Original Research

Adults With Mood Disorders Have an Increased Risk Profile for Cardiovascular Disease Within the First 2 Years of Treatment

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Objectives: People with bipolar disorder (BD) and major depressive disorder (MDD) are at risk for premature death from various physical illnesses. A large component of this risk may be accounted for by an elevated risk of metabolic syndrome (MeS) and coronary heart disease (CHD). The objective of our study was to examine patients' physical health prior to first treatment and over 2 years of follow-up.

Methods: Ten-year risk for CHD and incidence of MeS were calculated for newly diagnosed patients with MDD (n = 30) and BD (n = 24) at baseline and over a 2-year follow-up. Age and sex-matched control subjects were obtained from the National Health and Nutrition Examination Survey III dataset.

Results: At baseline, 11.2% of patients met diagnostic criteria for MeS and this increased to 16.8% at follow-up. Women had higher rates of MeS but rates were similar across diagnosis. There was a significant increase within all MeS criteria. The 10-year CHD risk was low for patients at baseline and follow-up but increased across the follow-up period. Changes in CHD and MeS risk were not associated with a specific type of pharmacotherapy, as all medication classes appeared to increase risk.

Conclusion: Prior to treatment, MeS and CHD risk rates for patients were similar to the general population, but their risk of CHD increased appreciably.

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Clinical Implications

- Our study highlights a concerning clinical trend. Changes in risk for both CHD and the component illnesses that make up MeS occurred early in treatment in a young, physically healthy population.
- While the focus in terms of risk management has been primarily on patients treated with atypical antipsychotics, we found significant changes also occurred in patients receiving antidepressants.
- Appropriate screening protocols and treatments need to be implemented early in the management of patients with mood disorders.

Limitations

- As our study was longitudinal and followed young patients over 2 years, we had a high attrition rate, limiting our sample size at the 2-year mark.
- While detailed information regarding medication use was obtained, the naturalistic nature of the study meant that patients often used numerous different medications, limiting precise comments on the risk carried by specific medication classes.
- The study sample was also ethnically homogenous, and lacking some ethnic groups that may be at highest risk for metabolic dysregulation, thereby limiting the generalizability of the findings.

Key Words: *obesity, bipolar major depression, metabolic syndrome, cardiovascular disease*

Defined by a cluster of metabolic risk factors, MeS in turn serves as a multiplex risk factor for CHD.[1] Numerous differing definitions of the MeS have been put forward by various agencies but the definition most consistently cited is that of the NCEP ATPIII introduced in 2001 and subsequently modified in 2004. By definition, MeS requires the presence of any 3 of the following 5 criteria: central obesity (a waist circumference of >102 cm [>40 in] in men, >88 cm [>35 in] in women); elevated triglycerides (>150mg/dL [>1.7 mmol/L] or specific treatment for this lipid abnormality); raised BP (systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension); raised fasting glucose (>100 mg/dL [>5.6 mmol/L] or treatment for type 2 diabetes); and reduced HDL cholesterol (<40 mg/dL [<1.03mm/L] in men, <50 mg/dL [<1.3 mmol/L] in women or specific treatment for this lipid abnormality).[2] People with MeS are twice as likely to die from, and 3 times as likely to have, a heart attack or stroke and have up to a 9-fold greater risk of developing type 2 diabetes, compared with people without MeS.[3–5] Given that up to 80% of the 200 million people with diabetes globally will die of CHD, MeS and diabetes now rank ahead of human immunodeficiency virus and acquired immune deficiency syndrome in morbidity and mortality.[6]

Rates of obesity in patients with chronic mental illness surpass that of the general population,[7,8] suggesting that this group might also be at risk of other features of MeS. Much of the focus on the risk for MeS in patients with psychiatric illnesses has been in patients with psychotic disorders,[9] largely because treatment with atypical antipsychotic medications is associated with features of MeS. Atypical antipsychotic medications are now included in treatment guidelines of BD[10] and are often used in the management of MDD,[11] drawing attention to the issue of MeS in patients with mood disorders as well.

