants, such as valproate, lamotrigine and carbamazepine, have been used in the treatment of BD as well. Valproate has been used in the management of acute mania and as a maintenance treatment. Lamotrigine is now considered to be among first-line treatments for bipolar depression and the maintenance therapy. Finally, carbamazepine has shown some efficacy in the treatment of BD as well (31). Other new anticonvulsants, such as gabapentin, topiramate or tiagabine, have been tried for bipolar treatment, however, their use in this indication is very rare and their effectiveness has not been reliably established, therefore, will not be discussed in this thesis.

Most studies of anticonvulsants and their effect on glucose metabolism have been done with epileptic subjects. In this population, valproate has been associated with weight gain and hyperinsulinemia in some studies (32-34) but not in others (35;36).

The few studies done with bipolar subjects so far do not support a direct adverse effect of valproate on glucose metabolism in this population. In one study, valproate use in women with BD did not show any specific association between valproate treatment and fasting insulin or HOMA-IR (homeostatic model assessment, an

estimate of insulin resistance (IR); insulin x glucose/22.5). During a two-year follow-up, no changes in insulin and IR were reported (37). In another study with bipolar patients, the authors compared indices of IR of obese patients with BD taking valproate (for a minimum of 6 months) and non-psychiatric obese subjects (38). They matched the groups for BMI, age, sex and ethnicity to better control for the key variables that contribute to IR. IR was estimated by HOMA-IR. There were no significant differences in HOMA-IR between patients and controls which would be expected if valproate had a direct effect on IR. It is interesting to speculate that valproate might decrease the increased risk of IR in bipolar patients to the level of general population. A prospective study with a similar design could help to clarify this question. Interestingly, HOMA-IR was not significantly different in patients taking atypical antipsychotics in addition to valproate when compared with patients not taking antipsychotics (38) (association between DM and atypical antipsychotics is discussed below).

Lamotrigine does not seem to have a negative effect on glucose metabolism (see below) nor has been associated with weight gain (36;39;40).

An interesting study by Kim & Lee (2007) looked at differences in the components of metabolic syndrome in premenstrual Korean females with epilepsy treated with lamotrigine, valproate, topiramate or carbamazepine monotherapy for at least 6 months (41). The authors did not find significant differences in fasting insulin or HOMA-indexes between the four groups. However, both values were non-significantly higher in the valproate group. No patients on lamotrigine and topiramate had metabolic syndrome. Five percent and 40 % of subjects taking carbamazepine and valproate respectively had metabolic syndrome. These differences in the rates of metabolic syndrome in the presence of no significant differences in IR could be related to weight gain (higher BMI in this study) associated with valproate when compared with the other anticonvulsants.

Castilla-Puentes (2007) prospectively assessed levels of HbA1c in bipolar subjects on various medications using a health service database. Patients with known DM were excluded from the analysis. Anticonvulsants and modern antidepressants were associated with decrease in HbA1c levels (42). Even though the results of this study

are difficult to interpret due to various possible confounders associated with the design (undetected co-morbidities, relying on reported diagnoses, reasons for checking HbA1c, changes in BMI, activity level, etc), they, nevertheless, point to the same direction as the other studies in bipolar patients treated with anticonvulsants.

#### 1.1.2.2 Antipsychotics

Atypical antipsychotics (AAP) are emerging treatments for BD. AAP are not used to treat only acute psychosis or agitation in BD but are being recognized for their effect in acute mood episodes as well as in the maintenance therapy. For example, the 2009 update of the CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines for the management of BD lists olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone monotherapy as first line treatments for acute mania, quetiapine monotherapy for acute depression, and olanzapine, quetiapine, risperidone (long acting injection) and aripiprazole monotherapy and adjunctive ziprasidone as first line options for maintenance treatment in BD (31).

Most of the evidence of metabolic alterations associated with AAP comes from studies of schizophrenia. AAP were reported to be associated with new onset DM, exacerbation of preexisting DM type 2, diabetic ketoacidosis and hyperosmolar hyperglycemic state (43;44). Glycemic control has been reported to improve in some cases upon discontinuation of antipsychotics. In schizophrenia, the risk of DM associated with AAP seems to be highest in patients under the age of 40 (45). Sernyak et al. (2002), found that AAP (including clozapine, risperidone, olanzapine and quetiapine) were associated with the diagnosis of DM in patients under the age 40 when compared with typical antipsychotics. In the age group of > 60, the risk of DM was not increased for any of the AAP. The authors speculated that AAP may hasten the onset of DM rather than precipitate it de novo (45). In other words, AAP may precipitate an early manifestation of DM in predisposed individuals who would otherwise develop DM later in life. Alternatively, the prevalence of DM in schizophrenia in older age may simply reflect the decreased life expectancy associated with this psychiatric illness.

Out of the atypical antipsychotics, clozapine and olanzapine are associated with the greatest occurrence of DM. Risperidone and quetiapine seem to have an intermediate effect, and ziprasidone and aripiprazole do not appear to be associated with DM (see Table 1) (46). The same is true in the case of the effect of AAP regarding the risk of weight gain.

Table 1: Second generation of antipsychotics and risk for diabetes mellitus (46)

| Drug | Risk for diabetes |
|---|---|
| Clozapine | + |
| Olanzapine | + |
| Risperidone | D |
| Quetiapine | D |
| Aripiprazole* | - |
| Ziprasidone* | - |

+ = increase effect; - = no effect; D = discrepant results
* Newer drugs with limited long-term data

Schizophrenia has been identified as an independent risk factor for DM, regardless of treatment with AAP (47). In the case of BD, this risk might be even higher than in schizophrenia as suggested by a study by Regenold et al. (2002) which found a greater risk of DM in BD (26%) than in schizophrenia (13%). In both disorders the risk of DM was higher when compared with age, gender and race – matched rates in the general population and was independent of treatment with antipsychotics (6). The sample size in this study was small, which may indicate that the study was underpowered to show significant association of DM with AAP. However, if AAP played a key role in the increased rates of DM in this case, the opposite – a higher prevalence of DM in patients with schizophrenia vs BD – would be expected since antipsychotics are the main treatment for schizophrenia.

In summary, AAP have a known adverse effect on glucose metabolism. However, treatment with antipsychotics does not seem to explain the entire risk of DM in bipolar patients. In the treatment of BD, AAP have been more widely used approximately since the mid 1990's (48) while alterations in glucose metabolism had been documented long before the era of AAP (7).

#### 1.1.2.3 Antidepressants and ECT

Other treatments used in BD, such as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI) or electroconvulsive treatment (ECT) have been associated with changes in glucose metabolism as well.

Tricyclic antidepressants have been associated with both hypo and hyperglycemia. In one paper presenting several case reports, imipramine was associated with a trend towards decreased glycosuria and glycemia in diabetic patients with depression (49). TCA in combination with derivates of sulfonylurea (drugs for treatment of DM) caused hypoglycemia (50). On the other hand, treatment with nortriptyline resulted in increased HbA1c (51). In rats, treatment with amitriptyline as well as treatment with trimipramine was associated with significant increase in blood glucose (52).

Several interesting reports concerning the serotonin system have been published. First, serotonin agonist fenfluramine was shown to improve insulin sensitivity in obese NIDDM (non-insulin dependent diabetes mellitus) without concurrent weight changes (53). Next, in a 4-week randomized, double blind, placebo controlled study by Maheux et al. (1997), treatment of obese patients with NIDDM with fluoxetine resulted in improved insulin sensitivity without any changes in weight and diet (54). Finally, several other studies found that treatment with fluoxetine resulted in improvement of FPG, HbA1c and weight loss, and treatment with sertraline lead to decreased HbA1c in diabetic patients with depression (55;56).

MAOI have been associated with a hypoglycemic effect in animal studies as well as in humans (57). Cooper et al. (1964) reported decrease in insulin requirement in diabetic patients upon initiation of MAOI. After discontinuation of MAOI, the insulin dose had to be increased again (58). It was also reported that MAOI improved DM in patients previously resistant to sulfonylurea (59). Similarly to lithium, but possibly via a different mechanism, MAOI seem to potentiate the hypoglycemic effect of insulin leading to improvement in insulin sensitivity.

Even non-pharmacological treatment, electroconvulsive treatment (ECT) in particular, seems to have a direct effect on glucose metabolism. Fakhri et. al. (1980)

reported a complete remission of diabetic symptoms after ECT in patients with recent onset NIDDM. Interestingly, remissions were not associated with weight loss (60).

All above mentioned treatments, including a non-pharmacologial treatment, have few things in common. First, they are associated with changes in glucose metabolism in one way or another. Second, they are effective for treatment of affective disorders. Third, some of them showed a beneficial effect on treatment of DM without the presence of a co-morbid mood disorder. However, it is still unclear whether in cases of co-morbid DM and affective disorder the beneficial effect on DM coincides with improvement of mood disorder when treated with the same drug. This might have practical implications in prediction of treatment response for affective disorder based on changes in glucose metabolism. More research in this area is needed.

In summary, it seems unlikely that psychotropic medication is the main cause of increased rates of DM in bipolar population. This, together with the fact that some medications effective in treatment of affective disorder have the potential to improve DM, raises a question whether affective disorder is associated with inherent changes in glucose metabolism during episodes, independently on treatment.

### 1.1.3 Are there spontaneous changes in glucose metabolism within episodes of bipolar disorder?

Some evidence suggests the existence of spontaneous changes in glucose tolerance in bipolar patients. In 1969, Van der Velde and Gordon found that 50% (16 out of 32) of hospitalized manic-depressive patients who were older than 40 years of age had a hyperglycemic response to oral administration of glucose. Four out of ten patients under age 40 showed a prediabetic glucose tolerance response. Most of the patients were on no medication, some were on lithium (9). The same authors studied changes in glucose tolerance within manic or depressive episodes in five patients. They observed spontaneous changes in glucose tolerance but did not find a simple correlation between particular type of episode and glucose tolerance (9).

Heninger and Mueller (1970) suggested that mania may be associated with an increase in insulin sensitivity (12). The outcomes of their study favored the assumption that in terms of insulin sensitivity, mania is the opposite of depression. They also observed that manic patients had increased insulin sensitivity when compared with manic patients treated with lithium. Depressed patients showed lower utilization of glucose in the glucose tolerance test than manic patients or manic patients treated with lithium.

Whether different phases of BD are associated with specific spontaneous changes in glucose tolerance is very difficult to ascertain. Although, the above studies suggest some spontaneous changes in glucose metabolism independent of medication, the results might be biased by many factors, such as concurrent medications, treatment with lithium, the interval between blood work and last dose of lithium; other confounders may include somatic co-morbidity, physical activity which is usually very different in manic and depressive phase, diet, stress, etc. All three last listed potential confounders are known to influence IR. Despite many limitations and obstacles inherent to research aimed at such a complex issue, a study, cross sectional or prospective, controlling for these confounders, might shed more light on this question.

