EPIDEMIOLOGY OF BIPOLAR DISORDER TYPE I (BD-I) IN THE UNITED STATES: A SYSTEMATIC REVIEW OF THE LITERATURE

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INTRODUCTION

- Bipolar disease (BD) is a chronic mood disease that features one or more manic/hypomanic episodes, which may be accompanied by a major depressive episode.
- BD type I (BD-I) is a subtype of the disease characterized by the presence of a manic episode.
- Since the number of prevalent cases of BD increases on the aging population and with the changes in diagnosis reporting practices, it is of the utmost importance to map its epidemiologic aspects to better allocate resources [1].

OBJECTIVES

- To perform a systematic literature review (SR) of studies in peer reviewed journals on 10 epidemiologic aspects of BD-I in the US: annual incidence, prevalence and respective trends; mortality rates and trends; associated comorbid disorders; stages, severity levels and natural progression.

METHODS

- The first step was to formulate several questions addressing the main epidemiologic questions about BD-I.

1: Incidence and prevalence of BD-I in the US

- What are the annual incidence rates for BD-I in US?
- What are the annual prevalence rates for BD-I in US?
- What are incidence trends or patterns for BD-I in US?
- What are prevalence trends or patterns for BD-I in US?

2: Comorbidity and mortality issues in BD-I

- What is the mortality associated with BD-I?
- What are the trends in mortality rates for BD-I?
- What are the common comorbidities associated with BD-I?

3: Staging and natural progression issues of BD-I

- What are the stages and severity levels of BD-I?
- What is the natural progression of BD-I?

- Then, search strategies were developed for each set, as shown on **Figure 1**. Prisma Flow diagram is shown on **Figure 2**.

Figure 1. Search Strategies to Retrieve Studies about Each Set of Questions

Search strategy for set 1: performed in 08/23/2016

MEDLINE: *bipolar AND disorder AND (epidemiol* OR incidence OR prevalence) AND systematic[sb] - Limited for a 10-year period (from 08/23/2006).* **Complement** to retrieve recent papers not included in the latest SR: *bipolar AND disorder AND (epidemiol* OR incidence OR prevalence) AND (cross sectional OR prospective OR retrospective OR longitudinal OR cohort)* - limiting for the time after the elected (most updated and appropriate) SR search period.

EMBASE: *'bipolar disorder'/exp OR 'bipolar disorder' AND ('epidemiology'/exp OR epidemiology OR 'prevalence'/exp OR prevalence OR 'incidence'/exp OR incidence) AND [embase]/lim AND [systematic review]/lim.* **Complement** to retrieve recent papers not included in the latest SR: 'bipolar disorder'/exp OR 'bipolar disorder' AND ('epidemiology'/exp OR epidemiology OR 'prevalence'/exp OR prevalence OR 'incidence'/exp OR incidence) AND [embase]/lim - **limiting for the time after the elected (most updated and appropriated) SR search period.**

Search strategy for set 2: performed in 08/27/2016

MEDLINE: *bipolar AND disorder AND (mortality OR comorbid* OR polypharmacy OR burden) AND systematic[sb]. - limited for a 10-year period (from 08/27/2006).* **Complement** for cardiovascular comorbidities: *bipolar AND disorder AND (comorbid* OR burden OR polypharmacy) AND (cardiovascular OR cerebrovascular OR coronary OR ischemic) - limited for a 10-year period (from 08/23/2006).*

