

Medical Comorbidity in Bipolar Disorder

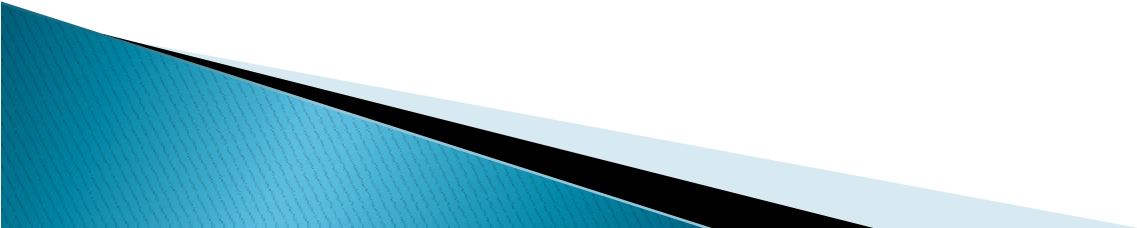
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Introduction

- } Comorbid medical illnesses can lead to:
 - elevated economic costs from medical expenditures,
 - lost productivity,
 - poorer psychiatric treatment outcomes,
 - changes in physical health-related quality of life

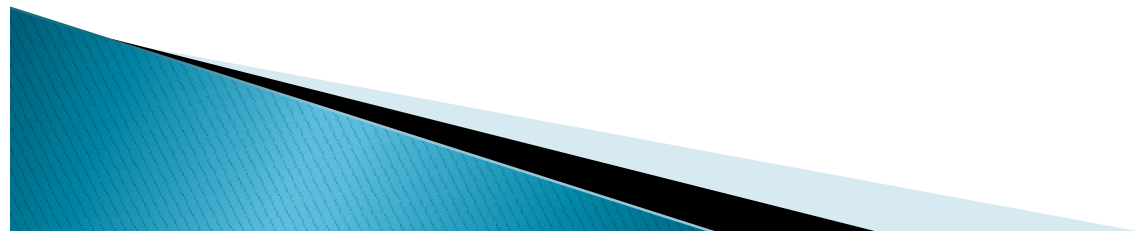
- } GMCs contribute to an earlier mortality, leaving BD patients with a life expectancy that is up to 30% shorter when compared to individuals in the general population



CENTORRINO et al., 2009;
KEMP et al., 2010;
KILBOURNE et al., 2009;
FAGIOLINI et al., 2009;

Introduction...

- } Medical comorbidity in BD is associated with several indices of illness severity, slower rate of recovery, QoL impairment and premature mortality.
- } Majority of multiple-episode BD patients have an active medical comorbidity at the time of psychiatric hospitalization.



BD
+
Circulatory disorders
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Circulatory disorders

- } A significantly higher prevalence of disparate cardiovascular disorders:
 - hypertension (34.8%),
 - ischemic heart disease (10.5%),
 - congestive heart failure (3.2%),
 - peripheral vascular disease (2.9%),

- } The rate of current and lifetime circulatory disorders was reported at 34.8 and 48.6%, respectively.

Kilbourne et al., 2004;
Fenn et al., 2005;

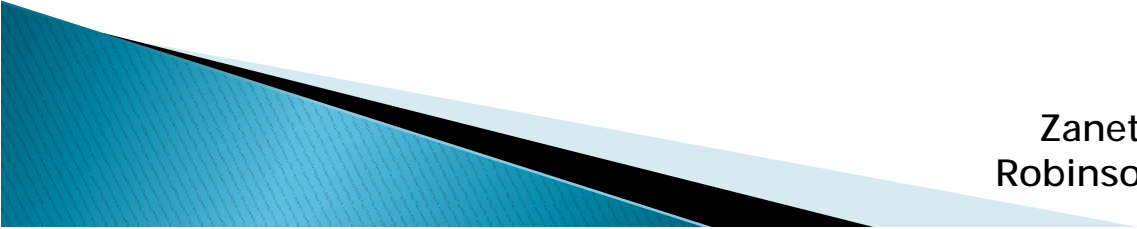
Circulatory disorders ...