## 1.2 Hypothalamic-pituitary-adrenocotical axis

Are alterations in hypothalamic-pituitary-adrenocotical axis (HPA) the missing clue in the increased co-morbidity between DM and BD?

Both BD and DM have been associated with HPA changes, such as hypercortisolemia and a lack of adequate cortisol suppression in response to dexamethasone. Hypersecretion of cortisol was found in depressed as well as manic patients and normalized after recovery (61). A similar pattern was shown with dexamethasone suppressive test (DST); abnormal response has been observed during depressive or manic phase with return to normal on complete recovery; suggesting that changes in HPA in BD might be state dependent (62-64). Further information with regards to the patterns of HPA function in individuals with bipolar spectrum disorders brought a 4-year prospective study of DST which suggested that HPA

dysregulation may be an enduring trait in BD. The authors studied patients with excellent response to lithium and found that patients showed DST positivity despite full remission, with patterns possibly indicating times of high risk of relapse (65). These results suggest that the underlying dysfunction is still ongoing even when the clinical symptoms are well controlled by lithium. The view of HPA dysregulation representing an enduring trait in BD is further supported by findings of HPA alterations in healthy relatives of probands with affective disorders (66).

Non-suppression to dexamethasone was found also in DM independently of mood. Hudson et al. (1984) administered DST to non-depressed patients with DM. To minimize the effect of possible susceptibility to affective disorder which could bias the results, part of the exclusion criteria for the non-depressed diabetic participants was a negative family history of affective disorder. Diabetics had significantly higher rates of non-suppression than controls in this study (67). In concordance with these results, Cameron et al. (1984), found non-suppression to dexamethasone in a mixed sample of patients with DM type 1 and DM type 2 (68). Higher activity of the HPA axis in DM was reported also by Bruehl et al. (2007). In their study, subjects with DM had elevated basal cortisol levels and higher cortisol levels after dexamethasone and CRH (corticotropin releasing hormone) administration when compared with controls without IR (69).

Another aspect of the HPA dysfunction in DM and affective disorders is reflected in biological rhythms of cortisol levels. A similarly altered, "flattened" circadian fluctuation pattern in cortisol values were found in DM as well as in melancholic depression (61;68). More research studying the circadian and long-term rhythms of cortisol levels/changes in HPA regulation is needed. As suggested by Deshauer et al. (1999), it might have a value in identifying times of higher risk of relapse of manic or depressive episodes (65). Alternatively, a certain pattern of the rhythms may identify patients with higher or lower susceptibility towards developing DM, thus, identify a subgroup of bipolar patients with possibly similar pathophysiology.

Although BD and DM share some similarities in HPA, the origin and nature of this relationship remains unclear.

If, we were to accept that HPA hyperactivity is a functionally overlapping disturbance that is present in both diseases, a number of hypotheses can be proposed as to the nature of its causation. For instance, we may hypothesize that the primary defect is in hippocampus which is involved in the regulation of the HPA axis. In particular, hippocampus provides negative feedback to the HPA axis. Disruption in the functioning of hippocampus can then result in abnormal HPA axis regulation leading to elevated levels of cortisol as seen in BD or DM (70). Using MRI, some studies have shown abnormalities in hippocampus in bipolar patients. Volumetric measures of the right hippocampus were significantly smaller in patients than in controls in a study by Swayze et al. (1992) (71). A trend towards smaller left hippocampal volume was found by Strasser et al. (2005) (72). Smaller hippocampal volumes were found also in adolescents with BD (73;74). Majority of studies, however, did not find a significant difference in hippocampal volumes of bipolar patients when compared with healthy controls (75-78). It is possible that changes in hippocampal volume in the negative studies were masked by the effect of psychotropic medications. This would be in keeping with the results of Bearden et al. (2008) who observed that untreated bipolar patients had a smaller volume of hippocampus when compared with bipolar patients treated with lithium (79). Despite these conflicting results and the unknown significance of the MRI findings, morphometric and neurocognitive studies clearly demonstrate deficits in hippocampal formation and its function in BD and further confirm the involvement of hippocampus in BD (80-83). Alternatively, the conflicting results might reflect the heterogeneity of BD which might be the main reason for difficulties with replication of findings when using different samples of bipolar patients. Possibly, a subgroup of BD patients with an increased susceptibility to DM might be more prone to hippocampal damage than other bipolar patients.

Volume reduction and other hippocampal deficiencies such as deficits in cognitive functioning were found in patients with DM type 2 (84-86). In one study, HbA1c was associated with hippocampal volume loss in middle aged individuals with well controlled DM (85). In terms of cognitive function, hippocampus is an important brain structure for learning and memory. Significant deficits in learning and memory were found in subjects with DM type 2 (86). Moreover, learning and memory impairment was demonstrated even in non-diabetic subjects with IR (87). In

concordance with the findings of memory and learning impairment in DM, deficits in hippocampal synaptic plasticity, specifically impairment of long-term potentiation (LTP) in the CA1 and CA3-field of the hippocampus and gyrus dentatus were reported in animal models of DM (88;89).

In diabetes, cognitive and morphological brain changes have been attributed to atherosclerosis. However, the above mentioned study by Kalmijn et al. (1995) showed that IR was associated with cognitive impairment even after accounting for the possible effects of atherosclerosis (87). Similarly, the study by Gold et al. (2007) showed that the only significant predictor of reduced hippocampal volume was HbA1C; other variables, such as BMI, hypertension and dyslipidemia, did not contribute to the results (85). The results of these studies therefore suggest that the changes in the volume of hippocampus in diabetic patients might be related directly to IR.

Little is known about the mechanism how peripheral IR affects the brain. Hippocampus has high co-localization of insulin and glucocorticoid receptors (90) and is more susceptible to damage by hypoglycemia than other brain regions (91). Animal studies demonstrated that glucocorticoids impair glucose transport into neurons and glia in hippocampus (92). Convit et al. (2005) proposed a theory that endothelial dysfunction, which is found in IR, results in a 'functional hypoglycemia' during activation of hippocampus which is normally associated with increased glucose demand. This 'functional hypoglycemia' together with increased cortisol results in a hippocampal damage (91).

Functional imaging studies, such as glucose utilization in brain, coupled with measurements of peripheral IR would help to clarify the connection between peripheral IR and brain energetics in both disorders.

In terms of causation, we can speculate that alterations in HPA may be an independent factor that contributes towards manifestation of either BD or DM or both in vulnerable individuals. It can be proposed that a threshold-like effect exists in this complex interaction between BD, DM and HPA. It is known that primary disturbances of HPA such as Cushing's syndrome are associated with IR as well as

mental changes manifesting as manic, depressive and/or psychotic symptoms. It is possible that in patients with genetic susceptibility towards DM or BD, even milder changes in HPA functioning might trigger the manifestation of affective symptoms or DM. For instance, if HPA dysregulation was a trait associated with BD, high cortisol levels and resulting hippocampal damage would lead to further HPA dysfunction and eventually trigger DM in patients depending on the degree of their genetic susceptibility towards DM. Alternatively, a subgroup of bipolar patients with a high risk of DM might have a more severe disturbance of the HPA axis than patients with a low susceptibility to DM. Future research could focus on investigation of possible concurrent changes in HPA function, IR and clinical patterns of BD, and a possible association on genetic level.

## 1.3 Bipolar disorder and signal transduction

### 1.3.1 Phosphoinositide cycle

There are a number of interesting overlapping functions of lithium and diabetes. Although it seems clear that lithium use does not precipitate the onset of DM, examining its specific mode of action may lend insight into the complex relationship of BD and DM. Lithium has been shown to be an effective treatment for BD and its effect on signal transduction has been relatively extensively studied. Changes in signal transduction induced by lithium may reflect the pathology on the signal transduction level in BD. Similarly, in the search for therapeutic intervention for diabetes, researchers have identified several promising targets. Among the primary candidates is the phosphoinositide cycle. An alteration in the phosphoinositide cycle can initiate a number of secondary changes in different signaling cascades relying upon the phosphoinositol pathway, and in gene expression in the central nervous system.

At first, I will briefly outline the phosphoinositide cycle (see Appendix A2). The phosphoinositide pathway is activated by a variety of neurotransmitters, such as serotonin, noradrenalin, acetylcholine or glutamate (93). These bind to G protein coupled receptors and subsequently activate phospholipase C (PLC). PLC than

converts a membrane phospholipid phosphoinositide 4,5-bisphosphate ($PIP_2$) into inositol 1,4,5-triphosphate ($IP_3$) and 1,2-diacylglycerol (DAG). DAG activates protein kinase C (PKC). $IP_3$ mediates the release of calcium from intracellular storage compartments. $IP_3$ is phosphorylized, or converted to free myo-inositol which is catalyzed by inositol monophosphatase (IMPase) and inositol polyphosphate 1-phosphatase (IPPase). Inositol is then available for resynthesis of $PIP_2$ through phosphatidylinositol (PI) and phosphatidylinositol phosphate (PIP). The enzyme IMPase is the rate limiting enzyme in inositol recycling and is also required for *de novo* synthesis of inositol (94).

The relationship between myo-inositol and diabetes was observed already more than fifty years ago when researchers noticed that diabetic patients were losing excessive amounts of myo-inositol in their urine (95). Early studies of the role of myo-inositol levels in diabetes were done with streptozocin or alloxan induced diabetic rats (96;97). Palmano et al. (1977) found that free cerebral inositol content is increased in rats made diabetic by either streptozocin or alloxan, with the most severely diabetic rats showing the greatest elevations (96). In humans, significant elevation of cerebral myo-inositol was found in a sample of type 1 and 2 diabetic patients compared to an age- and sex-matched controls (98). To date, the exact details regarding the role of myo-inositol in DM remain to be understood.

Although it is not clearly understood how myo-inositol levels may affect BD, we do know that one of lithium's primary actions is on the phosphoinositide cycle as mentioned above. Specifically, lithium inhibits enzymes inositol monophosphatase (IMPase) and inositol polyphosphate 1-phosphatase (IPPase), which play a major role in recycling of intracellular inositol phosphates (99;100). In the brain, myo-inositol is derived primarily from recycling of inositol phosphates. Magnetic resonance spectroscopy has demonstrated myo-inositol reductions in the frontal cortex of bipolar patients just five days after lithium administration (101). The lowering of myo-inositol levels occurred at times when no clinical changes were seen in the patients. This suggests that short-term myo-inositol depletion is not directly correlated with therapeutic response to lithium. However, as with other psychiatric medication, the lag in response might possibly be related to changes on

the genomic level as a result of downstream changes triggered by activation of the phosphoinositide pathway.

In summary, changes in myoinositol levels are present in both disorders. The significance of the changes is yet unknown. More research is needed to clarify the role of this pathway in either disorder.