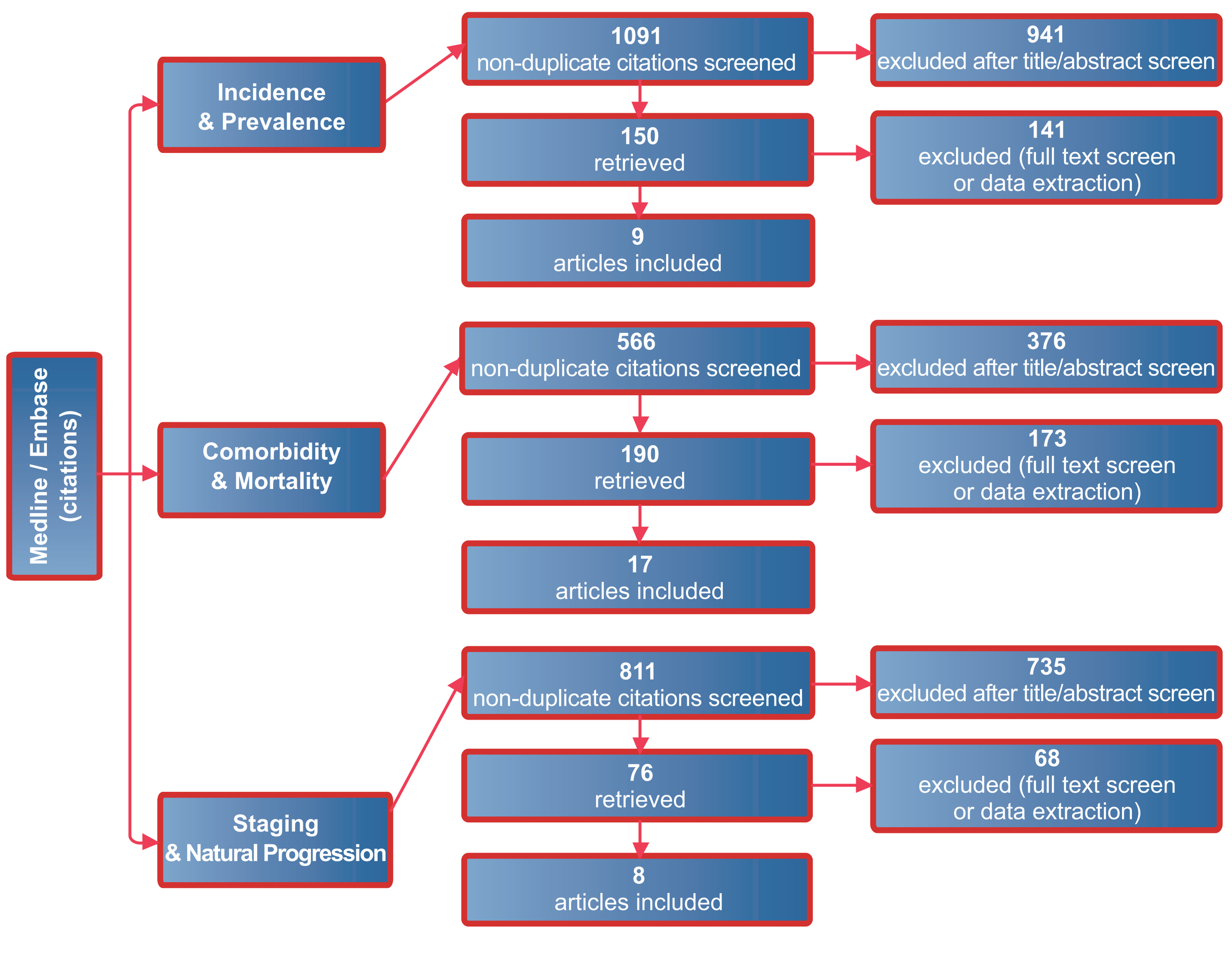
EMBASE: *bipolar AND disorder AND (mortality OR comorbid*) AND [systematic review]/lim.* **Complement** for cardiovascular comorbidities: *bipolar AND disorder AND (comorbid* OR burden OR polypharmacy) AND (cardiovascular OR cerebrovascular OR coronary OR ischemic)* - **limited for a 10-year period (from 08/23/2006).**

Search strategy for set 3: performed in 09/05/2016

MEDLINE: *bipolar AND disorder AND (progn* OR staging OR neuroprogression OR prodrom* OR disease course OR course of disease OR course of illness OR naturalistic) AND systematic[sb]* - **limiting for the time after the elected SR search period. Complement** for more recent papers not included in the SR retrieved by the strategy: *bipolar AND disorder AND (progn* OR staging OR neuroprogression OR prodrom* OR disease course OR course of disease OR course of illness OR naturalistic)* - **limiting for the time after the elected SR search period.**