- } Cerebrovascular disorders manifesting as stroke also occur at a relatively higher prevalence in the bipolar population.
- } Stroke is reported to affect 4.8% of older patients with BD.
- } After a 6-year follow-up period, the likelihood of developing a stroke is twice as high amongst patients with BD (3%) compared with patients undergoing appendectomy (1.5%) after adjusting for demographic characteristics, comorbid medical disorder and substance or alcohol dependence.

Kilbourne et al., 2005;
Lin et al., 2006

Circulatory disorders ...

- } 10% of individuals manifest incident BD after the age of 60.
- } Late-onset mania presentations are often associated with several cerebrovascular risk factors and negative family history.



Zanetti et al., 2007;
Robinson et al., 2003;

Circulatory disorders ...

- } Age-adjusted rates of circulatory disorders in BD are significantly higher, with a younger mean age at onset, when compared to the general population.
- } Although Htn is a prevalent comorbidity in BD, available evidence suggests it is not specific to BD, and may also differentially affect individuals with anxiety disorders and schizophrenia.

Johannessen et al., 2007;

Circulatory disorders ...

- } Impairment of endothelial function has recently been proposed as a trait marker amongst individuals with BD.
- } The excess mortality in BD is largely attributed to higher rates of circulatory disorders, inviting the need for prioritizing aspects of cardiovascular health in patient evaluation and management.



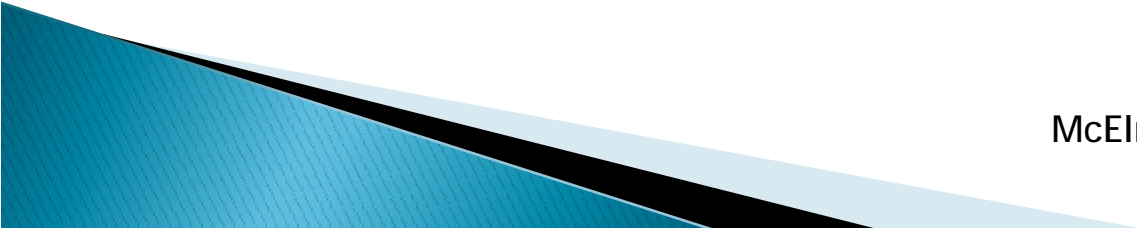
Rybakowski et al., 2006;

BD
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Obesity



Obesity

- } Extant evidence indicates an association between BD and obesity.
- } The average BMI is 27.76 kg/m²
- } 55% of patients are either overweight (28% BMI: 25–30 kg/m²) or obese (27% BMI: >30 kg/m²).



McElroy et al., 2002; McIntyre et al., 2006;
Wang et al., 2006;

Obesity ...

- } Several obesity-related risk factors are identified in the BD population including:
 - gender,
 - low income,
 - educational attainment,
 - physical activity level,
 - treatment with weight-gain-promoting agents,

- } Additional determinants of body weight are:
 - total daily intake of simple carbohydrates,
 - total energy intake,
 - caffeine consumption,
 - comorbid binge-eating disorder,
 - number of previous depressive episodes,

McElroy et al., 2002; McIntyre et al., 2006;
Elmslie et al., 2001;

Obesity...

- } Obesity affects the clinical presentation, course and outcome of BD.

- } Co-occurrence is associated with:
 - a multiepisode course of BD,
 - suicidality,
 - depression severity,
 - decreased probability of symptomatic remission,
 - shorter time to episode recurrence when compared to healthy-weight individuals with BD

Fagiolini et al., 2003;
Fagiolini et al., 2004;

BD
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Metabolic disorders
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Metabolic disorders

- } Prevalence of type 2 diabetes mellitus may be increased several-fold in BD
- } Similar to obesity and cardiovascular disease, co-occurring diabetes in the BD population is also associated with a more severe illness course, decrease in global functioning and other medical comorbidity.

McIntyre et al., 2005;

Table 2 Clinical identification of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
Triglycerides	≥150 mg/dl
High-density lipoprotein	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/85 mmHg
Fasting glucose	≥110 mg/dl

Metabolic disorders...