### 1.3.2 Na-K ATPase

Changes in sodium-potassium-activated adenosine triphosphatase (Na-K ATPase) activity may be another common feature in BD and DM.

Na-K ATPase activity has been found to be reduced in peripheral blood cells of bipolar patients during acute affective episodes with the tendency to return to normal activity during euthymia (102). Chronic lithium administration has been observed to result in an increase of Na-K ATPase activity in erythrocyte membranes (103).

Similarly, a decrease in Na-K ATPase activity was found also in animal models of DM. In particular, Na-K ATPase activity in brain was decreased significantly in streptozotocin induced diabetes in rats. The largest decreases were observed in the hippocampus (-30%) and the cerebral cortex (-26%) (104).

Changes of Na-K ATPase activity may be related to changes in myoinositol pathway. Exogenous inhibition of Na-K ATPase activity increases phosphoinositide hydrolysis (105). This may result in increase of intracellular myo-inositol as was found in BD or DM. Decrease in Na-K ATPase activity could then be the primary defect leading to further dysregulation in signaling that BD and DM have in common.

### 1.3.3 Lithium's insulin-like effects: Its role as an inhibitor of GSK-3β (glycogen synthase kinase 3ß)

IR is considered to be the earliest and major event in the development of DM type 2 (106;107). GSK-3ß, a serine/threonine kinase, was proposed to play a significant role in IR as a negative regulator of insulin signaling through phosphorylation of IRS-1 (insulin receptor substrate-1) (108). Phosphorylation of IRS-1 on Ser/Thr residues by GSK-3ß *in vitro* impairs insulin-stimulated Tyr phosphorylation of IRS proteins (108). Via this effect, GSK-3ß negatively regulates PI3-K phosphatidylinositol 3-kinase pathway which lies downstream to IRS-1, and mediates insulin induced glucose transport (109).

Another role of GSK-3ß in glucose metabolism is a regulation of glycogen synthesis via inhibitory phosphorylation of glycogen synthase (109). Studies have shown that patients with DM type 2 have impaired insulin mediated glycogen synthesis in muscle (110;111), a finding which is in keeping with a report of elevated level of GSK-3ß in skeletal muscle of type 2 diabetics by Nikoulina et al. (2000) (112). Furthermore, in muscle cells from diabetic subjects, activity of glycogen synthase is still altered even after prolonged maintenance under normoglycemic and normoinsulinemic conditions (110). These findings suggest a possible overexpression (112) or other dysregulation of GSK-3ß in a diabetic state.

I have already mentioned that clinical studies, such as the study by Van der Velde (1969), have shown a positive effect of lithium on glucose metabolism (9). This effect can be explained by two insulin-like actions of lithium. Both actions are mediated by lithium's inhibitory effect on GSK-3ß. First, lithium stimulates transport of glucose into cells. Specifically, studies showed that lithium stimulates glucose transport in adipocytes and muscle cells (113-115). Moreover, Chen (1998) found that lithium stimulated glucose transport in 3T3-L1 adipocytes in a dose-dependent manner, and lithium together with insulin increased glucose transport even more than did insulin alone (113). Second, lithium at therapeutically relevant levels mimics insulin's inhibitory effects on GSK-3β *in vitro* leading to activation of glycogen synthase (109). Lihium increased glycogen synthesis in adipocytes, muscle cells and hepatocytes (115-117). In another interesting study, Summers et al. (1999) treated

3T3-L1 adipocytes with lithium as well as with insulin. They found that lithium increased glycogen synthase activity and basal glycogen synthesis. Lithium together with insulin increased glycogen synthase activity and glycogen synthesis more than either agent alone (118). The results indicate partially additive effect of lithium and insulin on both glycogen synthesis as well as glucose transport. The partially additive effect on glycogen synthesis may be explained by the fact that either agent inhibits GSK-3 via a different pathway. Insulin increases glycogen synthesis via activating Akt/PKB (protein Ser/Thr kinase B) lying downstream of PI3K and leading to GSK-3 inhibition (119). On the other hand, lithium's effect on GSK-3 is not mediated via PI3-K signaling cascade, rather, lithium inhibits GSK-3 directly via competing for magnesium (120).

In summary, lithium inhibits the activity of GSK-3ß. Via this action, lithium increases glucose uptake and stimulates glycogen synthase. In addition, both insulin induced glucose uptake and glycogen synthesis are increased in the presence of lithium (118). This suggests that GSK-3ß may be a possible common treatment target for both disorders.

### 1.3.4 Protein Kinase C

Another possible link on the signal transduction level is protein kinase C (PKC). PKC is known to exist as a family of at least 12 phosphorylating isozymes and has a heterogeneous distribution in the brain. PKC is responsible for the regulation of many brain functions, such as neuronal excitability, neurotransmitter release, long-term alterations in gene expression and plasticity. PKC is located in the cytoplasmatic and membrane compartments of cells, and its activation requires its translocation from the cytosol to the membrane (121).

Studies of PKC in bipolar patients showed an elevated membrane-associated PKC activity in platelets of manic patients (122). Other study found a significantly higher PKC activity in platelets from patients with mania but not in patients with major depression and schizophrenia when compared with controls with no personal or family history of a mood or psychotic disorder (123). In agreement with these results,

an enhanced membrane-associated PKC activity was found in frontal lobes in post-mortem brain tissue from subjects with BD (124) .

Chronic administration of lithium decreases PKC activity. In particular, in an animal study, chronic treatment with lithium led to 30% reduction in membrane associated PKC activity in hippocampus, most notably in the subiculum and the CA1 regions (125).

Since PKC is one of the downstream targets of myo-inositol pathway, one could argue that changes in PKC are a consequence of an alteration in this pathway upstream to PKC. Interestingly, valproate – another drug used in treatment of BD – seems to regulate PKC activity via a mechanism mostly independent on myo-inositol (93). This suggests that PKC may be the main therapeutic target of lithium and a common target of therapeutics in BD. Indeed, tamoxifen – a relatively selective PKC inhibitor – has shown an antimanic effect in acute mania (126).

With respect to DM, PKC alterations concern mainly two areas – IR and vascular complications of DM. The etiology of IR is likely multifactorial; besides to the above mentioned GSK-3ß, PKC is one of the possible major contributors towards this condition (127). Increased PKC activity has been associated with DM type 2 in animals and humans (128;129). For instance, PKC activity was increased in animal models of dietary induced IR (130). Consistent with these results, a study by Chin et al. (1993) showed that transfected liver cells that over-express PKC become insulin resistant (131;132).

It seems that PKC may be one of the common mechanism linking BD and DM since its increased activity leads to IR and has been found to be increased in BD, at least during the manic phase.

With respect to the increased rates of deaths from cardiovascular reasons in bipolar patients one can speculate that the reported normalization of cardiovascular mortality in patients on lithium (133) might result from lithium`s effect on PKC which is known to be involved in the mechanism of vascular complications in DM. Finally, PKC may be a target for treatment of both DM and BD.

## 1.4 Are there common susceptibility genes in bipolar disorder and diabetes mellitus?

Genetic research may eventually form the bridge between the two disorders and help identify the underlying mechanisms linking the two disorders. Both DM and BD are recognized as having a strong genetic component. Both are complex disorders that develop as a consequence of interaction between environmental and genetic factors; and both are polygenic disorders where several or many genes define the susceptibility to the illnesses. In either disorder, quite a few susceptibility genes or loci have been identified over the years with mostly inconclusive results (134;135). Genetic findings are difficult to replicate. One of the possible reasons is phenotypic heterogeneity. A narrower definition of a phenotype might be a useful strategy to identify genes involved in the disease process (134;136;137) .

There is some evidence in the literature that certain clinical features can determine a subgroup of BD with common genetic background. Turecki et al. (2001) suggested that a positive response to lithium may be associated with chromosome 7q11.2 (138). Other studies suggested a genetic overlap with schizophrenia on chromosomes 13q and 22q. In this case, psychosis seems to be the common phenotypic feature associated with these chromosomes in both disorders (139-141). Similarly, co-morbid DM may define a subgroup of bipolar patients who share several genes predisposing them to BD and DM.

The genetic factors in complex disorders have been investigated using two main approaches – association studies of candidate genes and linkage studies. Several chromosomal regions or candidate genes showed positive results in both BD and DM suggesting a possible overlap in genetic susceptibility to these disorders. These include regions on chromosomes 4p (142-144), 4q (145;146), 6q (147-150), 11p (151-156), 12q (157-160), 18p (142;161-163), 20q (164-167) and Xq (168;169).

Let's have a look at chromosome 11p15, for an example. A linkage to 11p15 was found in some studies in BD (151;156;170). 11p15 region harbors several interesting genes including thyrosine hydroxylase (TH) gene, insulin (INS) gene and ABCC8 and KCNJ11 genes. TH is a rate limiting enzyme in the synthesis of catecholamines.

For its possible involvement in the pathophysiology of BD, TH gene has been investigated as a candidate gene for BD. Some studies found an association between TH gene polymorphisms and BD (154;171). In an association study by Chiba et al. (2000), TH gene microsatellite polymorphism was associated with IR in depression (172). ABCC8 and KCNJ11 are two of the most promising candidate genes for DM (152;153;155). In addition, an INS/TH haplotype has been associated with increased insulin secretion and insulin resistance (172).

Another example of a chromosomal region that is possibly involved in both disorders is 20q12-13. A linkage to this locus in DM type 2 has been reported by several authors (164;173). Using the candidate gene approach, Bento et al. (2004) and Palmer et al. (2004) investigated whether there is an association between DM and PTPN1 gene which is located within this area (174;175). The gene codes for PTP1B (protein tyrosine phosphatase 1B) which is involved in negative regulation of insulin receptor signaling by dephosphorylation of IRK (insulin receptor kinase) which is activated by insulin and leads to activation of PI3-K pathway. The studies found an association between certain PTPN1 polymorphisms and a haplotype with DM type 2, FPG and insulin sensitivity index. In BD, Turecki et al. (1998) investigated phospholipase C-γ1 gene (PLCG1) for an association and linkage in bipolar patients with good response to lithium. The PLCG1 is located on 20q12-13.1. Phospholipase C-γ1 is involved in the phosphoinositide signaling and, as discussed above, lithium's therapeutic effect is thought to be related to its inhibition of IMPase. The authors found an association between a PLCG1 polymorphism as well as some moderate evidence for linkage in BD when using the same PLCG1 marker as in the association study (167).

## 1.5 Summary of introduction

In the introduction I reviewed the effects of medications commonly used in the treatment of BD on glucose metabolism; lithium, anticonvulsants, antidepressants and antipsychotics in particular; as well as changes in glucose metabolism in BD that seem to be independent of treatment. Next, I explored the possible links between BD and DM based on alterations that the two disorders seem to have in common. In particular, I described HPA abnormalities and alterations in signal transduction

including the phosphoinositide cycle, Na-K ATPase, GSK-3β and PKC. Finally, I looked at the evidence from genetic research which suggests that BD and DM may share some factors of genetic susceptibility which may eventually explain the higher co-morbidity between BD and DM. Theoretically, some of these links may serve to define BD with co-morbid DM as a subgroup of patients within bipolar spectrum disorders. In the next part I will describe my clinical research aimed at investigating possible clinical correlates of DM in BD.

