Medical and substance-related comorbidity in bipolar disorder: translational research and treatment opportunities

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It is well established that individuals with bipolar disorder are differentially affected by substance-related as well as medical disorders (ie, cardiometabolic disorders, respiratory disorders, neurological disorders, and infectious diseases). Emerging evidence indicates that some comorbid conditions (eg, diabetes mellitus) in bipolar individuals may be subserved by overlapping neurobiological networks. Disturbances in glucocorticoid/insulin signaling and immunoinflammatory effector systems are points of pathophysiological commonality between bipolar disorder and "stress-sensitive" medical disorders. Subphenotyping bipolar disorder as a function of comorbidity and temporality of onset may provide an opportunity for refining disease pathophysiological models and developing innovative disease-modifying therapies.

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Community and clinic-based studies have documented a high lifetime prevalence of psychiatric and medical comorbidity in bipolar disorder. For example, the National Comorbidity Survey reported that 95% of respondents with bipolar disorder also met criteria for three or more additional lifetime psychiatric disorders.[1,2] In keeping with the view that individuals with bipolar disorder are susceptible to comorbid general medical disorders, the Canadian Community Health Survey documented significantly higher rates of cardiometabolic, respiratory, neurological, and infectious disorders in individuals with bipolar disorder.[3]

The hazardous effects of psychiatric and medical comorbidity provide the impetus for timely detection, diagnosis, treatment, and management of comorbidity in the bipolar population. For example, co-occurring disorders in bipolar disorder are associated with more severe subtypes (eg, mixed states), an earlier age at onset, an intensification of symptoms, poor symptomatic and functional recovery, suicidal behavior, diminished response to pharmacological treatment, decreased quality of life, as well as an unfavorable course and outcome.[1,4-6] Moreover, mortality studies indicate that medical comorbidity (eg,

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cardiovascular disease) is the most frequent specific cause of premature mortality in the bipolar population.[7] The overarching aim of this review is to prioritize future research vistas regarding comorbidity in bipolar disorder. Towards this aim, we succinctly review extant literature on medical and substance use comorbidity, and suggest translational research opportunities. More comprehensive reviews on the topic of comorbidity in bipolar disorder are published elsewhere.[5,8]

Method

We conducted a PubMed search of all English-language articles published between January 1994 and November 2007. The key search terms were: substance use disorder, alcohol, metabolic syndrome, diabetes, medical comorbidity, cardiovascular, respiratory, and infectious disorders, cross-referenced with bipolar disorder. The search was supplemented with a manual review of relevant article ref-

Comorbid condition	Mean rate of comorbidity (%)	Percentage range across studies (%)	Mean rate of comorbidity (%)	Range across studies (%)	References
	Current		Lifetime		
Arthritis	14	12-16	19	16-21	3,9-13
Asthma	3		18	6-35	9,14
Benign prostatic hyperplasia/ hypertrophy	3	1-5	8		3,9,10
Cancers	2	1-3	2	1-2	3,9,14,15
Cardiovascular comorbidities	23	11-35	26	4-49	9,10,13
Chronic obstructive pulmonary disease	9	8-11	6	3-9	10,16
Dementia/ Alzheimer's disease	3		5		9,10,14
Dermatologic comorbidities	7		28	20-45	3,9,10,14,15,17,18-20
Diabetes mellitus	10	4-17	11	2-26	9,10,17
Dyslipidemias including hypercholesterolemia, hyperlipidemia, hypertriglyceridemia	29	23-41	29		9
Endocrine comorbidities	23		29		3,9,10,14
Gastrointestinal comorbidities	12	7-18	35	11-56	9,14
Genitourinary comorbidities	9		39	21-56	10,11,13,14,21-24
Headache/ migraine	4		29	15-44	9
Hepatic comorbidities	17		21		9,10,15
Hepatitis C	7	2-14	16		25
HIV	21				3,10,13,17,26,40
Hypertension	26	2-39	24	10-33	10,14
Injuries	12		13		10
Lower back pain	15				17
Metabolic syndrome	30				9,14
Musculoskeletal comorbidities	23		63	50-75	27-29
Neurological comorbidities			35	17-53	14,17,30-35
Obesity	31	19-49	18	3-33	30,32,34,36
Overweight	54	36-68			9,10
Pancreatitis	2	1-4	2		10
Parkinson's disease	0.05				3,9,14,15,37
Pulmonary comorbidities	7	1-13	25	8-43	9,10
Renal comorbidities	2	1-2	7		9,10,26
Stroke	2	1-2	3		3,9,10,12,14,26,38
Thyroid disorders	12	7-19	13	7-16	39+-