- } The reported prevalence of the criterion items for the metabolic syndrome were:
 - Hypertension (39%),
 - Diabetes mellitus (8%),
 - Hypertriglyceridemia (48%),
 - Abdominal obesity (49%),
 - Abnormal HDL (23%)

- } The percentage of patients reporting a history of at least one suicide attempt is higher in BD individuals with comorbid metabolic syndrome compared to those without this comorbidity (55 vs. 36%).

Metabolic disorders ...

- } The age-adjusted prevalence of metabolic syndrome increases with age:
(6.7% among participants aged 20–29 years to 43.5% for participants 60–69 years of age).

Kahn et al., 2005; Grundy et al., 2005;

Metabolic disorders ...

- } Taken together, individuals with BD may have a higher risk for diabetes and other components of the metabolic syndrome.
- } Larger well-characterized patient samples are warranted to definitively ascertain the relative risk of metabolic syndrome and its correlates in the BD population.



McIntyre et al., 2007;

BD
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Respiratory disorders
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Respiratory diseases

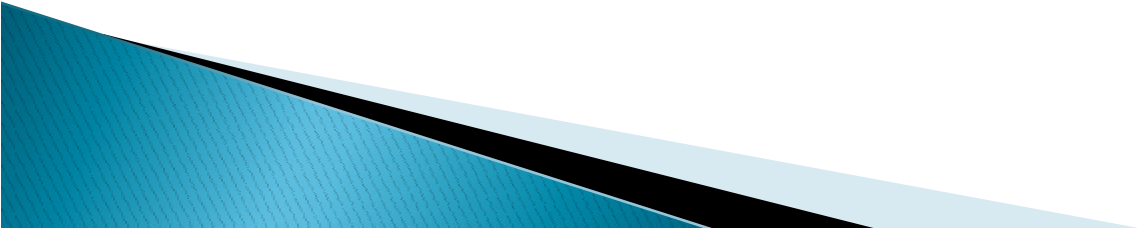
- } Respiratory comorbidity would be predicted in BD as several risk factors, e.g. medication and illness-associated immobilization, musculoskeletal trauma, hypercoagulability, diabetes mellitus, illicit drug use, obesity, habitual inactivity, and smoking cluster in this population.



Strudsholm et al., 2005;

Respiratory diseases ...

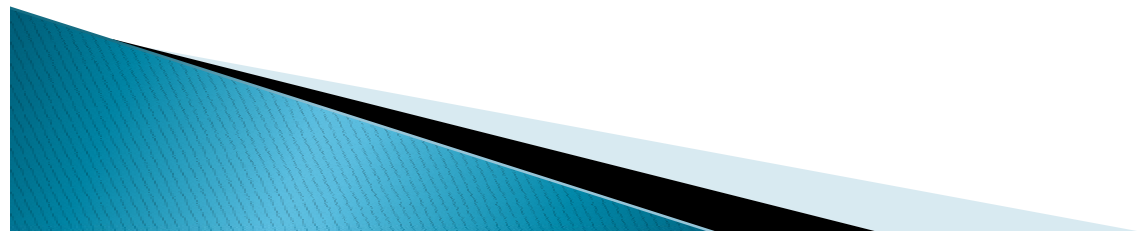
- } Risk for pulmonary embolism is not specific to BD and may be a cause of premature mortality amongst persons with persistent mental illnesses.
- } Increased prevalence of asthma (15.9 vs. 8.3%) and chronic bronchitis (7.9 vs. 3.1%) amongst individuals with BD relative to the general population.



Osby et al., 2001;
McIntyre et al., 2006;

Respiratory diseases ...

- } The modest evidentiary base reporting on respiratory diseases in BD does not allow for definitive conclusions regarding the hazard rate in this population.
- } Extant studies indicate that respiratory diseases constitute a significant burden of illness and premature mortality in the BD population.



BD
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Neurological disorders
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Neurological disorders

- } Migraine headache may be the most common comorbid neurological disorder in BD (39.8% among outpatients).
- } Patients with bipolar II disorder have a lifetime migraine prevalence of 64.7% to 77%.