# 2 Hypothesis and assumptions

To date, the relatively extensive research devoted to unraveling the pathophysiological and genetic basis of BD has not yielded conclusive results. One of the possible reasons is that the diagnosis of BD is too broad and comprises heterogeneous subgroups of bipolar spectrum disorders defined by so far unclear characteristics. One of the research strategies that could help to overcome the obstacle of heterogeneity is to use more homogeneous subgroups of the disorder defined by certain characteristics. Given the fact that BD is associated with a higher risk of DM and both disorders seem to share some underlying mechanisms, BD with co-morbid DM might represent such a subgroup. This subgroup may be characterized by a specific clinical presentation. In order to further investigate this issue, I hypothesized that bipolar patients with co-morbid DM represent a subgroup of BD which differs from bipolar patients without co-morbid DM in clinical characteristics. Given the complexity of this co-morbidity and the possible underlying mechanisms, I further hypothesized that patients with co-morbid DM will have more severe course of BD as measured by various clinical variables, and a higher prevalence of somatic complications.

This would, in turn, support the assumption that BD and DM share some pathophysiological mechanisms.

The results of the study could be used for a better phenotypic characterization of a subgroup of BD for future research. The results may also have direct implications for clinical care. Depending on the results of this study, this sample may serve as a starting point for further genetic studies of BD.

# 3 Methods

Participants for the study were recruited through the Maritime Bipolar Registry which is a project aimed at collecting clinical data on patients with bipolar affective disorders in the Maritime Provinces of Canada, including Nova Scotia and Prince Edward Island. The Maritime Bipolar Registry is a community based project. Patients are referred by their treating physicians, typically by their psychiatrists or family physicians. Interested individuals contact the study coordinator who schedules an appointment to obtain informed consent and to conduct the interview. The project was approved by research ethics board.

The information used in the study was collected at the interview and from the patients' charts. After obtaining the consent to participate in the study, patients were interviewed in person by myself, other trained physicians, and/or trained research nurses. All interviewers underwent extensive training prior to being able to conduct the interviews. Specifically, the same research team members interviewed patients in a blind fashion for genetic studies which are dependent on accurate phenotypization, thus, accurate diagnosis.

The diagnostic interviews followed the Schedule for Affective Disorders and Schizophrenia, Lifetime version (176). In addition, the diagnostic interview was expanded to obtain further information about the affective illness (see Appendix A3: Worksheet). These include details on pateints' clinical course using lifetime charting approach, course of the illness, history of suicidal behaviour, psychiatric co-morbidity, psychiatric family history, history of treatment, and treatment response which was determined by using an 11-point scale developed by Martin Alda and colleagues (177;178) (see Appendix A4). Psychiatric diagnoses were based on DSM-IV-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; see Appendix A5) (179). Cases were presented and reviewed at research meetings where the consensus diagnosis was determined. Medical co-morbidity including DM, hypertension and thyroid disorder was based on previous diagnosis and evidence of treatment. Ethnically, most participants were of Irish, Scottish and French Acadian origin.

At the time of the analysis, the Registry included data from 252 patients. Only patients with diagnosis of BD I (Bipolar I Disorder), BD II (Bipolar II Disorder) and BD NOS (Bipolar Disorder Not Otherwise Specified) were considered for the study (see Appendix A5 for DSM IV criteria). Thirty out of the 252 subjects were excluded from the study for following reasons: 18 had consensus diagnosis of schizoaffective disorder, one had diagnosis of cyclothymia; diagnosis was deferred in 10 cases, and no information regarding medical condition was available for one participant. The total number of subjects included in the diabetes study was 222. Of the 222 subjects, 26 had co-morbid DM (25 had DM type 2 and one had DM type 1).

## 3.1 Statistical analysis

I used BMDP 7.0 Statistical Software for statistical analysis. Continuous data were analyzed using Mann-Whitney *U* test and categorical data were analyzed using chi-square test. In addition, for variables contributing to between group differences, stepwise logistic regression was performed with DM as a dependent variable and age, sex, hypertension, BMI and treatment with antipsychotics as independent variables.

The variables included in the analysis were as follows:

### 3.1.1 Categorical variables

Sex, socioeconomic status, ethnic origin, psychiatric diagnosis (BD I, BD II and BD NOS) rapid cycling (see Appendix A5 for definition of rapid cycling), psychosis with episodes (a history of at least one affective episode with psychotic features), treatment with a moodstabilizer (lifetime), treatment response (see Appendix A4; © Martin Alda, 2002) for: lithium, lamotrigine, valproate or carbamazepine (no effect, partial, complete, inadequate trial, unknown)*, treatment with antidepressants (lifetime), treatment with antipsychotics (lifetime), electroconvulsive treatment (lifetime), course of illness (episodic, chronic)**, co-morbid psychiatric diagnosis (yes, no, unknown), history of suicidal behavior during episodes of mood disorder (a history of at least one suicide attempt), diabetes mellitus, hypertension, and thyroid disorder.

* Determination of treatment response using the Alda scale: complete response 7 – 10; partial response 4 – 6; no effect ≤ 3.

** course of illness: As determined in the Worksheet, see Appendix A3: single episode, completely episodic, episodic residual, chronic fluctuating, chronic. Completely episodic = full remissions between episodes; episodic residual = residual symptoms present but does not meet DSM IV TR criteria for an episode; chronic fluctuating = criteria for an episode/s met continuously for ≥ 2 years, symptom severity fluctuating; chronic = criteria for an episode/s met continuously for ≥ 2 years, symptom severity not fluctuating. For the statistical analysis, single episode, completely episodic and residual episodic course were coded as episodic course; chronic and chronic fluctuating course were coded as chronic course.

### 3.1.2 Continuous variables

Age, age of onset of depression (when diagnostic criteria were first met), age of onset of mania (when diagnostic criteria were first met), GAF (Global Assessment of Functioning, see Appendix A6) scale, height (self-report), weight (self-report), and BMI (Body Mass Index).

# 4 Results

The prevalence of DM in the sample was 11.7% (26/222 subjects; 95%CI, 7.8% to 16.7%). The sex distribution was not significantly different between the two groups of patients with and without DM. In particular, there were 72 men and 124 women without DM and 14 men and 12 women with DM. Probands with DM were significantly older than those without DM. The average ages were 52.5 (SD 9.6) years for subjects with co-morbid DM and 42.8 (SD 12.3) years for subjects with BD and no DM. The distributions of diagnoses were similar in the 2 groups. In the group with co-morbid DM, 17 subjects had BD I, 8 had BD II, and 1 had BD NOS. Among subjects without DM, 134 had BD I, 57 had BD II, and 5 had BD NOS (see Table 2).

Significant differences in clinical characteristics between bipolar patients with and without co-morbid DM are presented in Table 2. Differences in categorical variables are further depicted in Fiugre 1.

In terms of clinical course of BD, when compared with nondibetic subjects, subjects with co-morbid DM more often had a chronic pattern ($\chi^2 = 7.7$, df = 1, p = 0.006), significantly more rapid cycling ($\chi^2 = 5.7$, df = 1, p = 0.02), and lower scores on GAF Scale ($U = 1701$, p = 0.01).

BMI of the total sample was in the overweight category (29.5, SD 6.4). Subjects with co-morbid DM had higher BMI, with a mean in the obese range (33.7, SD 6.0), compared with nondiabetic subjects, who were on average in the overweight range (28.8, SD 6.3). In agreement with the generally accepted association of hypertension and DM, the group with DM had higher rates of hypertension as well ($\chi^2 = 8.9$, df = 1, p = 0.003).

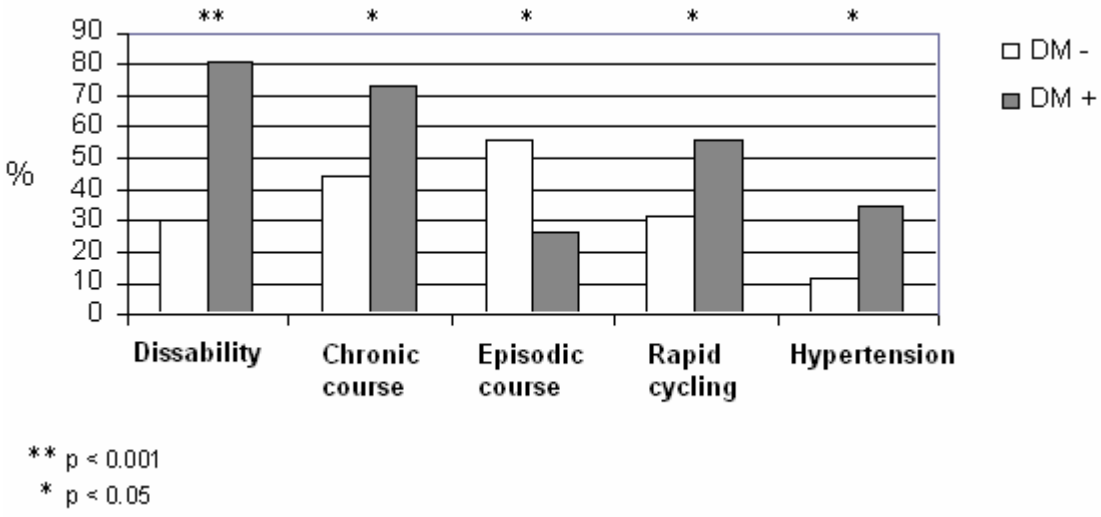
Disability rates for BD were also significantly higher in the DM group. Eighty-one per cent of individuals with co-morbid DM were on long-term disability, compared with only 30 % of probands without DM ($\chi^2 = 26.9$, df = 1, p < 0.001).