EMBASE: *bipolar AND disorder AND (progn* OR staging OR neuroprogression OR prodrom* OR disease course OR course of disease OR course of illness OR naturalistic) AND [systematic review]/lim.* **Complement** for more recent papers not included in SR retrieved by the strategy: *bipolar AND disorder AND (progn* OR staging OR neuroprogression OR prodrom* OR disease course OR course of disease OR course of illness OR naturalistic)* - **limiting for the time after the elected SR search period.**

Figure 2. PRISMA Flow diagram


Medline / Embase (citations)
Incidence & Prevalence
1091 non-duplicate citations screened
941 excluded after title/abstract screen
150 retrieved
141 excluded (full text screen or data extraction)
9 articles included
Comorbidity & Mortality
566 non-duplicate citations screened
376 excluded after title/abstract screen
190 retrieved
173 excluded (full text screen or data extraction)
17 articles included
Staging & Natural Progression
811 non-duplicate citations screened
735 excluded after title/abstract screen
76 retrieved
68 excluded (full text screen or data extraction)
8 articles included

RESULTS

- There were 11 SR [1-11] and 5 primary studies [12-16] of interest retrieved.

BD-I Prevalence trends

- Data regarding trends in BD-I prevalence are conflicting.
- While some multinational and local studies show an increase in the prevalence rates of BD-I among adults, adolescents and children [2,17-19], others point to a decrease [14,15].
- Most studies stress that differences in diagnostic criteria and the increase in awareness and diagnoses may have played an important role in these discrepancies.
- Results from a multi-country meta-analysis showed that the diagnostic tool had a significant impact on prevalence estimates but there were no significant differences in prevalence across gender, economic status and bipolar subtype [4].
- The prevalence of BD-I according to the US National Institute of Mental Health (NIMH) is 1% (lifetime) and 0.6%. (12-month).
- The mean age of onset is around 20 years, with more than 70% of cases already diagnosed by the age of 30 years.
- Data strongly suggest an increase in the prevalence of BD-I in the last decades, possibly due to an increase in diagnoses, awareness and/or more precise diagnostic criteria.
- The prevalence of BD is higher in the primary care (PC) setting, which suggests that physicians working on PC should be aware of the disorder's symptoms and the possibility of such diagnosis.

BD-I Incidence and trends

- Investigation on the incidence of BD/BD-I is scarce, with no data on incidence in the US found in the literature.
- A Dutch cohort showed a BD-I incidence rate of 7 per 100 thousand person-years (PY) in the Netherlands [20], while a Danish registry-based research pointed to a local increase in the incidence of BD from 18.5 per 100 thousand PY (1995) to 28.4 per 100 thousand PY (2012) [21].
- **Table 1** shows the most relevant studies on BD-I prevalence / incidence in US population.