McIntyre et al., 2007;

Neurological disorders ...

- } Persons with BD had a significantly higher prevalence of migraine compared with the general population (24.8 vs. 10.3%).
- } The sex-specific prevalence of comorbid migraine in BD was 15% for males and 35% for females.

McIntyre et al., 2007;

Neurological disorders ...

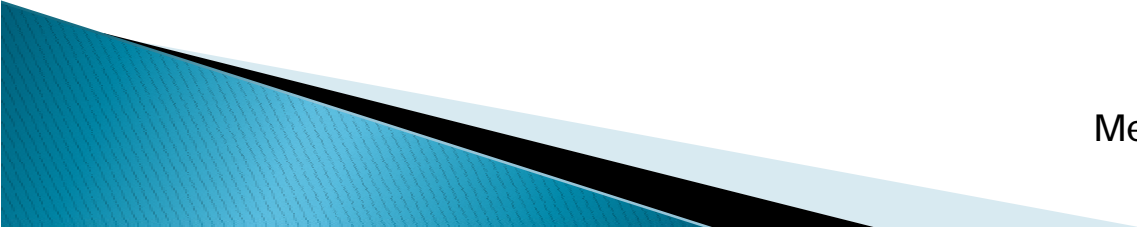
- } Males with BD and comorbid migraine were more likely to:
 - live in a low income household,
 - receive welfare and social assistance,
 - report an earlier age of onset of BD,
 - have a higher lifetime prevalence of comorbid anxiety disorders

- } Females with BD and comorbid migraine when compared to migraine-unaffected females with BD:
 - reported more comorbid medical disorders,
 - more likely to require help with activities of daily living

McIntyre et al., 2007;

Neurological disorders ...

- } Two large epidemiological studies reporting on mood disorder co-occurrence in migraine population suggest that although MDD may be the most common co-occurring mood syndrome, the relative risk for BD may be higher.



McIntyre et al., 2007;
Merikangas et al., 1990;
Breslau et al., 1994;

Neurological disorders ...

- } Multiple sclerosis (MS) is consistently identified as a co-occurring condition in BD.
- } The direction of the association is most compelling with respect to BD co-occurring in MS cohorts, with less evidence reporting the reciprocal association.
- } Taken together, epidemiological and clinical studies indicate that the prevalence of BD in the MS population is approximately 10% or greater.

Minden et al., 2000;

Neurological disorders ...

- } Individuals with seizure disorder often manifest a symptom construct phenotypically similar to BD.
- } As with stroke and MS, the seizure foci affect the likelihood of comorbidity with BD.
- } The similarities between seizure disorder and BD in pharmacological treatment may suggest a possible pathophysiological overlap.

Harden et al., 2002;
Post et al., 2004;

Neurological disorders ...

- } Taken together, migraine, MS and epilepsy comorbidity are more prevalent amongst individuals with BD than in the general population.
- } Migraine appears to be the most common neurological comorbidity with a bidirectional relationship to BD.
- } The association between migraine and BD may be most pronounced in bipolar spectrum conditions.

McIntyre et al., 2007;

BD
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Thyroid disorders
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Thyroid disorders

- } Disorders of the hypothalamic–pituitary–thyroid (HPT) axis are commonly reported in individuals with BD compared to the general population.
- } Rates of hyper- and hypo-thyroidism as well as subclinical alterations in the HPT axis are increased, and associated with rapid cycling and diminished treatment responsiveness.

McIntyre et al., 2007;

Thyroid disorders ...

- } Lithium treatment interferes with the synthesis and secretion of thyroid hormone often resulting in subclinical hypothyroidism.
- } Routine surveillance of thyroid function is a consensually agreed upon standard of care in the management of the BD patient.

McIntyre et al., 2007;

BD
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Renal disorders
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Renal disorders

- } Several abnormalities of renal function including diabetes insipidus, nephrotic syndrome, and end-stage renal disease are reported in the BD population.
- } Renal pathology in BD is ascribed largely to the nephrotoxic effects of lithium treatment.
- } Metabolic factors may also be salient mediators of renal pathology.