**Table 2: Demographic and clinical data of bipolar patients with and without co-morbid diabetes mellitus**.

| Variable | BD (N = 196) | BD + DM (N = 26) | Statistic | *p* |
|---|---|---|---|---|
| Age: mean (SD) | 42.8 (12.3) | 52.5 (9.6) | $U = 3789$ | < 0.001 |
| Sex (M : F) | 72 : 124 | 14 : 12 | $X^2 = 2.8$ | 0.09 |
| Diagnosis | | | $X^2 = 0.2$ | 0.91 |
| BD I | 134 | 17 | | |
| BD II | 57 | 8 | | |
| BD NOS | 5 | 1 | | |
| Course | | | $X^2 = 7.7$ | 0.006 |
| episodic | 56% | 27% | | |
| chronic | 44% | 73% | | |
| Rapid cycling | 32% | 56% | $X^2 = 5.7$ | 0.02 |
| GAF: mean (SD) | 67.2 (17.9) | 57.8 (15.4) | $U = 1701$ | 0.01 |
| Disability (for BD) | 30% | 81% | $X^2 = 26.9$ | < 0.001 |
| Antipsychotic treatment | 57% | 72% | $X^2 = 1.9$ | 0.16 |
| BMI: mean (SD) | 28.8 (6.3) | 33.7 (6.0) | $U = 2895$ | < 0.001 |
| Hypertension | 12% | 35% | $X^2 = 8.9$ | 0.003 |

BD= bipolar disorder, DM = diabetes mellitus, BMI = body mass index, GAF = Global Assessment of Functioning, NOS = not otherwise specified, *U* = Mann-Whitney U test

**Figure 1: Differences in categorical variables between bipolar patients with and without co-morbid diabetes mellitus.**



We did not find significant between-group differences in treatment with antipsychotics ($\chi^2$ = 1.9, df = 1, p = 0.16), nor was the use of antipsychotic medication correlated with any of the variables. However, there was a trend toward higher use of antipsychotics in the group with DM (Table 2). Table 3 shows details on antipsychotic treatments in the diabetic group.

**Table 3: Treatment with antipsychotics in the diabetic group**

| **Antipsychotic** | **N** | **Antipsychotic, daily dose** | **Started treatment** |
|---|---|---|---|
| Typical* | 5 | thioridazine 250 mg<br>flupentixol decanoate 40 mg i.m. q 2 weeks<br>chlorpromazine 100 mg<br>loxapine 10 mg<br>trifluoperazine, unknown dose | 1998<br>1997<br>unknown<br>1998<br>1960 |
| Atypical* | 5 | risperidone 4 mg<br>risperidone 2 mg<br>olanzapine, unknown dose<br>olanzapine 20 mg<br>olanzapine 15 mg | 1997<br>unknown<br>unknown<br>1999<br>4 months ago |
| Both (typical + atypical)* | 1 | quetiapine 200 mg + trifluoperazine 15 mg | unknown |
| Not currently taking antipsychotics | 5 | various antipsychotics in the past | |
| **TOTAL** | **16** | | |

* within last 6 months of the interview

In the stepwise logistic regression analysis, the only independent variables associated with a diagnosis of DM were age ($\chi^2$ = 16.5, df = 1, p < 0.001) and BMI ($\chi^2$ = 10.9, df = 1, p = 0.001).

# 5 Discussion

## 5.1 General discussion

The prevalence of DM in our sample was 12% as opposed to expected 3-4% for the studied population and is similar to the rates reported in other studies; namely, those of Lilliker (1980) and Cassidy et al. (1999) (3;5). Further, we found that BD patients with and without co-morbid DM differed in their clinical characteristics. The main differences emerged in the clinical course of BD (chronic vs episodic, as well as rapid cycling) and in disability rates, GAF score, BMI, and hypertension.

Given the growing interest in new-onset DM associated with antipsychotic drugs (15-17), one could assume that treatment with antipsychotics would be among the principal causes of the increased frequency of DM in BD patients. However, this study did not find a significant association between DM and antipsychotic treatment. These results are consistent with those of Regenold et al. (2002) (6). These authors investigated the prevalence of DM in psychiatric patients with BD I, schizoaffective disorder, major depression, schizophrenia and dementia. They did not find a significant connection between antipsychotic use and DM in their samples. The results are also in keeping with the early reports of glucose abnormalities in manic depressive patients (7) preceeding the use of these medications.

BD is an illness that is associated with changes in lifestyle that can lead to alterations in glucose metabolism. In particular, bipolar episodes are associated with changes in physical activity, sleep, appetite and weight. In logistic regression, obesity was a factor that significantly contributed to the results, which is in keeping with the fact that obesity has been linked to IR. Interestingly, in another study, our team found that bipolar patients who respond well to lithium have a lower BMI than other bipolar patients (180). Both, lithium's insulin like effect as well as lifestyle might contribute to such an outcome.

Our sample of 26 subjects with DM was too small to assess whether there is a link between different types of prophylactic treatments and the frequency of DM. For similar reasons, differences related to different types of antipsychotics could not be

established. Sixteen patients with DM had a history of taking antipsychotics at some point during their illness (see Table 3). Out of those, only 11 were treated with antipsychotics at the time of the interview which would give us too small a sample to draw conclusions from.

At conferences, where I presented the results of this study, I was asked whether the results indicate any causal relationship between the two disorders, or simply, if DM causes BD or vice versa. A causal relationship can not be solved by means of a cross-sectional study. The observed associations should be viewed as such and not necessarily interpreted as causal relations. Moreover, it is unlikely that a simple causal relationship exists between BD and DM. Rather, the relationship is quite complex and many different factors, biological and environmental contribute to the manifestation or impairment of either condition. Since both disorders are relatively common in the general population and have a complex and polygenic genetic background, it is possible that a threshold-like effect exists in manifestation of either disorder. This threshold might depend on combination and/or severity of different factors that interact together.

This study is limited by the difference in age between subjects with co-morbid DM and those without. This difference could partly explain the higher rates of hypertension in the DM group, which was older. The results of logistic regression are compatible with this explanation: after correction for the effect of age, the association between hypertension and DM was not as marked as in the pairwise analysis.

An inherent limitation of this study is its cross-sectional design. The interpretation of the results of a cross-sectional study is fraught with difficulties related to inter-correlations between the putative risk factors, such as age, BMI, antipsychotic use, or severity of the illness. For instance, one explanation of the elevated risk of DM could be that antipsychotic treatment increases the risk of diabetes. However, both the pairwise analysis and logistic regression did not suggest significant association between antipsychotic treatment and DM. On the other hand, it may well be that there is a subgroup of patients with more severe course of illness and worse

prognosis, with predisposition towards IR and a higher risk of DM who are more likely to be treated with antipsychotics.

A relative limitation of this study was that the diagnosis of DM and other studied medical conditions were obtained by history. Therefore, it is possible that some patients without known DM were falsely identified as healthy and were included in the nondiabetic group. The results of this study might then underestimate the prevalence of DM in the sample. In future research, this issue could be dealt with by screening for DM or IR (such as HOMA-IR).

When compared with previous research, one of the main strengths of this study is its community based sample. Most of the research to date has been conducted in hospitals or academic centres. The community based sample reflects a broader spectrum, ranging from mild to severe forms of BD, which is therefore more representative of the whole population suffering from BD than would be a sample recruited through tertiary centres. Patients treated through tertiary centres typically suffer from more severe form of BD. They are more likely to be treated with antipsychotics and have more disruptive lifestyle. As a consequence, they might have more co-morbid conditions including cardiovascular disease, obesity, hypertension or DM. Generalization of such findings would be difficult. From this point of view, our sample better reflected the inherent risk of DM in bipolar patients and clinical characteristics in general bipolar population. Results of this study are very likely less biased by the use of antipsychotics than would be a research performed in tertiary facilities.

## 5.2 Hypothetical background of the clinical correlates of co-morbid bipolar disorder and diabetes mellitus

Findings of the study are consistent with the proposed link between DM and BD outlined in the introduction; beginning with the higher prevalence of DM in our sample. So far, the exact reason for the worse clinical outcome of patients with co-morbid DM is unknown. However, given the possible HPA/hippocampus link, we can speculate that it might, for example, reflect a chronic HPA dysregulation and/or possible damage associated with IR/DM. A subgroup of patients with a high

vulnerability towards DM might be more likely to develop brain damage resulting in a complicated and a difficult to treat course of BD.

Before discussing the possible effects of DM/IR on brain, it is worthwhile to point out that there is a paucity of research related to changes in glucose metabolism during the course of BD and, up to my knowledge, there are no studies investigating changes in glucose metabolism in chronic BD or BD with rapid cycling. It is not clear whether for example rapid cycling has any correlation with changes in glucose metabolism/brain energetics. In a way, it is surprising that no one has looked into this issue yet given the disabling character of the illness. It is known that acute hypoglycemia is accompanied with changes in mental status which can resemble symptoms of a psychiatric disorder. An analogical assumption could be that a fluctuation of glucose levels might influence the clinical presentation of BD leading to more rapid changes in psychiatric symptoms mirroring the fluctuation in glucose metabolism. A prospective study looking at changes in glucose metabolism during the course of rapid cycling BD might help to understand the nature of this specifier and have implications in the management of this disabling condition.

The mechanism how IR/DM affects the brain is not yet clearly understood. It might be related to a dysregulation of the HPA, which is one of the possible links between BD and DM. Convit (2005) suggested a model of the link between IR and hippocampal damage, which is shortly outlined in the introduction part (2005) (91). Looking at the model in more detail, he proposed that IR is associated with 'functional hypoglycemia' in hippocampus. This 'functional hypoglycemia' reflects impaired ability to increase regional metabolism in response to increased demand during activation of hippocampus (due to abnormalities in endothelial-dependent vasodilatation associated with IR), resulting in relative regional hypoglycemia (91;181). This could explain the deficits on cognitive tasks requiring activation of hippocampus, which were found in IR (86;87;91). Long-term functional hypoglycemia may lead to hippocampal damage and volume loss (91). Since hippocampus is involved in regulation of the HPA, its damage could lead to hypercortisolemia which would, in turn, cause more damage to hippocampus via reducing glucose transport and glucose utilization in hippocampus (92;182); resulting in further dysregulation of the HPA and creating a vicious circle (91;181). Since

affective episodes are associated with HPA abnormalities, which, in some cases, seem to improve upon remission of episodes (61;62;64), this vicious circle might complicate the recovery from episodes and contribute to the chronic and more disabling character of BD in patients with DM. On the other hand, long-term hypercortisolemia in patients with more severe course of BD may lead to hippocampal damage, causing further damage to the HPA and eventually result in increased IR or DM in vulnerable individuals. Additional damage might result from chronic hyperglycemia which was suggested to cause damage to hippocampus via impairment of glucose transport or directly by increased production of superoxides and advanced glycation end products (183).

Given the possible brain damage associated with IR, patients with co-morbid DM will likely have a different profile on neuroimaging or cognitive testing than patients without co-morbid DM. In other words, they might represent a subgroup of bipolar patients with a higher risk of brain damage due to IR. This may be a reason for the conflicting results of neuroimaging studies in BD described in the introduction, hippocampal abnormalities in particular, and difficulties with replication of the findings. Neuroimaging and neurocognitive studies looking at differences in relation to DM/IR might help to clarify this issue. Such studies may also help to differentiate between changes in brain associated with BD vs changes related to DM/IR (see below).

Further to the point of worse outcome associated with co-morbid DM, it is possible that normalization of metabolic changes is an important factor for long-term remission of BD. Metabolic correlates might be helpful in predicting an increased risk of recurrence of a mood episode or may prove to be a marker of effective or ineffective treatment. Prospective research investigating changes in glucose metabolism during the course of BD and long-term outcome may help to better understand this issue.