Table I. Current and lifetime prevalence rates of medical comorbidity in bipolar disorder.
Adapted from ref 8: McIntyre RS, Soczynska JK, Beyer JL, et al. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. *Curr Opin Psychiatry*. 2007;20:406-416.

erence lists. Articles selected for review were based on the author's consensus on the adequacy of sample size, the use of standardized diagnostic instruments, validated assessment measures, and overall manuscript quality.

Medical and substance use comorbidity in bipolar disorder

Table I provides an overview of the comorbidity of other medical conditions and substance use with bipolar disorder.

Cardiometabolic disorders

Circulatory disorders

The age-adjusted rate of circulatory disorders in the bipolar population is significantly higher, with a younger mean age at onset, when compared with individuals in the general population. High rates of hypertension comprise a risk factor for sudden cardiovascular death and cerebrovascular accidents.[40] Cardiovascular disease risk reduction should be a primary behavioral strategy in bipolar individuals based on results from mortality studies.[26,41,42]

Obesity

Results from several cross-sectional and longitudinal studies indicate that overweight, obesity, abdominal obesity, and mood disorders co-occur.[30,33,36,43-46] The high rate of co-occurrence of obesity and mood disorders provides the basis for hypothesizing that both phenotypes share common moderating and mediating variables.[30,32,36,47,48] Risk factors for obesity identified in individuals with bipolar disorder are gender, income, educational attainment, physical activity level, and treatment with weight-gain-promoting agents.[32,36] Additional determinants of body weight are total daily intake of simple carbohydrates, total caloric intake, caffeine consumption, comorbid binge-eating disorder, and number of previous depressive episodes.[32,49]
Intensified research efforts have reported that obesity is associated with a multiepisodic course, suicidality, depression severity, decreased probability of symptomatic remission, and shorter time to episode recurrence, when compared with healthy-weight individuals with bipolar disorder.[50,51]

Type 2 diabetes mellitus

Compelling evidence suggests that the prevalence of type 2 diabetes mellitus is increased several-fold in bipolar disorder *(Table II)*. Moreover, results from descriptive studies evaluating metabolic disorders in US and European academic centers indicate that the prevalence of National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III, US) or International Diabetes Federation (Europe)-defined metabolic syndrome is also increased in bipolar individuals.[17,52,53]
Taken together, individuals with bipolar disorder are differentially affected by hyperglycemia, abnormal glucose tolerance, and type 2 diabetes mellitus, as well as several other components of the metabolic syndrome.

Respiratory diseases

Individuals with bipolar disorder evince higher rates of pulmonary disorders including pulmonary embolism, bronchitis, chronic obstructive pulmonary disease, and asthma. The high rates of pulmonary disorders are due to the clustering of established risk factors in the bipolar population (eg, medication and illness-associated immobilization [eg, seclusion and restraints], musculoskeletal trauma, hypercoagulability, diabetes mellitus, illicit drug use, obesity, habitual inactivity, and smoking).[3,7,37,54]

Neurological disorders

Rates of migraine headache, seizure disorder, multiple sclerosis, traumatic brain injury, and cerebrovascular accidents are increased in the bipolar population.[8] The most common neurological comorbidity in bipolar disorder, notably bipolar II disorder, is migraine headache. For example, results from the Canadian Community Health Survey indicated that individuals with bipolar disorder exhibited a threefold (24.8% vs 10.3%) greater adjusted rate for migraine headache when compared with the general population.[21] Other epidemiological studies have similarly reported a greater hazard for migraine amongst bipolar populations.[55] The probability that an individual with bipolar disorder is affected by a comorbid neurological disorder is partially influenced by the topographical localization of the neurological pathology.[21,39,56-59]