Gitlin, 1999;
McIntyre et al., 2005;

BD
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Infectious disorders
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Infectious diseases

- } Individuals with persistent mental illness are at risk for infectious diseases largely due to:
 - substance use disorders,
 - high-risk sexual behavior
 - other risk factors

- } Amongst the BD population, the reported incidence rates for infectious diseases such as hepatitis C (2–14%) and HIV (1–3%) are significantly higher than rates reported in the general population.



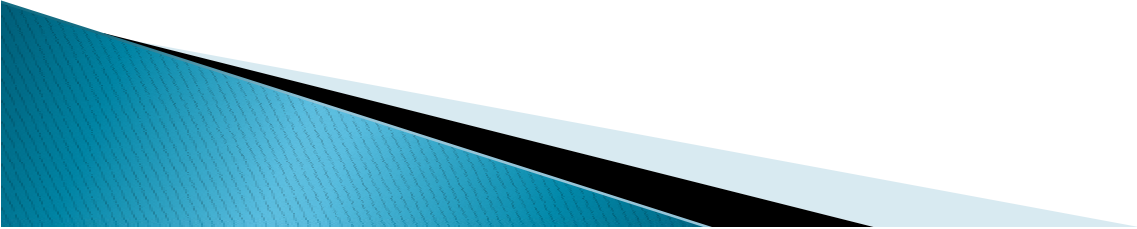
McIntyre et al., 2007;

Table 1 Current and lifetime prevalence rates of medical comorbidity in bipolar disorder

Comorbid condition	Current		Lifetime		References
	Mean rate of comorbidity (%)	Range across studies (%)	Mean rate of comorbidity (%)	Range across studies (%)	
Arthritis	14	12–16	19	16–21	[3,11–13]
Asthma	3		18	6–35	[3,11–15]
Benign prostatic hyperplasia/hypertrophy	3	1–5	8		[3,16]
Cancers	2	1–3	2	1–2	[3,11,12]
Cardiovascular comorbidities	23	11–35	26	4–49	[3,12,16,17]
Chronic obstructive pulmonary disease	9	8–11	6	3–9	[3,11,15]
Dementia/Alzheimer's disease	3		5		[11,18]
Dermatologic comorbidities	7		28	20–45	[3,14,16]
Diabetes mellitus	10	4–17	11	2–26	[3,11,12,15–17,19–22]
Dyslipidemias including hypercholesterolemia, hyperlipidemia, hypertriglyceridemia	29	23–41	29		[3,11,19]
Endocrine comorbidities	23		29		[3]
Gastrointestinal comorbidities	12	7–18	35	11–56	[3,11,12,16]
Genitourinary comorbidities	9		39	21–56	[3,16]
Headache/migraine	4		29	15–44	[11,13,15,16,23–26]
Hepatic comorbidities	17		21		[3]
Hepatitis C	7	2–14	16		[3,11,17]
Human immunodeficiency virus	21				[27]
Hypertension	26	2–39	24	10–33	[3,8,11,12,15,19,28]
Injuries	12		13		[11,16]
Lower back pain	15				[11]
Metabolic syndrome	30				[19]
Musculoskeletal comorbidities	23		63	50–75	[3,16]
Neurological comorbidities			35	17–53	[29–31]
Obesity	30	19–49	18	3–33	[16,19,32–37]
Overweight	49	28–68			[32–34,37,38**]
Pancreatitis	2	1–4	2		[3,11]
Parkinson's disease	0.05				[11]
Pulmonary comorbidities	7	1–13	25	8–43	[3,12,16,17,39]
Renal comorbidities	2	1–2	7		[3,11]
Stroke	2	1–2	3		[3,8,11]
Thyroid disorders	12	7–19	13	7–16	[3,8,11,12,14,16,40]

Limitations

- } Studies reporting on medical conditions that co-occur with BD have predominantly focused on:
 - single chronic illnesses,
 - on discrete patient populations such as the elderly,
 - those with the bipolar I subtype,
 - individuals participating in RCTs,



MATTHEWS et al., 2008; ORTIZ et al., 2010;
GILDENGERS et al., 2008;
PERRON et al., 2009;
KEMP et al., 2009; THOMPSON et al., 2006;

LiTMUS

- } LiTMUS (Lithium Treatment-Moderate dose Use Study) is an NIMH-sponsored trial designed to test whether the strategy of using tolerable doses of lithium in combination with other medications for BD is superior to optimized treatment (OPT; guideline-informed, evidence-based, and personalized treatment based on current symptoms, prior treatment history, and course of disorder) without lithium.