## 5.3 Bipolar disorder with co-morbid diabetes mellitus as a subgroup of bipolar disorder and implications for further research

The results of this study are compatible with the assumption that BD with co-morbid DM is a subgroup of BD that is characterized by more complicated course of BD which may be a result of common alterations on multiple levels as described above. Given the polygenic nature of both disorders, it is possible that the risk of DM exists on a continuum ranging from low to high risk depending on the number of present alterations, their interactions, and interactions with environmental factors. In addition, BD and DM may represent a subset of patients whose characteristics change over time due to possible brain damage resulting from the disease process, and who might be more vulnerable to the effects of environmental factors such as stress, diet or physical activity. Despite all these complicating factors, the research presented in this thesis supports the view that BD with co-morbid DM represents a subgroup of bipolar patients who share some common mechanisms and may be used as an alternative phenotype for molecular-genetic studies.

Another use of this phenotype for future research is searching for further trait markers (also called endophenotypes or biological markers) associated with BD. Before discussing the options for further research using this approach, I will briefly outline the principle behind the strategy of implementing endophenotypes. As mentioned earlier, correct identification of phenotypes is critical for molecular-genetic research. However, the DSM-IV diagnosis of BD includes a genetically heterogeneous group of disorders, which may be the cause of difficulties with finding significant results and with their replication when using different samples. BD is a disorder with complex genetics and incomplete penetrance; involved genes likely have small to moderate effect, and clinically the manifestation of BD ranges from mild to severe forms. All these factors make a correct assessment of a phenotype for these studies difficult and, as a result, complicate the identification of genes involved in the disorder. One of the strategies to reduce the heterogeneity of the sample and increase the chances of finding susceptibility genes in complex disorders is through identification of specific traits accompanying the illness called endophenotypes or biological markers. This strategy aims to select a subgroup of patients who share

certain traits that are associated with a smaller number of genes (monogenic traits, in ideal case) thus, increasing the probability of finding significant results for genes with small to moderate effect. The principles of using endophenotypes in the research of psychiatric disorders have been described in the literature (134;137;184) and have been successfully used in some complex disorders (185-187). Gershon and Goldin (1986) and Leboyer et al. (1998) suggested following criteria for identification of an endophenotype (184;137): 1. marker is associated with illness in the population, 2. marker is heritable, 3. is state independent, 4. co-segrates with illness in families and 5. is found in unaffected family members more often than in the general population.

How can a subgroup of bipolar patients with co-morbid DM help in searching for further endophenotypes? For example, BD is associated with cognitive dysfunction that persists into euthymic phase and is present also in unaffected relatives of patients with BD (188-194). Therefore, cognitive patterns may represent endophenotypes in BD. However, BD has an increased risk of DM/IR which can affect the brain as well. As outlined in the introduction, cognitive changes similar to those found in BD were found in DM (85;86;188;194). Thus, some of the dysfunction found in BD may be related to changes resulting from IR/DM rather than those associated with BD. Clarification of alterations related to DM/IR as opposed to BD may be helpful in defining a neurocognitive endophenotype for further research in BD.

Other examples include studies of changes in gene expression following treatment of cell cultures with medications used in BD and DM. Such research might for instance help to identify mechanisms of actions of the treatments. The advantage of this type of study is that comparing gene expression patterns in cultured cells from the same subject is very likely to reduce false positives and background signal, thus increasing the chance of identifying true differences based on treatment.

## 5.4 Implications for treatment of bipolar disorder

The theoretical and clinical parts of this thesis have direct implications for treatment and management of patients with BD.

When treating patients with BD, it is important to keep in mind their already increased risk of abnormalities in glucose metabolism which can be further complicated by medication which showed a negative effect on glucose metabolism. In BD this concerns mainly the use of atypical antipsychotics (AAP). Nowadays, it is likely that the use of AAP in bipolar patients will increase since AAP have been listed among first line treatments for BD (31;40) and might be a convenient option for both, the patient and the physician. To better demonstrate this point, I will give an example from common clinical practice: most AAP have shown some prophylactic as well as antimanic effect (31). In the case of a severe manic episode, many psychiatrists may resort to an antipsychotic (for their tranquilizing effect and perceived safety and convenience as opposed to medications such as lithium) which would then be continued even after improvement of acute symptoms without considering other options that could be better for long-term mood stabilization of the particular patient and without considering possible complications for future management (such as the side effect profile and resulting non-compliance, long-term costs, etc.). This study further emphasizes that the risks and benefits of a particular treatment should be carefully considered and assessed in every individual case.

This study calls for improvement in screening and monitoring of possible abnormalities in glucose metabolism/DM in all patients with BD, treated or untreated. I would like to emphasize this issue in the view of the results of relatively recent studies which showed that blood work, plasma glucose in particular, is still not a routine part of psychiatric care in BD. In particular, Suppes et al. (2007) performed an online survey among 500 US psychiatrists and discovered that only 57% of physicians check baseline levels of fasting or non-fasting plasma glucose before initiating treatment in bipolar patients. The percentage was slightly more optimistic (69%) when looked at monitoring of the above parameters during treatment (195). In Europe, a similar survey was carried out among 718 psychiatrists and revealed that baseline fasting or non-fasting glucose levels were checked by 62% psychiatrists and

only 60% monitored the levels during the course of treatment with pharmacotherapy (196). Via increasing the awareness of the higher risk of DM in BD and the more complicated course with worse outcomes associated with this co-morbidity, this study might prompt physicians to improve this part of patients' care.

Some evidence outlined in the theoretical part of this thesis suggests that acute episodes of BD are associated with changes in insulin sensitivity that might be independent of medication and possibly improve upon remission of mood episodes. In addition, some medications used in BD seem to have a positive effect on glucose metabolism. As I already mentioned above, we can speculate that normalization or changes in glucose metabolism are a necessary prerequisite for long-term remission of BD. This hypothesis opens a broad field for future research, such as, for example, longitudinal studies of glucose metabolism during the course of the illness; or search for new effective treatments for BD.

# 6 Summary

To my knowledge, this was the first study investigating the clinical correlates of BD in patients with co-morbid DM. The results of this study suggest that patients with co-morbid BD and DM have more severe course of BD when compared with bipolar patients without DM in terms of chronicity. Also mood instability is greater in patients with co-morbid DM as indicated by higher rates of rapid cycling. Patients with co-morbid BD and DM are at a higher risk for hypertension and obesity. Patients with co-morbid DM have poorer quality of life and contribute significantly to the socioeconomic burden of BD. Treatment with antipsychotics could not account for the entire risk of developing DM in bipolar patients. The results of this study are in keeping with the possible link between BD and DM outlined in the introduction, and with the hypothesis that BD with co-morbid DM is an alternative phenotype that can be useful in further research devoted to BD and DM. In the discussion I outlined some of the possible ways of using this phenotype for future research.

Considering patients' management, the results have following implications for clinical care and prognosis of BD. This study may help to increase awareness of the elevated risk of DM in BD and prompt clinicians to take this into consideration when initiating therapy, especially therapy with AAP. The results of this study point to the need for more active screening for glucose metabolism abnormalities in patients with BD and may lead to an increased awareness of potential complications and risks. Especially patients with poor outcome should be closely monitored, and more severe course of the illness should point to the need of active screening for abnormalities in glucose metabolism. Bipolar patients with known co-morbid DM might require more intensive psychiatric care. Considering the positive effect of some psychotropic medications and ECT on glucose metabolism outlined in the introduction, patients should be closely monitored during the course of their treatment, especially during times of treatment changes, and might need adjustments of their antidiabetic medications to prevent possible complications resulting from hypoglycemia. Last but not least, patients with BD should be aware of their increased susceptibility towards DM and should be encouraged to implement healthy lifestyle choices early in their illness. It is possible that healthy lifestyle, aimed at the prevention of cardiovascular

disease/DM could increase the chances of having a more favorable, less chronic course of their bipolar illness.

This study is a starting point for further research investigating the nature of the link between DM and BD. Research based on the results is currently ongoing and involves a case-control study and molecular-genetic studies aimed at clarifying the genetic background of BD.

Genetic research should help to clarify the biological and environmental mechanisms involved in BD and DM, the mechanisms of actions of treatments used in BD and DM, and possible genes involved in DM and BD. Better understanding of these processes is essential in the search for new, targeted treatments for both DM and BD, for successful prediction of treatment response and for possible prevention of manifestation of the illness in the first place.

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**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AAP | atypical antipsychotics |
| BD | bipolar disorder |
| BD I | bipolar I disorder |
| BD II | bipolar II disorder |
| BD NOS | bipolar disorder not otherwise specified |
| BMI | body mass index |
| CRH | corticotropin releasing hormone |
| DAG | 1,2-diacylglycerol |
| DM | diabetes mellitus |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders |
| DST | dexamethasone suppressive test |
| ECT | electroconvulsive treatment |
| FPG | fasting plasma glucose |
| GAF | Global Assessment of Functioning scale |
| GSK-3β | glycogen synthase kinase 3β |
| HbA1c | hemoglobin A1c |
| HOMA-IR | homeostatic model assessment; an estimate of insulin resistance; insulin x glucose/22.5 |
| HPA | hypothalamo-pituitary-adrenocortical axis |
| IDDM | insulin dependent diabetes mellitus |
| IGT | impaired glucose tolerance |
| IMP | inositol monophosphate |
| IMPase | inositol monophosphatase |
| IP3 | inositol-1,4,5-triphosphate |
| IPPase | inositol polyphosphate 1-phosphatase |
| IR | insulin resistance |
| IRK | insulin receptor kinase |
| IRS-1 | insulin receptor substrate-1 |
| LTP | long-term potentiation |
| MAOI | monoamine oxidase inhibitor |
| MRI | magnetic resonance imaging |
| Na-K ATPase | sodium potassium adenosine triphosphatase |
| NIDDM or DM | non-insulin dependent diabetes mellitus, diabetes mellitus type 2 |
| PI | phosphatidylinositol |
| PI3-K | phosphatidylinositol 3-kinase |
| PIP | phosphatidylinositol phosphate |
| $PIP_2$ | phosphoinositide 4,5-bisphosphate |
| PKA | protein kinase A |
| PKC | protein kinase C |
| PLC | phospholipase C |
| PLCG1 | phospholipase C-γ1 gene |
| PTP1B | protein tyrosine phosphatase 1B |
| PTPN1 | protein tyrosine phosphatase, nonreceptor-type, 1 gene |
| SADS-L | Schedule for Affective Disorders and Schizophrenia – Lifetime version |
| SSRI | selective serotonin reuptake inhibitors |
| TCA | tricyclic antidepressants |
| TH | thyrosine hydroxylase |

