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Diagnosis and Management of Bipolar Disorders in Primary Care

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Abstract: **Bipolar Illness (BD) has an around the world life time frequency of about 2.4% reported throughout Americas, Europe, Asia, Middle East and New Zealand. The course of BD is relentless and characterised by recurrent state of mind episodes creating considerable dysfunction in the impacted individual. Worldwide, the disorder ranks 5th in contributing to a loss of working and imparts significant individual and societal issue. The South Asian area homes one-fifth of individuals with mental illness around the world and yet, much stays to be explored concerning the dominating course patterns of BD in Asia and the associated elements Scientists have in fact kept in mind a fairly higher frequency of BD-I amongst those with Asian ethnic background when compared with the Caucasians. The present review determines the local qualities of BD course patterns and the involved elements. Regional and cross-national studies expose a mania-predominant course in BD in Asian nations. Extended depressive episodes and comorbid stress and anxiety disorders intensify the course of BD-II. Particular threat factors such as the young age of start and higher episode frequency are useful predictors of bipolar diatheses. Substance use disorder comorbidity is more common in males whereas anxiety and suicidal behaviours are more frequent in women with BD. Comorbid stress and anxiety and personality disorders likewise encumber the health problem course. Logistic reasons and lack of knowledge of side-effects were specifically related to poor adherence. An 'eveningness' chronotype and bad sleep quality were connected with regular recurrences. Seasonal patterns vary amongst ladies and males, particularly for depressive episodes. There are region-specific attributes in bipolar illness course and aspects influencing such course patterns compared to the remainder of the World. Future research from Asia will try to study the neurobiological underpinnings of such attributes and plan appropriate methods to deal with the same.**

Keywords: **Bipolar Illness (BD), region-specific attributes, neurobiological underpinnings.**

1. INTRODUCTION

Bipolar Illness (BD) has a worldwide life time prevalence of about 2.4% reported across Americas, Europe, Asia, Middle East and New Zealand *(Merikangas et al., 2011)*. The course of BD is persistent and characterised by recurrent state of mind episodes conjuring up considerable dysfunction in the impacted individual *(Angst and Sellaro, 2000)*. Worldwide, the disorder ranks 5 th in adding to a loss of working and imparts significant person and societal concern *(Pompili et al., 2014; Whiteford et al., 2013)*. The South Asian area houses one-fifth of people with mental illness worldwide and yet, much remains to be explored regarding the dominating course patterns of BD in Asia and the associated factors *(Trivedi et al., 2007)*. Scientists have actually noted a relatively greater prevalence of BD-I amongst those with Asian ethnic background when compared with the Caucasians *(Hwang et al., 2010)*. Uncertainty looms over the aspects involved in impacting the health problem course. The dubiety shall be attributed to the scarcity of large-scale epidemiologic studies evaluating affective disorders in this region *(Chiu, 2004)*. Understanding of the disease course, outcome and moderating elements of bipolar illness in Asia will strengthen the psychological healthcare delivery system. The same can serve a better understanding of the bipolar illness by the clinicians and assist the policy makers in developing effective strategies to take on the prominent factors. We intended to review the released literature from Asian countries regarding the course of bipolar affective disorder, its varied types and the impact of numerous aspects on the illness course. The findings are compared to the currently released wealth of Western literature.

2. METHODOLOGY

The 'PubMed' and 'Cochrane' databases were used for the literature search. Cross-referencing from the articles of interest was also undertaken. Search keywords used were 'bipolar', 'course', 'bipolar I', 'bipolar II', 'substance use', 'psychiatric comorbidities', 'adherence', 'sleep', 'seasonality' and 'geography'. To ascertain the regional characteristics, names of the 48 Asian countries were individually typed to get an adequate number of published articles. Relevant literature from the West was also searched and was used for pertinent discussion under various sections. The studies that discussed the prevailing course patterns, and those, which provided information on effects of multiple individual variables on the course of BD, were included. There were no time limits set for the literature search. Articles were mainly in English. Data from articles published in non-indexed journals, academic dissertations and conference papers were not included. The screening and inclusion of items are explained in Figure 1.