Kemp et al., 2014;

LiTMUS

- } The Cumulative Illness Rating Scale (CIRS) was used to assess medical comorbidity burden.
- } High medical burden was defined as a CIRS total score ≥ 4 and affected 53% (n=139) of patients with BD.
- } The most common medical conditions included:
 - obesity (38%), migraines (25%), hypertension (17%), hyperlipidemia (16%), and asthma (14%)
 - Cigarette smoking was reported by 45% of individuals with BD

Kemp et al., 2014;

LiTMUS

- } Patients with significant medical comorbidity experienced a greater number of lifetime depressive (an average of 10 additional depressive episodes over their lifetime) and manic/hypomanic episodes (an average of 15 additional manic or hypomanic episodes over their lifetime) and were prescribed a greater number of psychotropic medications than patients with low medical comorbidity burden.

Kemp et al., 2014;

LITMUS

- } Despite the high rate of overweight and obesity in this sample, patients were often unaware of having clinically relevant abnormalities in blood pressure and lipids, suggesting that potential treatment opportunities for individuals with BD may frequently be missed.

Kemp et al., 2014;

Summary

- } Taken together, compared to MDD and schizophrenia, fewer studies have documented general medical comorbidity in the BD population.
- } Available evidence indicates that several GMCs affect the BD population.
- } Multiple comorbid medical conditions (i.e. three or more) affect more than 40% of individuals with BD.

Summary ...

- } The observed higher prevalence of medical comorbidity in individuals with multiple-episode BD likely relates to age, and exposure to adverse effects of psychotropic medication.
- } The relatively lower somatic burden at first presentation for BD invites the need for opportunistic screening and primary prevention strategies to be a component of individualized management planning in any newly diagnosed BD patient.

Mediators and moderators of the BD

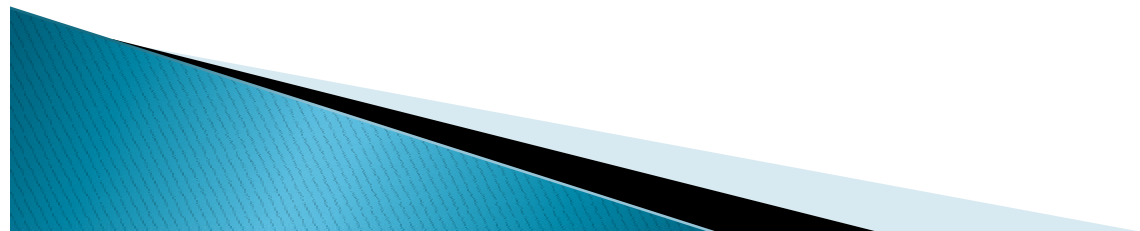
- } Several nonspecific factors are overrepresented in this patient population including poverty, lower educational attainment and urbanization.
- } Individuals with persistent mental illnesses are less likely to receive sufficient primary, preventive, or integrated healthcare when compared to individuals without a mental disorder.

Mediators and moderators of the BD...

- } Factors more specific to the BD population relate to the phenomenology, comorbidity, anamnesis (e.g. childhood adversity) and treatment of this disorder.
- } Longitudinal course of BD is dominated by depressive symptoms and episodes which are associated with several negative health behaviors.
- } A linear relationship between the duration of lifetime depressive episodes and medical comorbidity in BD is preliminarily reported.
- } Moreover, both depressive phenomenology and general medical comorbidity are independent QoL detractors.

Mediators and moderators of the BD...

- } Binge eating disorder is positively associated with obesity in persons with BD.
- } Substance use disorder has been shown to be inversely associated with overweight and obesity.