Author and year	Study design	Patients	Comments
Gildea et al, 1943	Oral and intravenous dextrose tolerance test	N=30 Manic-depressive (pre-DSM) N=6 manic, N=18 depressed, N=6 agitated depression Patients mostly treated Age: 18-64	- 0/34 (0%) IV dextrose tolerance tests abnormal - 6/30 (20%) oral dextrose tolerance "retarded decline" in blood sugar - "(no) evidence of an intrinsic disorder of carbohydrate metabolism"
Van der Velde et al, 1968a	Oral glucose tolerance test	N=42 Manic-depressives ("mostly unmedicated") Age: 18 - 71 N=42 Schizophrenic patients All patients >40 years old	- 16/42 (38%) manic-depressive patients exhibit "hyperglycemic response" - 6/42 (14%) schizophrenics patients exhibit "hyperglycemic response"
Van der Velde et al, 1968b	Oral glucose tolerance test	N=17 Manic- Depressives (lithium naïve) Age: 48 – 86	- 9/17 (53%) manic-depressive patients exhibited a "hyperglycemic response"
Lilliker, 1980a	Retrospective chart review	N=203 Manic-depressives (DSM-II) DM defined as patients who were given a clinical diagnosis based on fasting blood sugar or substantiated medical history Patients mostly treated	- 20/203 (10%) were diagnosed with DM - 4/79 males, 16/124 females (13%) - patients older than 45 years old, prevalence of DM 18% women, 6% men - patients older than 65 years, prevalence of DM 23% and 16%, for women and men respectively
Lilliker,1980b	Retrospective chart review	N=4508 total number of individuals discharged between 1973-78 with diabetic diet recorded in dietary record Patients mostly treated Age: 18 –79	- 16/129 (12.4%) manic-depressive on diabetic diet - 38/1134 (3.3%) schizophrenic - 121/4379 (2.8%) overall
Lustman et al, 1986	Cross-sectional evaluation	N=114 diabetic patients random recruitment evaluated with National Institute of Mental Health Diagnostic Interview Schedule (DSM-III) Mean Age – 40 +/- 15.1	- 81/114 (71%) had a lifetime history of one criteria-defined psychiatric illness - 3/114 (3%) diagnosed with manic depression - 37/114 (33%) diagnosed with depression - significant difference in glycated hemoglobin was observed in patients with a recent psychiatric illness (10.8%) to those never psychiatrically ill (9.6%) - psychiatric patients reported more symptoms of poor metabolic control and more distress associated with the symptoms than did patients never psychiatrically ill
Cassidy et al, 1999	Retrospective chart review	N=345 BD patients (DSM-III-R) DM diagnosis based on clinical analysis of blood glucose. Patients mostly treated Age: 20 –74	- 36/357 (10%) diagnosed with DM - Total number of psychiatric hospitalizations significantly greater in diabetic group than in the age-matched comparison (non-diabetic BD patients)

Table II. Prevalence of diabetes mellitus (DM) in bipolar disorder (BD).
Adapted from ref 8: McIntyre RS, Soczynska JK, Beyer JL, et al. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. *Curr Opin Psychiatry*. 2007;20:406-416. References cited in original article.