Table 1. Relevant studies on BD-I prevalence / incidence in US population

Study	Publication type / population characteristics	Main results*	Comments
Ferrari 2016 [1]	SR + MA model for prevalence data 38 studies Multinational, cross-sectional or longitudinal Minimum follow up: 2 years	Bipolar Spectrum Global Age-standardized prevalence: 0.7% US Age-standardized prevalence: 0.8% (female), 0.7% (male) Past-year global prevalence peak at age 25-34 years	Only 4 US based studies No data specific for each BD subtype
Clemente 2015 [2]	SR with MA 25 multinational studies (24 with data on BD-I) 9 US-based studies Community or population-based Age ≥15 years	Global population data: Lifetime BD-I prevalence: 1.06% (CI95% 0.81 - 1.31) 12-month BD-I prevalence: 0.71% (CI95% 0.56 - 0.86)	Lifetime BD-I prevalence by DSM criteria: DSM-IV: 1.92% DSM-III: 0.47% DSM-IIIR: 1.18% (p<0.001)
Ferrari 2011 [4]	SR + pooled data on prevalence 29 studies (5 US-based) Only population-based studies	Data refers to BSD No differences on prevalence per economic status of the country Prevalence significantly differs depending on the diagnostic tool used	All studies included in a updated SR [1]
Van Meter 2011 [10]	SR with MA 12 studies 6 US-based Ages: 7 to 21 years-old	Mean BSD prevalence Global: 1.8% (CI95% 1.1 - 3) US: 1.7% BD-I mean prevalence Global: 1.2% (CI95% 0.7 - 1.9)	BSD includes mania and hypomania No specific data on BD-I prevalence in US
Kessler 1994 [15]	Cross-sectional survey US population-based Conducted between 1990-1992 8,098 respondents Age: 15-54 years	BD-I prevalence: lifetime: 1.6% 12-month: 1.3%	Response rate= 82.6% Diagnostic criteria: DSM-III-R Diagnostic tool: UM-CIDI
Merikangas 2007 [12]	Cross-sectional survey US population-based Conducted between 2001-2003 9,282 respondents Age ≥18 years	BD-I prevalence Lifetime: 1% (subthreshold: 2.4%) 12-month: 0.6% (subthreshold: 1.4%) Mean age of onset: 18.2 years Mean number lifetime episodes: 77.6 Response rate: 70.9%	Age of onset and number of lifetime episodes self-reported retrospectively Diagnostic criteria: DSM-IV Diagnostic tool: CIDI v3.0
Judd 2003 [14]	Cross-sectional survey US population-based Conducted between 1980-1985 18,252 respondents Age ≥18 years	BD-I lifetime prevalence: 0.8%	BD-I characterized by a manic episode Diagnostic criteria: DSM-III Diagnostic tool: DIS
Grant 2005 [13]	Cross-sectional survey US population-based Conducted between 2001-2002 43,093 respondents Age ≥18 years	BD-I prevalence Lifetime: 3.3% (CI95% 2.76 - 3.84) 12-month: 2% (CI95% 1.82 - 2.18) Age of onset: 22.3 years (mean); 18.9 years (median) Response rate= 81%	Diagnostic criteria= DSM-IV Diagnostic tool= AUDADIS-IV
Roberts 2007 [16]	Cross-sectional survey Population-based: Houston metropolitan area Conducted in 2000 4,175 respondents Age: 11-17 years	Mania 12-month prevalence: 0.39% (CI95% 0.18 - 0.61)	Respondents enrolled in large HMOs Diagnostic criteria: DSM-IV criteria; diagnostic tool: DISC-IV

__AUDADIS-IV__= Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version; __BD__= Bipolar Disorder; __BD-I__= Bipolar Disorder Type I; __BSD__= Bipolar Spectrum Disorder; __CIDI__= World Health Organization's Composite International Diagnostic Interview; __DIS__= Diagnostic Interview Schedule; __DISC__: Diagnostic Interview Schedule for children; __DSM__= Diagnostic and Statistical Manual of Mental Disorders; __ECA__= US National Epidemiological Catchment Area database; __HMO__: Health Maintenance Organizations; __MA__= Meta-analysis __MDE__= Major Depressive Episode; __NCS__= National Comorbidity Survey; __NCS-R__= National Comorbidity Survey Replication; __NESARC__= National Epidemiologic Survey on Alcohol and Related Conditions; __SR__= Systematic Review; __UM-CIDI__= University of Michigan - Composite International Diagnostic Interview

**Results described were those related to incidence/prevalence, even when the study addressed other issues*

COMORBIDITY & MORTALITY

Patients living with BD/BD-I have high rates of comorbid disorders, such as:

- Alcohol use disorder (23.7% to 40.9%) [12,22,23] and any illicit drug use disorder (18%-30.4%) [12,22,23]

The risk for dependence is also higher than that of the general population.
Comprehensive Meta-Analysis version 2 (CMA, Biostat Eaglewood, NJ) was used to convert raw data to the odds ratios (ORs) shown here. Furthermore, a random effects model was chosen over a fixed effects model as prevalence rates would likely vary between populations of different races, ages, nationalities and availability and exposure to licit and illicit substances [22].