Longitudinal cohort studies such as the community-based Framingham Heart Study[12] and the Framingham Offspring Study[13] provide a means to assess the contribution of risk factors on cardiac morbidity and mortality. This original assessment protocol has generated an age- and sex-specific algorithm using categorical ratings of risk defined by smoking status, systolic BP or treatment for hypertension, total and HDL cholesterol, and diabetes to accurately predict CHD.[2,14] This model of estimating 10-year CHD risk has never been applied to patients with MDD or BD. We therefore used the modified Framingham algorithm and the updated MeS criteria adopted by the NCEP and the ATPIII to evaluate whether never-treated patients differ from the general population by risk rates for heart disease. We further evaluated whether patients developed an elevated risk for heart disease and MeS during longitudinal follow-up. For comparison purposes, we estimated the 10-year CHD risk and prevalence of MeS in age- and sex-matched control subjects obtained from the NHANES III database at each time point.

Abbreviations used in this article

AD	antidepressant
ATPIII	Adult Treatment Panel III
BD	bipolar disorder
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
HDL	high-density lipoprotein
MDD	major depressive disorder
MeS	metabolic syndrome
NCEP	National Cholestoral Education Program
NHANES	National Health and Nutrition Examination Survey
SCID	Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

Methods

Subjects

Fifty-four patients aged between 16 and 40 years (mean age 29.6, SD 10.10; 24 women) admitted to the Regional Mood Disorders Program at St Joseph's Centre for Mountain Health Services with an episode of mania or depression were followed longitudinally for an average of 21.33 months (SD 9.00; range 6 to 48). All participants in our study were properly informed and signed a written consent. Our study was approved by the Research Ethics Board of St Joseph's Healthcare, Hamilton. Demographic and clinical characteristics of our study sample are in Table 1. Baseline assessments were done prior to any pharmacotherapy for cohort 1 (n = 31), while the baseline assessment for cohort 2 was obtained between 6 and 18 months after the onset of treatment (n = 23).

A diagnosis of MDD or BD was confirmed by the SCID[15] and all patients were able to provide informed consent and complete self-report measures. All study participants were treatment-naive, having never received prior treatment for psychiatric illness. Exclusion criteria included: previous treatment with psychotropic medication, a history of a neurological disorder except migraines, untreated medical illness, a history of anorexia nervosa or bulimia nervosa as assessed by the SCID, a primary Axis II diagnosis, a lifetime history of substance dependence or alcohol abuse within 6 months, or patients aged 16 years or younger or 50 years or older. The Hamilton Depression Rating Scale[16] and the Young Mania Scale[17] were used to monitor mood weekly. Treatment followed published guidelines[10,11] and patients were assessed weekly until euthymic, and then monthly. Cross-sectional samples of control subjects were identified from the NHANES III database and were matched with patients at baseline (n = 104) and at follow-up (n = 104) by age, race, and sex.

Table 1 Demographic and clinical characteristics of study sample

Characteristic	Baseline *n* = 31	Year 1 *n* = 22	Year 2 *n* = 20	Year 3 *n* = 15	Year 4 *n* = 15
Sex, *n*					
Male	20	15	10	10	8
Female	11	7	10	5	7
Diagnosis, *n*					
UD	20	12	14	9	7
BD	11	10	6	6	8
Age, mean (SD)	25.9 (7.0)	25.4 (6.4)	20.6 (7.7)	34.3 (11.2)	35.7 (11.7)
Age at onset of illness, mean (SD)	16.7 (4.0)	17.5 (3.7)	21.2 (8.2)	24.9 (11.4)	25.7 (12.9)