Author and year	Study design	Patients	Comments
Newcomer et al, 1999	Oral glucose tolerance test: 15-, 45-, 75- min post ingestion blood sampling	Schizophrenia N=10, BD N=10, Healthy controls N=11 (DSM-III-R) Patients mostly treated Age: 35.1+/- 10.2	- Study designed to assess glucose-induced changes in memory performance - Plasma glucose higher in schizophrenia than BD and normal control - Higher insulin levels in both schizophrenia and BD than normal controls
Regenold et al, 2002	Retrospective chart review	N=243 BD (DSM-IV) DM defined based on clinical diagnosis in chart, OR the prescription of insulin or oral hypoglycemics (upon discharge) Comparison with four other diagnostic groups Patients mostly treated Age: 50-74	- Rates of type II DM among the five groups were: schizoaffective 10/20 (50%), BD-I 14/53 (26%), major depression 12/65 (18%), dementia 6/64 (95%). Schizophrenia 9/71 (13%) - Diabetic patients had higher body mass index (BMI), but not a significantly higher use of psychotropic medication - Compared with national norms, DM rates were significantly elevated in BD-I, and schizoaffective patients
Ruzickova et al, 2003	Retrospective analysis of the Maritime Bipolar Registry	BD-I N=151 BD-II N=65 BD Not otherwise specified N=6 (DSM-IV) DM ascertained based on previous diagnosis and evidence of treatment Patients mostly treated Age:15 –72	- 26/222 (12%) had DM - BD with comorbid DM were older (53 +/- 9 vs 43 +/- 12), chronically ill, rapid cycling, lower Global Assessment of Function score - BD with comorbid DM higher long-term disability, higher BMI (34 +/- 6 vs 29 +/- 6), higher rate of hypertension
Kessing et al, 2004	Retrospective Danish national registry	BP-I N=121 BP-II N=45 BP NOS=5 (DSM-IV) Metabolic syndrome defined based on National Cholesterol Education Program (NCEP) Adult Treatment Panel III Age: >18	- 83/171 (49%) had abdominal obesity - 81/171 (48%) were hypertriglyceridemic or were on a cholesterol-lowering medication - 38/171 (23%) had low HDL-cholesterol - 67/171 (39%) had high blood pressure - 13/171 (8%) were high in fasting glucose or were on antidiabetic medication - 51/171 (30%) met criteria for the metabolic syndrome (presence of least 3 of the above)
Kreyenbuhl et al, 2006	Retrospective chart review	Schizophrenia and DM N=50 Major mood disorder and DM N=45 Without mental illness and DM N=48 Age: 18 –65	- 54% of the diabetic patients with schizophrenia, 64% with a mood disorder, and 71% without a mental illness met the NCEP definition of metabolic syndrome
Carney and Jones, 2006	Retrospective administrative claims database	N=3557 bipolar I disorder; control (C) population=726,262	- Uncomplicated diabetes BD N=146 (4.1%); C=17205 (2.4%) - Complicated diabetes BD N=63 (1.8%); C=4401 (0.6%)

Table II. Continued

Thyroid disorders and infectious diseases

Disorders of the hypothalamic pituitary thyroid (HPT) axis are commonly reported in individuals with bipolar disorder.[60] Rates of hyper- and hypothyroidism, as well as subclinical alterations in the HPT axis are increased, and associated with rapid cycling and diminished treatment responsiveness.[61] Bipolar individuals are also at risk for infectious diseases (eg, hepatitis C, human immunodeficiency virus [HIV]) largely due to risk factor clustering (eg, lower socioeconomic status and substance use disorders).[15,39]

Substance use disorders

The Epidemiological Catchment Area (ECA) Study and National Comorbidity Survey (NCS) reported a lifetime prevalence of alcohol dependence of 13.5% and 14.1%, respectively in the US general population. The lifetime prevalence of non-alcohol drug dependence was also reported at 6.1% and 7.5%, respectively. Results from the ECA and NCS studies cohere with results from the recent National Epidemiological Survey on Alcohol and Related Conditions (NESARC) that documented a greater hazard for alcohol and drug abuse or dependence amongst bipolar individuals.[62,63]
The harmful effects posed by substance use disorder in bipolar populations have been documented in many studies.[5,64] Taken together, alcohol and substance use disorder are associated with high rates of treatment nonadherence, low rates of recovery, greater risk of aggression and violence, increased rate of attempted and completed suicide, as well as a less favorable response to conventional treatment.[65]

Comorbidity research in bipolar disorder: future vistas

Medical comorbidity and substance use disorders are prevalent and hazardous conditions in the bipolar population. Future research vistas should attempt to parse out neurobiological mediators that subserve medical comorbidity as well as temporality of onset. Such efforts may inform mechanistic models as well as individualized treatment planning.

Biological mediators of "stress-sensitive" medical disorders

Glucose-insulin homeostasis

The differential occurrence of "stress-sensitive" medical disorders in the bipolar population suggests that interacting effectors mediating stress are a point of pathophysiological commonality. In keeping with this view, a testable hypothesis is that some features of bipolar disorder are affected by disturbances in metabolic networks. For example, it is documented that neurocognitive deficits are a prevalent and enduring trait abnormality associated with impairment in psychosocial functioning and reduced quality of life in bipolar disorder.[66-75] Moreover, reports of disparate neurocognitive deficits (eg, nonverbal and verbal intelligence, information processing, visuospatial ability, attention, executive function, learning, and memory) have been documented in diabetic populations for several decades (ie, diabetic encephalopathy).[76] Taken together, these separate lines of evidence indicate glucose-insulin homeostatic network disturbances are critical mediators of abnormal central nervous system structure and function in mood disorders.[75,77-84]