## APPENDICES

# Appendix A1: Leading causes of years of life lived with disability (YLDS)

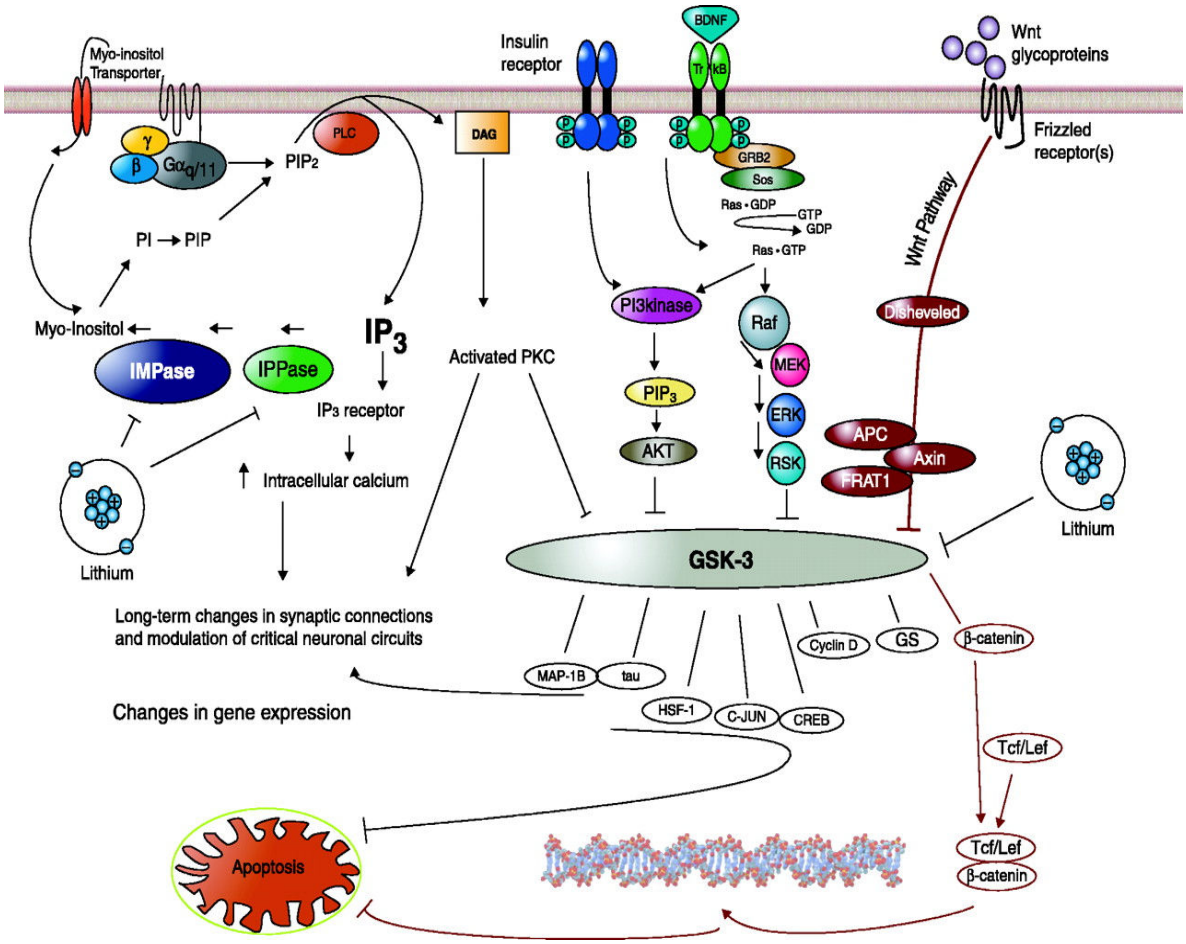
In all ages and in 15–44-year-olds, by sex, estimates for 2000; Report on mental health

| | Both sexes, all ages | % total | Males, all ages | % total | Females, all ages | % total |
|---|---|---|---|---|---|---|
| 1 | Unipolar depressive disorders | 11.9 | Unipolar depressive disorders | 9.7 | Unipolar depressive disorders | 14.0 |
| 2 | Hearing loss, adult onset | 4.6 | Alcohol use disorders | 5.5 | Iron-deficiency anaemia | 4.9 |
| 3 | Iron-deficiency anaemia | 4.5 | Hearing loss, adult onset | 5.1 | Hearing loss, adult onset | 4.2 |
| 4 | Chronic obstructive pulmonary disease | 3.3 | Iron-deficiency anaemia | 4.1 | Osteoarthritis | 3.5 |
| 5 | Alcohol use disorders | 3.1 | Chronic obstructive pulmonary disease | 3.8 | Chronic obstructive pulmonary disease | 2.9 |
| 6 | Osteoarthritis | 3.0 | Falls | 3.3 | Schizophrenia | 2.7 |
| 7 | Schizophrenia | 2.8 | Schizophrenia | 3.0 | Bipolar affective disorder | 2.4 |
| 8 | Falls | 2.8 | Road traffic accidents | 2.7 | Falls | 2.3 |
| 9 | Bipolar affective disorder | 2.5 | Bipolar affective disorder | 2.6 | Alzheimer's and other dementias | 2.2 |
| 10 | Asthma | 2.1 | Osteoarthritis | 2.5 | Obstructed labour | 2.1 |
| 11 | Congenital abnormalities | 2.1 | Asthma | 2.3 | Cataracts | 2.0 |
| 12 | Perinatal conditions | 2.0 | Perinatal conditions | 2.2 | Migraine | 2.0 |
| 13 | Alzheimer's and other dementias | 2.0 | Congenital abnormalities | 2.2 | Congenital abnormalities | 1.9 |
| 14 | Cataracts | 1.9 | Cataracts | 1.9 | Asthma | 1.8 |
| 15 | Road traffic accidents | 1.8 | Protein–energy malnutrition | 1.8 | Perinatal conditions | 1.8 |
| 16 | Protein–energy malnutrition | 1.7 | Alzheimer's and other dementias | 1.8 | Chlamydia | 1.8 |
| 17 | Cerebrovascular disease | 1.7 | Cerebrovascular disease | 1.7 | Cerebrovascular disease | 1.8 |
| 18 | HIV/AIDS | 1.5 | HIV/AIDS | 1.6 | Protein–energy malnutrition | 1.6 |
| 19 | Migraine | 1.4 | Lymphatic filariasis | 1.6 | Abortion | 1.6 |
| 20 | Diabetes mellitus | 1.4 | Drug use disorders | 1.6 | Panic disorder | 1.6 |
| | **Both sexes, 15–44-year-olds** | **% total** | **Males, 15–44-year-olds** | **% total** | **Females, 15–44-year-olds** | **% total** |
| 1 | Unipolar depressive disorders | 16.4 | Unipolar depressive disorders | 13.9 | Unipolar depressive disorders | 18.6 |
| 2 | Alcohol use disorders | 5.5 | Alcohol use disorders | 10.1 | Iron-deficiency anaemia | 5.4 |
| 3 | Schizophrenia | 4.9 | Schizophrenia | 5.0 | Schizophrenia | 4.8 |
| 4 | Iron-deficiency anaemia | 4.9 | Bipolar affective disorder | 5.0 | Bipolar affective disorder | 4.4 |
| 5 | Bipolar affective disorder | 4.7 | Iron-deficiency anaemia | 4.2 | Obstructed labour | 4.0 |
| 6 | Hearing loss, adult onset | 3.8 | Hearing loss, adult onset | 4.1 | Hearing loss, adult onset | 3.6 |
| 7 | HIV/AIDS | 2.8 | Road traffic accidents | 3.8 | Chlamydia | 3.3 |
| 8 | Chronic obstructive pulmonary disease | 2.4 | HIV/AIDS | 3.2 | Abortion | 3.1 |
| 9 | Osteoarthritis | 2.3 | Drug use disorders | 3.0 | Panic disorder | 2.8 |
| 10 | Road traffic accidents | 2.3 | Chronic obstructive pulmonary disease | 2.6 | HIV/AIDS | 2.5 |
| 11 | Panic disorder | 2.2 | Asthma | 2.5 | Osteoarthritis | 2.5 |
| 12 | Obstructed labour | 2.1 | Falls | 2.4 | Maternal sepsis | 2.3 |
| 13 | Chlamydia | 2.0 | Osteoarthritis | 2.1 | Chronic obstructive pulmonary disease | 2.2 |
| 14 | Falls | 1.9 | Lymphatic filariasis | 2.1 | Migraine | 2.1 |
| 15 | Asthma | 1.9 | Panic disorder | 1.6 | Alcohol use disorders | 1.5 |
| 16 | Drug use disorders | 1.8 | Tuberculosis | 1.6 | Rheumatoid arthritis | 1.4 |
| 17 | Abortion | 1.6 | Gout | 1.3 | Obsessive–compulsive disorder | 1.4 |
| 18 | Migraine | 1.6 | Obsessive–compulsive disorder | 1.3 | Falls | 1.4 |
| 19 | Obsessive–compulsive disorder | 1.4 | Violence | 1.2 | Post-traumatic stress disorder | 1.4 |
| 20 | Maternal sepsis | 1.2 | Gonorrhoea | 1.1 | Asthma | 1.3 |

[a] Neuropsychiatric conditions (see Annex Table 3) are highlighted.