UD = unipolar depression

Metabolic Syndrome and 10-Year CHD Risk

Patients were required to present in a fasting state for all blood work, and laboratory measurements were obtained to satisfy criteria for both MeS and a 10-year CHD risk score. These measurements included: waist circumference, triglyceride levels, systolic and diastolic BP, fasting glucose levels, and HDL cholesterol levels. BP was performed as a single, seated determination, and waist circumference was measured between the lower costal margin and iliac crest. A medical assessment that included a systematic review of the patient's medical history was completed, and information was obtained on smoking status, medical conditions, and all current medications. All variables were obtained at baseline and followed at 6-month intervals for up to a 4-year period (mean 21.33, SD 9.00). Baseline CHD data on medication-naive patients were available for 31 patients, while a subset of 23 patients had baseline measurements taken after pharmacotherapy had been initiated. The 2 groups did not differ significantly by age or sex. Follow-up data were available on all 54 patients. Levels of 10-year CVD risk were calculated using criteria set forward by Wilson et al.[14]

Pharmacotherapy

Detailed records were maintained for all psychiatric medications patients received during the study, including type, dose, and duration. Patients were grouped based on the class of medication they received, using a classification system devised by Yumru et al[18]: ADs—escitalopram, citalopram, sertraline, fluoxetine, fluvoxamine, venlafaxine; mood stabilizers—lithium, sodium valproate, lamotrigine, carbamazipine; and atypical antipsychotics—quetiapine, olanzapine, and risperidone. Inclusion in a medication category required a medication be taken consistently for a minimum of 10 days. Patients were then placed into 1 of 3 categories using a hierarchal system based on the weight gain potential of each medication class: patients receiving atypical antipsychotics were placed in the atypical antipsychotics group, regardless of other medications received; patients receiving both mood stabilizers and ADs were placed in the mood stabilizers category; and patients on ADs only were placed in the AD group. Insufficient data on medication history were available to classify 3 patients and 1 patient could not be classified within the available categories.

Statistical Analyses

Metabolic Syndrome

We calculated the number of patients meeting criteria for MeS, as well as changes within individual criteria for: central obesity; elevated triglycerides; raised BP; raised fasting glucose; and reduced HDL cholesterol. Changes in prevalence rates of these criteria were compared in patients over baseline and at follow-up assessment using McNemar's chi-square test for within-subjects variables. Raw measurements of each of these criteria (for example, waist circumference) were also compared over time using a mixed-design ANOVA, treating interval (baseline, compared with follow-up) as a within-subjects factor and sex (male, compared with female) and diagnosis (MDD, compared with BD) as between-subjects variables. Specifically, we used a Wald test of significance of fixed effects, which yields a chi-square value that can be interpreted against a standard distribution table. Finally, we compared prevalence rates between patients and samples of NHANES III control subjects matched cross-sectionally at each time point using the Pearson chi-square test for between-subjects variables. A 1-way between-subjects ANOVA was used to assess the effects of medication class (AD, compared with mood stabilizers, compared with atypical antipsychotics) on both MeS criteria and on the raw measurement variables.

10-Year CHD Risk

Changes in CHD risk levels over time were compared in patients using a mixed-design ANOVA, treating interval (baseline, compared with follow-up) as a within-subjects factor and sex (male, compared with female) and diagnosis (MDD, compared with BD) as between-subjects variables. A

Table 2 Prevalence rates of MeS at baseline and over time

Characteristic	Hypertension	Central obesity	Reduced HDL	Elevated triglycerides	Elevated glucose	MeS	Total	%
Baseline								
Patients	15	18	6	14	2	6	54	11.11
Male	9	10	1	8	1	2	30	6.67
Female	6	8	5	6	1	4	24	16.67
MDD	11	13	6	7	1	5	34	14.71
BD	4	5	0	7	1	1	20	5.00
NHANES	13	38	40	39	8	20	104	19.23
Male	12	17	16	21	7	9	57	15.79
Female	1	21	24	18	1	11	47	23.40
Recent								
Patients	15	18	11	12	3	9	54	16.67
Male	7	11	5	6	2	4	30	13.33
Female	8	7	6	6	1	5	24	20.83
MDD	11	13	8	7	2	6	34	17.65
BD	4	5	3	5	1	3	20	15.00
NHANES	19	33	32	31	7	15	104	14.42
Male	15	13	18	14	7	9	57	15.79
Female	4	20	14	17	0	6	47	12.77

1-way ANOVA was used to assess the effects of medication class on CHD risk levels in these subjects. CHD risk levels at baseline and at follow-up were compared in patients and cross-sectionally matched control subjects using between-subjects ANOVAs treating group (patients, compared with control subjects) and sex (male, compared with female) as between-subjects variables. Owing to restrictions on degrees of freedom, the same analyses were repeated treating diagnosis (MDD, compared with BD) and medication class (AD, compared with mood stabilizers, compared with atypical antipsychotics), rather than sex as a between-subjects variable.