Mediators and moderators of the BD...

- } Individuals with BD report significantly higher rates of adverse childhood experiences when compared to individuals with other persistent mental disorders and/or the general population.
- } Childhood adversity may constitute a nontraditional risk factor for incident cardiovascular disease and obesity.
- } It could be hypothesized that the co-occurrence of BD and 'stress-sensitive' medical disorders may be partially mediated by the enduring physiological effects of distal trauma.

Mediators and moderators of the BD...

- } SGAs are associated with abnormalities in metabolic homeostasis, obesity and cardiovascular disease.
- } Other classes of psychotropic agents are also associated with metabolic disruption as well as other endocrine abnormalities, cutaneous syndromes, seizure, hepatic and renal failure.

Mediators and moderators of the BD ...

- } Oxidative stress is posited to be a salient mediator for several chronic medical disorders.
- } CNS is vulnerable to the effects of oxidative stress.



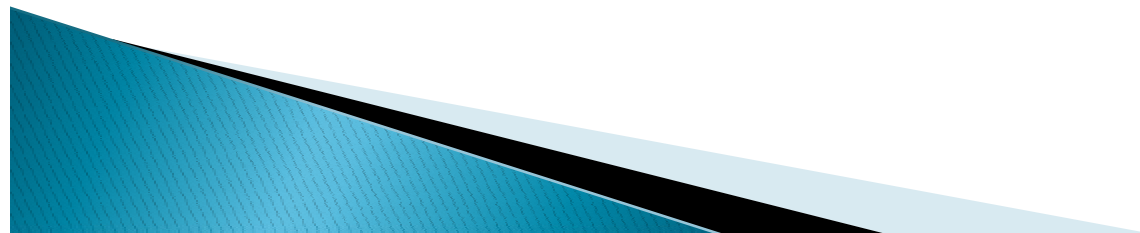
McIntyre et al., 2007;

Mediators and moderators of the BD...

- } Alterations in the HPT axis are perhaps the most replicated abnormalities in the mood disorder population.
- } Neuroendocrine studies have documented that up to 50% of depressed BD patients are DST non-suppressors indicating a disturbance in the negative feedback loop.
- } Disturbances in HPT signaling with resultant chronic hyper-cortisolemia is a critical mediator .

Mediators and moderators of the BD...

- } Taken together, several psychobiological factors as well as behavioral features of BD, the effects of psychotropic medication and aspects regarding healthcare service delivery may conspire to increase the risk for somatic health issues in the bipolar population.

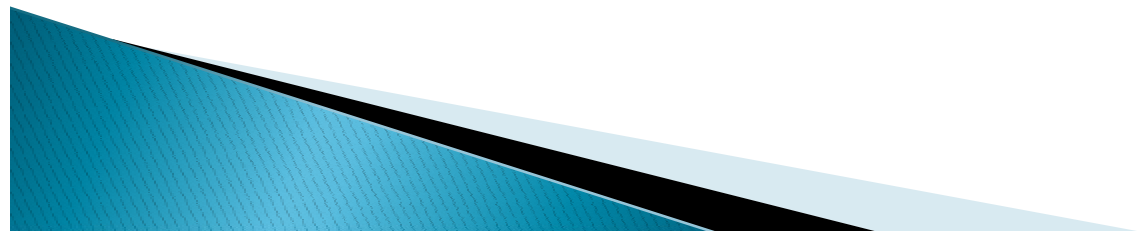


Organization of care delivery and research vistas

- } More effective treatment for depressive symptoms of BD may lower the risk for medical comorbidity.
- } Individuals with bipolar II disorder may have an increased propensity (vs. bipolar I disorder) to medical comorbidity and may possibly accrue greater benefit from appropriate remission-focused depression treatment.

Organization of care delivery and research vistas...

- } Evidentiary base informing therapeutic decisions in the comorbid BD patient remains inadequate.
- } This deficiency is in part the consequence of the routine exclusion of patients with BD and comorbidity from pivotal RCTs for all phases of bipolar illness.



Organization of care delivery and research vistas...