The World Health Report 2001
http://www.who.int/whr/2001/chapter2/en/index.html

## Appendix A2: Lithium and signal transduction

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## Appendix A3: Bipolar clinic / Maritime registry data worksheet

**Chart Number** _____

First Name _____Sex ___ (1=male, 2=female) Age:_____

Last Name _____Birth Date ____/_____/_____(mm/dd/yy)

Height _____ Weight _____

Marital Status _____ # of Children _____ SES _____

Ethnic Background: A) Father: _____B) Mother: _____(2 digit codes)

Address _____ Telephone #: _____

_____ Postal Code _____

Exam Date ___/_____/_____ (mm/dd/yy) Most Recent Update ____/____/_____

Current Level of Function _____ (GAF Scale)

Age of Onset (D): _____ Age of Onset (M): _____

***when diagnostic criteria is met** ***when diagnostic criteria is met**

Age of First Hospitalization _____ Availability of Information _____

**DSM-IV Consensus Lifetime Diagnoses: (in chronological order)**

1. _____._____ Age of Onset_____ Text _____
2. _____._____ Age of Onset_____ Text _____
3. _____._____ Age of Onset_____ Text _____
4. _____._____ Age of Onset_____ Text _____
5. _____._____ Age of Onset_____ Text _____
6. _____._____ Age of Onset_____ Text _____

**FAMILY HISTORY**

| | Father | Mother | Sisters | Brothers | Sons | Daughters |
|---|---|---|---|---|---|---|
| Bipolars | | | | | | |
| Unipolars | | | | | | |
| Schizoaffective | | | | | | |
| Schizophrenia | | | | | | |
| Others & Unspecified | | | | | | |
| Total Unaffected | | | | | | |
| Total Available | | | | | | |

- **Enter actual number**

Number of first degree relatives who have attempted suicide: _____

Number of first degree relatives who have completed suicide: _____

## CLINICAL COURSE OF THE ILLNESS

| | Episode Onset (mm/dd/yy) | Duration (weeks) | Polarity | Psychotic Features | Quality of Remission (treated or untreated) | Treatment Setting | Type of Treatment |
|---|---|---|---|---|---|---|---|
| **1** | | | | | | | |
| **2** | | | | | | | |
| **3** | | | | | | | |
| **4** | | | | | | | |
| **5** | | | | | | | |
| **6** | | | | | | | |
| **7** | | | | | | | |
| **8** | | | | | | | |
| **9** | | | | | | | |
| **10** | | | | | | | |
| **11** | | | | | | | |
| **12** | | | | | | | |
| **13** | | | | | | | |
| **14** | | | | | | | |
| **15** | | | | | | | |

## CODES

**Polarity:**
1= M (mania)
2= m (hypomania)
3= D (Major Affective Disorder)
4= d (sub-clinical)
5= MD
6= DM
7= X (mixed)
8= RC (rapid cycling)

**Psychotic Features:**
1= none
2= mood congruent psychotic features
3= mood incongruent psychotic features

**Quality of Remission**
0= still in episode
1= complete
2= partial
3= poor remission

**Treatment Setting**
1= none
2= out-patient
3= in-patient
4= unknown

**Type of Treatment**
0= none
1= Mood Stabilizer
2= Antidepressants
3= Neuroleptics
4= Benzodiazines
5= Psychoeducation
6= Psychotherapy
7= ECT
8= Rehabilitation
9= Other

- **Summary description of clinical course: _____**

0= single episode
1= completely episodic
2= episodic residual
3= chronic fluctuating
4= chronic
5= not applicable

| **PHARMOCOLOGICAL TREATMENT FOR TARGET MOOD SYMPTOMS: Include major treatment trials only.** | | | | | |
|---|---|---|---|---|---|
| Drug | Onset Date (mm/dd/yy) | Duration (weeks) | Dosage | Compliance | Therapeutic Effect |
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |

**CODES:**

**Compliance**
1= compliant
2= mostly compliant
3= non-compliant
4= cannot classify

**Therapeutic Effect**
1= no effect
2= partial effect
3= complete response
4= inadequate trial

**COMMENTS:**

| SIGNIFICANT PSYCHIATRIC SUBSYNDROMAL SYMPTOMS | | |
|---|---|---|
| | YES | NO |
| Social Anxiety | | |
| Panic Disorder | | |
| General Anxiety | | |
| OCD | | |
| Substance Abuse | | |
| Attention Deficit | | |
| Learning Disability | | |
| Primary Insomnia | | |
| Personality Disorder | | |
| Other<br>* specify | | |

**History of Suicidal Behaviour:**
Total number of suicide attempts: _____

Total number of potentially lethal attempts: _____

Age of first suicide attempt: _____

**Medical History of:**

a. Diabetes yes/no Type: _____

Age of Onset: _____

b. Hypertension yes/no c. Menstrual Irregularities yes/no

Age of Onset: _____ Age of Onset: _____

d. Thyroid problems yes/no e. Head Injury/Other Neurological Event

Age of Onset: _____ yes/no

Age of Onset: _____

**Functional History:**

| | **Date** | **# of Months** | **Due to Bipolar Illness (yes/no)** |
|---|---|---|---|
| Periods of Unemployment | | | |
| Family Member Care Required | | | |
| Welfare/ Disability Payments | | | |

# Appendix A4: Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder

Name: _____Date: _____ Drug: _____Evaluated By: _____

**Criterion A**

The criterion A is used to determine an association between clinical improvement and the treatment. The rating should apply to the period of treatment considered adequate in duration and dosage. The illness activity should be judged by frequency, severity, and duration of episodes.

10 = Complete response, no recurrences in the course of adequate treatment, no residual symptoms, and full functional recovery
9 = Very good response, no recurrences, but the patient may have minimal residual symptoms (transient anxiety, sleep disturbance, dysphoria, irritability) not requiring any intervention
8 = Very good response. Illness activity reduced by more than 90%
7 = Good response. Illness activity reduced by 80 - 90 %
6 = Good response. Reduction in activity of illness by 65 - 80%
5 = Moderate response. Reduction in illness activity by 50 - 65%
4 = Moderate improvement. Reduction in illness activity by 35 - 50%
3 = Mild improvement. Reduction of illness activity by 20 - 35%
2 = Mild improvement. Reduction of illness activity by 10 - 20%
1 = Minimal improvement. Reduction of illness activity by 0 - 10%
0 = No change or worsening

**A Criterion Score:** _____

**Criteria B**

The criteria B are used to establish whether there is a causal relationship between clinical improvement and the treatment. Score 0, 1 or 2 points for each item:

***B1: Number of episodes before / off the treatment:***
0 = 4 or more episodes
1 = 2 or 3 episodes
2 = 1 episode

**B 1:** _____

***B2: Frequency of episodes before / off the treatment.***
0 = Average to high, including rapid cycling
1 = Low, spontaneous remissions of 3 or more years on average
2 = 1 episode only, risk of recurrence cannot be established

**B 2:** _____

***B3: Duration of the treatment.***
0 = 2 or more years
1 = 1 - 2 years
2 = Less than 1 year

**B 3:** _____

***B4: Compliance during period(s) of stability.***
0 = Excellent, e.g. documented by drug levels in the therapeutic range
1 = Good, more than 80% levels in the therapeutic range
2 = Poor, repeatedly off treatment, less than 80% levels in the therapeutic range

**B 4:** _____

***B5: Use of additional medication during the period of stability***
0 = None except infrequent sleep medication (1 per week or less); no other mood stabilizers, antidepressants or antipsychotics for control of mood symptoms
1 = Low-dose antidepressants or anti-psychotics as an "insurance", or prolonged use of sleep medication
2 = Prolonged or systematic use of an antidepressant or anti-psychotic

**B 5:** _____

**B Criteria Score:** _____

**Total Scale Score:** _____
(Subtract B from A)

## Appendix A5: DSM-IV-TR diagnostic criteria

### DSM-IV-TR diagnostic criteria for mood episodes, Bipolar Disorder I, II and NOS, definition of rapid cycling specifier

**Hypomanic Episode**

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if mood is only irritable) and have been present to a significant degree:

1. inflated self-esteem or grandiosity
2. decreased need for sleep
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility
6. increase in goal-directed activity or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to direct physiological effects of a substance or a general medical condition.

**Manic Episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if mood is only irritable) and have been present to a significant degree:

1. inflated self-esteem or grandiosty
2. decreased need for sleep
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility
6. increase in goal-directed activity or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences

C. The symptoms do not meet criteria for a Mixed Episode

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self o others, or there are psychotic features.

E. The symptoms are not due to direct physiological effects of a substance or a general medical condition.

**Major Depressive Episode**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. In children and adolescents may be irritable mood.
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly everyday as indicated by either subjective report or observation made by others.
3. significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. diminished ability to think or concentrate, or indecisiveness, nearly every day
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance or a general medical condition

E. The symptoms are not better accounted for by Bereavment.

**Mixed Episode**

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least 1-week period

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or

to necessitate hospitalization to prevent harm to self o others, or there are psychotic features.

C. The symptoms are not due to direct physiological effects of a substance or a general medical condition.

**Bipolar I Disorder**

Presence (or history) of at least one Manic Episode (Single Manic Episode); or previous history of at least one Manic or Mixed Episode + Most Recent Episode Hypomanic or Manic or Mixed or Depressed or Unspecified; or previous history of at least one Major Depressive Episode + Most Recent Episode Mixed or Manic.

X. The mood symptoms are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

A recurrence is defined as either a change in polarity or an interval of at least 2 months without affective symptoms.

**Bipolar II Disorder**

A. Presence (or history) of one or more Major Depressive Episodes.

B. Presence (or history) of at least one Hypomanic Episode.

C. There has never been a Manic Episode or a Mixed Episode.

D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Bipolar Disorder NOS (Not Otherwise Specified)**

Includes disorders with bipolar features that do not meet criteria for any specific Bipolar Disorder (e.g. Reccurrent Hypomanic Episodes, very rapid alternation between manic and depressive symptoms that do not meet minnimal duration criteria for a mood disorder, situations in which the clinician has concluded that Bipolar Disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance induced).

**Rapid Cycling Specifier**

At least four episodes of a mood disturbance in the previous 12 months that meet criteria for a Major Depressive, Manic, Mixed or Hypomanic Episode

Episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity.

Adapted from: Diagnostic and Statistical Manual of Mental Disorders. 4th Edition, Text Revision (2000). American Psychiatric Association. Washington, DC.

# Appendix A6: Global Assessment of Functioning scale (GAF)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical or environmental limitations

| | |
|---|---|
| 91-100 | Superior and, is sought out by others because of his or her many positive qualities. No symptoms |
| 81-90 | Absent or minimal symptoms ( e.g., mild anxiety before an exam ), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns ( e.g., an occasional argument with family members ) |
| 71-80 | If symptoms are present, they are transient and expectable reactions to psychosocial. stressors ( e.g., difficulty concentrating after family argument ); no more than slight impairment in social occupational, or school functioning ( e.g., temporarily falling behind in schoolwork ). |
| 61-70 | Some mild symptoms ( e.g., depressed mood and mild insomnia ) OR some difficulty in social occupational, or school functioning ( e.g., occasional truancy or theft within the household ), but generally functioning pretty well, has some meaningful interpersonal relationships. |
| 51-60 | Moderate symptoms ( e.g., flat affect and circumstantial speech, occasional panic attacks ) OR moderate difficulty in social, occupational, or school functioning ( e.g., few friends, conflicts with peers or co-workers ). |
| 41-50 | Severe symptoms ( e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting ) OR any serious impairment in social, occupational or school functioning ( e,g., no friends, unable to keep a job ). |
| 31-40 | Some impairment in reality testing or communication ( e.g., speech is at times illogical, obscure, or irrelevant ) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood ( e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school ). |
| 21-30 | Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment ( e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation ) OR inability to function in almost all areas ( e.g., stays in bed all day, no job, home, or friends ). |
| 11-20 | Some danger of hurting self or others ( e .g., suicidal attempts without clear expectation of death; frequently violent; manic excitement ) OR occasionally fails to maintain minimal personal hygiene ( e.g., smears feces ) OR gross impairment in communication ( e.g., largely incoherent or mute ). |
| 1-10 | Persistent danger of severely hurting self or others ( e.g., recurrent violence ) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.0 Inadequate information |

Adapted from the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 4th Edition, Text Revision (2000). American Psychiatric Association. Washington, DC.