Results

Metabolic Syndrome

Despite overall increases in the percentage of patients meeting criteria for MeS (Table 2), changes in prevalence rates of MeS and its individual criteria were not significant ($P > 0.05$). However, patients showed significant changes in HDL cholesterol ($F = 8.44$, $df = 1,50$, $P < 0.01$) and glucose ($F = 8.25$, $df = 1,50$, $P < 0.01$) levels over baseline and follow-up assessment. These effects were not mediated by sex or by diagnosis; both men and women and patients with MDD and BD showed equivalent rates of increase over time. We were also able to identify a significant increase in waist circumference in patients for whom baseline assessments were done prior to any medication ($F = 4.59$, $df = 1,27$, $P < 0.05$); this effect was not apparent in the aggregate data. There were no significant increases in the remaining metabolic criteria (diastolic BP, systolic BP, high-density lipids, and triglycerides [$P > 0.05$]). There was no evidence that medication class influenced these results; medication class did not interact with measurement intervals for any of the variables measured ($P > 0.05$). All MeS criteria changed significantly over the follow-up period. A Wald test of significance of fixed effects and covariates yielded: $\chi^2 = 206.82$, $df = 14$, $P < 0.001$ for glucose; $\chi^2 = 190.68$, $df = 14$, $P < 0.001$ for HDL cholesterol; $\chi^2 = 111.78$, $df = 14$, $P < 0.001$ for BP; $\chi^2 = 294.00$, $df = 14$, $P < 0.001$ for triglycerides; and $\chi^2 = 43.03$, $df = 14$, $P < 0.001$ for waist circumference.

Prevalence rates of MeS did not differ between patients and control subjects at baseline and at follow-up testing ($P > 0.05$); there was no evidence that sex or diagnosis mediated this finding ($P > 0.05$). The proportion of control subjects meeting criterion for reduced HDL exceeded that of patients at baseline testing ($\chi^2 = 12.89$, $df = 1$, $P > 0.05$); however, this was no longer the case at follow-up testing where an equal proportion of patients and control subjects met this criterion. By contrast, a greater proportion of patients met criterion for hypertension than did control subjects at baseline testing ($\chi^2 = 5.69$, $df = 1$, $P > 0.05$). This was particularly the case for women and for patients with MDD (χ^2s = 9.35 and 7.03, $df = 1$, $P > 0.05$, respectively); differences between male patients and control subjects were not significant, nor was the

difference between patients with BD and the comparison dataset ($P > 0.05$). At follow-up, female patients met this criterion at a higher proportion than would be predicted ($\chi^2 = 6.97$, $df = 1$, $P > 0.05$), while the difference between patients with MDD and the control sample were no longer significant, $P > 0.05$.

10-Year CHD Risk

Overall, patients showed an elevation in CHD risk over baseline and follow-up testing ($F = 15.96$, $df = 1,50$, $P < 0.001$). There was some evidence that this effect was mediated by sex; the interaction between group and sex approached significance ($F = 3.13$, $df = 1,50$, $P = 0.08$). Whereas female patients showed an increase in risk for CHD over time ($t = 7.00$ $df = 23$, $P < 0.01$), male patients did not ($P > 0.05$). CHD risk increased at an equal rate in MDD and BD patients ($P > 0.05$). There was no evidence that medication class influenced these results; no differences emerged in rates of CHD risk increase across patients treated with ADs, mood stabilizers, and atypical antipsychotics ($P > 0.05$).