Inflammatory networks

A growing body of literature indicates that cytokine-mediated inflammatory processes are implicated in the pathophysiology of numerous medical and neurological conditions.[85] Cytokines are nonantibody proteins that act as mediators of physiological and pathophysiological cellular processes. For example, elevated proinflammatory cytokines (eg, interleukin [IL]-1, tumor necrosis factor [TNF]·) have been associated with an accumulation of amyloid-β, the pathophysiological hallmark of Alzheimer's disease.[86-88]
Peripherally and centrally-derived cytokines traverse the blood-brain barrier at circumventricular organs.[89,90] Furthermore, cytokines play a key role in the activation of the hypothalamic-pituitary-adrenal (HPA) axis and peripheral glucocorticoid signaling. Chronic activation of the HPA axis has been associated with immunosuppression, as well as alterations in noradrenergic, dopaminergic, and serotonergic pathways.[91]
It is well established that proinflammatory cytokines induce "sickness behavior," a symptom complex phenotypically similar to the somatic depressive symptoms of

anorexia, fatigue, reduced pain threshold, and insomnia. Proinflammatory cytokine activation is also associated with a reduction in cognitive performance and abnormal brain activation patterns.[92,93] For example, elderly persons with high IL-6 plasma concentrations are more likely to exhibit a decline in cognitive function.[94] Infusion of an endotoxin to healthy individuals has also been demonstrated to induce cognitive deficits in both verbal and visual memory.[95] Preliminary results also document an elevated proinflammatory cytokine profile (eg, IL-8, TNF-α) in bipolar disorder during active depressive or manic states.[92,96,97]

Substance use comorbidity: subphenotyping temporality of onset and shared neurobiology?

The effect of temporality of onset of bipolar disorder on alcohol/substance use disorders may provide a more refined view of the association between bipolar disorder and comorbidity syndromes.[98] For example, Strakowski et al reported that the relative onset of alcohol use disorders in bipolar disorder affects the subsequent courses of illness in patients with both conditions.[99] Individuals for whom the alcohol use disorder antedates the onset of bipolar disorder were significantly more likely to be older, have higher educational attainment, have a later age at onset of bipolar disorder, exhibit psychosis, recover from the index episode, and less likely to evince mixed states. Conversely, individuals presenting with bipolar illness first exhibited more rapid cycling, mixed states, more time with affective episodes, and symptoms of an alcohol use disorder during follow-up.

A separate analysis evaluating co-occurring cannabis use in the course of bipolar disorder after a first hospitalization for mania reported that the effect of the sequence of onset of bipolar in cannabis use disorder was less pronounced than observed in co-occuring alcohol and bipolar disorder. The cannabis-first group exhibited a higher recovery rate, although when adjusted for potential mediating variables the results did not persist. Cannabis use was associated with more time spent in affective episodes and rapid cycling.[99]

A defining characteristic of addiction is the overpowering motivational strength and decreased ability to control the desire to obtain a substance despite economic, social, and/or health-related consequences.[44,100,101] Obesity is increasingly viewed as a consequence of an addictive behaviour; that is, foraging and ingestion habits persist and strengthen despite the threat of catastrophic consequences.[100,102-108] Moreover, it is conjectured that both obesity and substance use disorders are subserved by an overlapping, and aberrant, reward-motivation neural network (eg, ventral tegmental-nucleus accumbens circuit).[100,109-113] Further evidence for the role of dopamine as a salient neurotransmitter in brain reward circuitry is provided by neuroimaging studies which report an inverse relationship between body mass index (BMI) and the striatal density of dopamine D_2 receptors.[100,114-117]

A testable hypothesis is that the inverse relationship between alcohol use and BMI may be a phenotypic expression of a competing brain reward system. A candidate neurotransmitter salient to this process may be dopamine.[100,101,118,119] For example, pharmacological blockade of, or experimental damage to, forebrain dopamine systems (eg, the ventral tegmental-nucleus accumbens circuit) has been shown to attenuate free feeding and lever-pressing for food reward while suppressing the rewarding effects of cocaine, amphetamine, nicotine, and alcohol.[101]

In keeping with the view that aberrant neural circuitry may subserve substance use disorders and overweight/obesity in bipolar disorder, McIntyre et al, utilizing data from the cross-national CCHS epidemiological study, reported that overweight/obese bipolar individuals had a significantly lower rate of substance dependence (13.0% vs 21.4%) as compared with the normal weight bipolar individuals.[120] Similarly, substance-dependent bipolar individuals displayed a lower rate of overweight/obesity as compared with non-substance-dependent bipolar individuals (39% vs 54%). The negative association between overweight/obesity and substance dependence amongst the bipolar respondents remained statistically significant in multivariate analysis controlling for several possible confounding variables.