- Alcohol abuse: OR= 3.248 (95%CI 2.081 - 5.068) [22]
- Alcohol dependence: OR= 5.783 (95%CI 4.3 - 7.777) [22]
- Any illicit drug dependence: OR= 7.869 (95%CI 5.207 - 11.891) [22]
- Illicit drug disorder BD/BD-I vs. BD-II: OR= 7.48 vs. 3.3 [22]

Other mental disorders are also more common in patients living with BD/BD-I and have a negative impact in the number of euthymic days. [24] These are the prevalence ranges reported for:

Obsessive Compulsive Disorder

- Patients with BD: 10.6% to 17% [25,26]
- Patients with BD-I: 10.7% to 25.2% [12,24,25,27]

Generalized Anxiety Disorder

- Patients with BD: 15.1% to 20.4% [26,28]
- Patients with BD-I: 14.4% to 38.7% [12,23,24,27,28]

Any anxiety disorder

- Patients with BD: 45.3% [26]
- Patients with BD-I: 42% to 86.7% [12,23,24,27,29]

Panic Disorder

- Patients with BD: 19.3% [26]
- Patients with BD-I: 16.8% to 30.76% [12,23,24,27]

Social anxiety disorder

- Patients with BD-I: 13.3% [27]
- Patients with BD: 19.9% [26]

Post-Traumatic Stress Disorder

- Patients with BD: 17.3% [26]
- Patients with BD-I: 10.8% to 30.9% [12,27]

Specific phobias

- Patients with BD: 10.8% [26]
- Patients with BD-I: 10.8% to 47.7% [12,23,27]
- Clinical disorders are also more prevalent in patients living with BD/BD-I. These following prevalence rates were reported for patients with BD-I: type 2 diabetes dellitus (6.4% to 12.1%) [30,31]; metabolic syndrome (24%)[32]; hypertension (19.1%)[31]; coronary artery disease (0.9% to 10.1%)[31,33], hyperlipidemia (19.8% to 22.1%)[31,33] and kidney disease (3%)[31]

Mortality (due to natural or unnatural causes) is higher in patients with BD than in the general population. [34,35]

STAGING AND NATURAL PROGRESSION

- Staging models report the following phases in BD-I: earlier phase (before diagnosis), prodromal phase (mild, nonspecific symptoms, most patients undiagnosed), initial phase (first episode), relapsing phase (progression) and end-stage disease (refractoriness)
- BD-I patients spend about half of their life ill, especially due to depressive symptoms
- The most relevant studies on this topic are shown on **Table 2**.

Table 2. Relevant studies addressing staging and natural progression issues related to bipolar disorder including US population

Study	Methods	Comments
Muneer 2016 [36]	SR pertaining to staging models in BD	Describes three staging models proposed based on evidence of risk factors for BD, course of disease and neuroprogression, and biological findings (neuroimaging, biomarkers)
Kapczinski 2014 [37]	SR pertaining to staging models in BD	Describes five staging models proposed based on evidence of risk factors for BD, course of disease and neuroprogression, and biological findings (neuroimaging, biomarkers)
Faedda 2014 [38]	SR on prodromal phase/clinical risk factors for BD	16 prospective studies included
Skjelstad 2010 [39]	SR addressing symptoms and signs of the initial prodrome of subjects diagnosed with BD	8 studies included (7 retrospective)
Gignac 2015 [40]	SR with meta-analysis of prospective longitudinal cohorts recruiting patients with diagnosis of BD-I addressing recurrence data after a first episode of mania.	8 studies representing a total of 734 first-episode patients (5 with 1-year follow-up and 4 with 4-year follow-up)
Forte 2015 [41]	SR addressing long-term morbidity in BD-I, BD-II and unipolar depressive disorders.	12 studies on BD-I comprising a total of 2,760 subjects with a mean exposure of 7.78 years
Judd 2002 [42]	US longitudinal study enrolling BD patients through 1978 - 1981.	146 BD-I patients with 12.8 years of follow-up
Carvalho 2014 [43]	SR addressing the prevalence of rapid cycling in BD	Mean weighted prevalence based on a total of12 studies comprising 8,230 patients for current and 934 patients for lifetime prevalence

__BD-I__ = Bipolar Disorder type I; __SR__= Systematic Review; __STOP-EM__= Systematic Treatment Optimization Program

CONCLUSION

- BD is a chronic and disabling disease with onset in early adulthood. Knowledge of epidemiologic features may help increase awareness and early diagnosis, although there is a gap in our understanding of prevalence and incidence rates over time, with no US studies regarding BD incidence found. Also, physicians must be attentive of the high comorbidity rates associated with this disorder.

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Disclosures

- Greene is an employee of Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ
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