Patients did not differ in CHD risk from their matched control subjects at the time of baseline testing ($P > 0.05$). Sex ($F = 5.03$, $df = 1,154$, $P < 0.05$), but not diagnosis ($P > 0.05$), appeared to mediate CHD risk at follow-up testing. Female patients showed an elevated CHD risk relative to their matched control subjects ($t = 3.76$, $df = 69$, $P < 0.001$); this was not the case for male patients, where no significant differences emerged, although a trend was apparent ($P = 0.05$). As expected, male patients and control subjects had elevated CHD risk relative to female patients and control subjects at both time points (Fs = 49.68 and 17.75, $df = 1,154$, $P < 0.001$).

Discussion

Cross sectional studies have highlighted the risk of MeS in MDD and BD but we know little about the evolution of MeS in this group. In our sample, patients with BD or MDD did not differ significantly from the general population regarding prevalence rates of MeS prior to initiation of treatment. While the contribution of pharmacotherapy to the development of obesity and metabolic deregulation in patients with a mood disorder is significant, the role of intrinsic abnormalities within the hypothalamic–pituitary–adrenal axis, as well as the consequences of lifestyle alterations such as sedentary behaviour and poor nutrition may also be important.[19] While our study cannot speak to the etiological factors underlying the emergence of MeS, we did observe a numerical increase in patients meeting diagnostic criteria for MeS from 11% to 17% during the follow-up period. Although the number of people meeting diagnostic criteria for MeS did not change statistically, there were statistically significant changes in 3 of the 5 criteria after only a 2-year period in a young population (mean age 25.9, SD 7.0). Only one of these criteria significantly increased when the initial assessment was made after patients had been exposed to medication, despite the similar interval between time 1 and time 2 assessments in both groups; 21.5 months, SD 10.7, compared with 21.1 months, SD 6.2, respectively. This finding suggests that alterations occur rapidly within the first few years of treatment.

We also observed a gender effect, with MeS higher in women than in men. While the reverse is true regarding MeS prevalence in the general population, a large cross-sectional population-based survey examining MeS in patients with MDD also found a positive association between depression and the presence of MeS among women but not among men.[20] A similar gender effect was observed in the Clinical Antipsychotic Trials of Intervention Effectiveness trial of patients with schizophrenia.[9] Although the reason for this is not known, MDD has been linked to elevated levels of visceral obesity, and the protective role of sex observed in nondepressed patients seems to be lost in patients with psychiatric illness.[21] Psychiatric illness is also associated with increased rates of diabetes, which again seems to be mediated by visceral adiposity.[22] Inflammation, a finding associated with psychiatric illness and visceral obesity[23] also confers a greater cardiovascular risk to women, thus the increase in visceral obesity may manifest risk via various pathways.

During the years separating the NHANES III dataset, which was collected from 1983 to 1994, and the more recent NHANES 1999 to 2000 studies, there has been a statistically significant age-adjusted increase in the prevalence of MeS in women, but not in men.[24] This increase is thought to be related, in part, to the rise in obesity in women.[25] During this same time interval, the prescription of ADs[26] and antipsychotics[27] has almost doubled.

The NCEP and ATPIII considered patients with existing CHD or CHD equivalents in the group at highest risk for CHD (>20%), the other 2 categories being 10-year CHD risk of 10% to 20% (intermediate) and less than 10% (low).[2] Our results indicate that this risk for patients with a mood disorder is still low in the first few years of treatment. As age is a component in calculating the CHD risk, the young age of our population would predict this low score. Unlike the risk from the NHANES sample, however, our patients had a risk profile that was increasing at an unpredicted rate. While weight is not a component of the CHD risk calculation, obesity contributes to heart disease and leads to the development of other lipid abnormalities. We observed a significant increase in BMI in our sample[28] and, without intervention, this increase may manifest as increased CHD risk. The increase in CHD risk again showed that women were impacted more than men, with the risk in this group doubling over a short time. An analysis of national surveys conducted in the United States about 10 years apart showed no appreciable difference in the distribution of a 10-year risk of developing CHD. While individual risk factors such as smoking are decreasing, others such as diabetes have remained unchanged and the prevalence of obesity (defined as a BMI > 30 kg/m^2) is increasing. However, despite this, there has been a decline in mortality from CHD, an outcome that is related, in part, to improved diagnosis and treatment.[29,30]