Conclusion

A concatenation of descriptive study results have provided compelling evidence that the bipolar population is differentially affected by several medical disorders and substance-use disorders. Shifting priority towards subphenotyping bipolar disorder as a function of comorbidity offers an opportunity to refine disease models and possible etiological determinants.

Dissection of the observable characteristics of complex disorders (ie, excluding dimensions of the syndrome that

are inessential to its core definition) holds promise to reduce heterogeneity, thereby enhancing the resolution of linkage analysis. For example, a susceptibility gene for breast cancer, a prototypical multifactorial medical disease, was discovered after data for families with early-onset breast cancer, and a high vulnerability to ovarian cancer, were analyzed separately from data for families with late-onset breast cancer.[121]

Recent associations between bipolar disorder and other chronic inflammatory disorders suggest that individuals with bipolar disorder and comorbid inflammatory-based medical disorders may constitute a distinct population.[122] Subphenotyping bipolar and substance use disorders on the basis of sequence of onset, as well as associations with other addictive disorders (eg, food consumption) are hitherto understudied. Emerging evidence indicates that temporality of onset defines separate subpopulations of bipolar disorder with differential course, outcome, and treatment response.

Despite the ubiquity of comorbidity in bipolar disorder, the evidentiary base informing therapeutic decisions in the comorbid bipolar patient remains woefully inadequate.[123-126] Nevertheless, clinicians should endeavor to ensure that individuals with bipolar disorder receive treatment as part of a chronic disease management model which includes self-management, integrative community-based programs, age-specific assessments for medical risk factors and laboratory abnormalities multimodality remission-focused treatments, and a longitudinal provision of care.[3,9-11] ❑

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Comorbilidad médica y relacionada con sustancias en el trastorno bipolar: investigación traslacional y oportunidades terapéuticas

Está bien establecido que los individuos con trastorno bipolar son afectados de manera distinta por trastornos médicos o relacionados con sustancias (por ejemplo, trastornos cardiometabólicos, trastornos respiratorios, trastornos neurológicos y trastornos infecciosos). La evidencia que está surgiendo señala que algunas condiciones comórbidas (como la diabetes mellitus) en los sujetos bipolares pueden ser facilitadas porque se comparten redes neurobiológicas. Las alteraciones en las señales de glucocorticoides/insulina y en los sistemas efectores inmunoinflamatorios son puntos fisiopatológicos en común entre el trastorno bipolar y trastornos médicos "sensibles al estrés". El determinar subfenotipos del trastorno bipolar en función de la comorbilidad y temporalidad de la aparición del cuadro puede proporcionar una oportunidad para refinar modelos fisiopatológicos y desarrollar terapias innovadoras que modifiquen la enfermedad.

Comorbidité médicale et liée à des substances toxiques dans les troubles bipolaires : recherche translationnelle et opportunités thérapeutiques

Les sujets ayant des troubles bipolaires sont affectés de façon différente par des affections liées à l'utilisation de substances toxiques ou par des affections médicales (cardiométaboliques, respiratoires, neurologiques et maladies infectieuses). Des données récentes indiquent que l'enchevêtrement des réseaux neurobiologiques favoriserait certains états comorbides, comme le diabète, chez les sujets bipolaires. Ainsi, les troubles bipolaires et les pathologies liées au stress ont en commun des anomalies de la signalisation glucocorticoïdes/insuline et des systèmes effecteurs immuno-inflammatoires. Certains sous-phénotypes de trouble bipolaire (selon la comorbidité et la période de déclenchement du trouble) peuvent être utilisés pour mettre au point des modèles physiopathologiques de maladies et permettre le développement de traitements innovants.

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