- } All patients should be screened for:
 - lifestyle habits,
 - exercise routine,
 - eating patterns,
 - comorbid binge eating disorder or bulimia nervosa,
 - caffeine dependence,
 - smoking,
 - thyroid dysfunction

Organization of care delivery and research vistas...

- } All patients should be routinely monitored for weight and BMI status.
- } Baseline blood work should include measures of FBS and lipid fractionation.
- } Medication selection and sequencing in BD needs to consider the hazardous effects posed by treatment on the patient's overall health.

Conclusion

- } Individuals with BD are at increased risk for several GMCs including:
- cardiovascular disease,
 - respiratory disorders,
 - thyroid disease,
 - hepatitis C,
 - type-2 diabetes,
 - obesity,
 - neurological disease,

GOLDSTEIN et al., 2009;
MCINTYRE et al., 2006; KEMP et al., 2009;
KUPKA et al., 2002;
MATTHEWS et al., 2008;
VAN WINKEL et al., 2008;
GOLDSTEIN et al., 2001; MCELROY et al., 2002;

Conclusion...

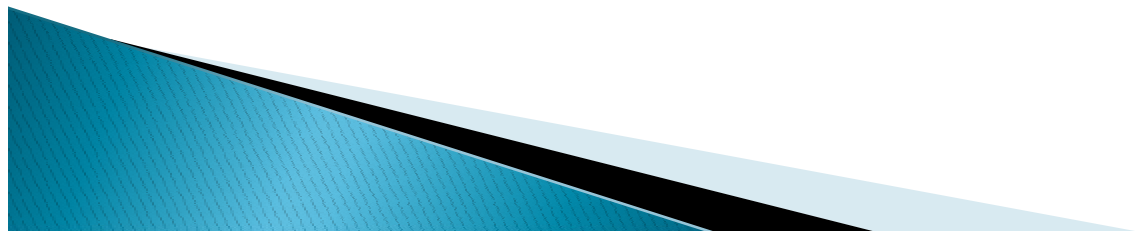
- } For certain illnesses, such as cardiometabolic disorders, the relationship with BD appears bidirectional.
- } Individuals with BD often display poor self-care behaviors characterized by limited exercise and high-calorie diets that can increase the propensity for developing obesity and type-2 diabetes.
- } Conversely, specific cardiometabolic conditions have been shown to predispose to the development of depressive symptoms and have been associated with longer and more severe mood episodes and shorter times to illness recurrence.



KILBOURNE et al., 2007;
THOMPSON et al., 2006; 2010 et al., 2010; VAN REEDT DORTLAND et al., 2010;

Conclusion...

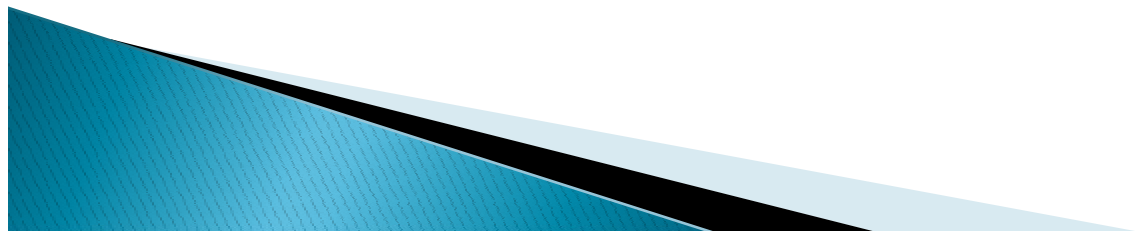
- } The prevalence and harmful dysfunction associated with medical comorbidity in BD invites the need for prioritizing somatic health issues.
- } A clarion call for an integrated and cohesive system of healthcare delivery is warranted in order to reduce overall illness burden in BD.



Conclusion...

- } Clinicians should endeavor to ensure that individuals with BD receive:
 - age-specific assessments for medical risk factors & laboratory abnormalities
 - contemporaneous engagement in primary/secondary prevention strategies

- } Translational research approaches may help clarify the direction of causality as well as mediators and moderators of the BD–medical comorbidity covariation.



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