It is not known whether the improvement in mortality related to CHD applies to patients with mood disorders. MDD and BD will affect about 10% to 15% of the population,[31] and people with this illness lose 25 years or more of life expectancy, with most of the excess premature death due to CHD.[32] In general, 50% to 80% of patients with chronic mental illness are smokers[33] and patients have rates of obesity in excess of those found in the general population.[8] Patients with severe mental illness are also less likely to receive either appropriate drug therapies or diagnostic and interventional procedures post acute myocardial infarction, an omission that leads to increased mortality secondary to reductions in quality of care.[34] This discrepancy in care is compounded by higher rates of hypertension, dyslipidemia, and diabetes in patients with severe mental illnesses than in the general population.[35–37]

Most medications used to treat mood disorders carry an inherent risk of weight gain. Most studies identify the atypical antipsychotic medications as conferring the most weight gain, followed by mood stabilizers, followed by ADs.[38] As weight gain is linked to metabolic abnormalities, we would expect to see this pattern emerging with MeS prevalence as well.[39] However, we did not find any difference in MeS diagnosis or in an increase in the number of metabolic criteria met based on medication exposure, although a significant limitation of our study is that the power was low to detect such a difference. However, our finding of an equal risk profile conferred by all 3 classes of medications has also been observed in a cross-sectional study examining rates of MeS in patients with BD receiving atypical antipsychotics alone or in combination with mood stabilizers.[18] Recent work by Andersohn et al[40] also found that treatment with ADs is associated with an increased risk of diabetes, providing further evidence that this class of medication confers an iatrogenic risk of CHD and MeS.

Conclusion

Physical comorbidity with at least 1 component of MeS is common in patients with mood disorders. These data suggest that these changes begin early in the illness, highlighting the need for proper screening and monitoring to be implemented at the initial stages of treatment. Studies are required to evaluate the efficacy of various interventions for managing metabolic dysregulation in patients with mood disorders. There also remains a need to elucidate the mechanism by which psychotropic medications negatively impact metabolic parameters.

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Résumé : Les adultes souffrant de troubles de l'humeur ont un profil de risque accru de maladie cardiovasculaire dans les 2 premières années de traitement

Objectifs : Les personnes souffrant de trouble bipolaire (TB) et de trouble dépressif majeur (TDM) sont à risque de décès prématuré des suites de diverses maladies physiques. Une grande partie de ce risque peut être attribuée à un risque élevé de syndrome métabolique (SM) et de coronaropathie (CP). L'objectif de notre étude était d'examiner la santé physique des patients avant le premier traitement et durant un suivi de 2 ans.

Méthodes : Le risque de CP sur 10 ans et l'incidence de SM ont été calculés pour des patients ayant reçu récemment un diagnostic de TDM (n = 30) et de TB (n = 24) au départ et durant un suivi de 2 ans. Des sujets témoins jumelés selon l'âge et le sexe ont été obtenus de l'ensemble des données de l'ênquete américaine *National Health and Nutrition Examination Survey III.*

Résultats : Au départ, 11,2 % des patients satisfaisaient aux critères diagnostiques du SM, pourcentage qui augmentait à 16,8 % au suivi. Les femmes avaient des taux plus élevés de SM mais les taux étaient semblables entre les diagnostics. Il y a eu une augmentation significative à tous les critères du SM. Le risque de CP sur 10 ans était faible pour les patients au départ et au suivi, mais il augmentait durant la période du suivi. Les changements du risque de CP et de SM n'étaient pas associés à un type spécifique de pharmacothérapie, car toutes les classes de médicaments semblaient accroître le risque.

Conclusion : Avant le traitement, les taux de risque de SM et de CP pour les patients étaient semblables à ceux de la population générale, mais leur risque de CP a augmenté sensiblement.