3. RESULTS AND DISCUSSION

3.1. The course of bipolar disorder:

Most of the Asian research studies carried out retrospective data analyses for assessing the disease course of BD. Few studies have actually conducted potential follow-up to establish the disease course *(Chopra et al., 2006; Khess et al., 1997)*. On studying the typology of mood recurrences, manic episodes predominated the health problem course of bipolar illness observed in the Asian *(Avashthi et al., 1996; Chopra et al., 2006; Karthick et al., 2015a; Khanna et al., 1992; Ramdurg and Kumar, 2013; Rangappa et al., n.d.; Yazıcı and Cakır, 2012)* and the Middle East areas (Osher et al., 2000). One study discovered that the patients invested more percent time in the manic phases when the total duration of disease is considered *(Karthick et al., 2015a)*. Mania is reported to be the index episode by some scientists *(Karthick et al., 2015a; Khanna et al., 1992)*. The aspect of manic predominance was further studied in more information and hence unfurled the debatable principle of Unipolar Mania (UPM).

3.1.1. Recurrent unipolar mania and mania-predominant polarity:

Comparable to the global literature, recurrent unipolar mania (UPM) was specified by the existence of only manic reoccurrences in the whole disease course without any mixed or depressive episodes *(Aghanwa, 2001; Perugi et al., 2007)*. Asian researchers have attempted to differentiate the clinical aspects between Recurrent Unipolar Mania (UPM) and Manic-Depressive Illness/Bipolar Mania (BPM). Apart from a more youthful age of start in UPM, studies were not able to clearly distinguish UPM and BPM concerning the phenomenology, frequency of reoccurrences, period of illness, gender distribution amongst lots of other factors *(Aghanwa, 2001; Srinivasan et al., 1985)*. When the stricter definition of "just manic reoccurrences" is relaxed, a majority of Asian research studies report that though patients had both manic and depressive reoccurrences, the previous had a greater prevalence over the course of disease *(Aghanwa, 2001; Baldessarini et al., 2012b; Bopp et al., 2010; Chopra et al., 2006; Judd et al., 2002; Khanna et al., 1992; Osher et al., 2000; Ramdurg and Kumar, 2013)*. The relevant research studies from Asia are summarized in Table 1.

3.1.2. Comparison of Bipolar I and Bipolar II subtypes:

Prevalence:

Research studies argue that BD-I to be more prevalent than BD-II (95% more common). Such studies likewise reveal that BD-I patients had a very first (index) episode as mania *(Lee et al., 2009; Leelahanaj et al., 2013)*. On the contrary, one study from the South-east Asian region reports that BD-II (76%) could be more widespread than BD-I (17%) with anxiety occurring as the index episode *(Peh and Tay, 2008)*.

The illness course:

In both BD-I and BD-II, depressive episodes had longer periods, induced greater subjective distress and functional problems *(Lee et al., 2009; Leelahanaj et al., 2013)*. Research studies have provided more recent insights on the longitudinal course patterns of BD-II. Based upon the course profiles, two groups are identified. Those referred to as 'hypomania occurring within the very first year' (which is more common) and those who have 'cyclothymic functions presenting with young age at start and numerous self-destructive efforts' *(Kurumaji et al., 2014)*. BD-II showed more consistent seasonal patterns when compared to BD-I. Seasonality was connected with aggravating of cycles in the course of disease *(Kim et al., 2015)*.

Comorbidities:

Just like the West, adequate literature from Asia reveals that comorbid anxiety disorders are more common with BD-II overloading the disease course with included concern *(Chang et al., 2012; MacQueen and Young, 2001; Sugaya et al., 2013)*. A study from Taiwan associated such an association due to the aberrant polymorphisms in DRD3 genes underlying a dysfunctional dopamine system which in turn leads to increased mental vulnerability to developing stress and anxiety disorders *(Chang et al., 2013)*. Further, there is an increased association of youth behavioural disorders such as the Attention Deficit Hyperactivity Disorder (ADHD) in BD-II compared to that in BD-I *(Joo et al., 2012)*. These observations highlight the increased problem on BD-II due to comorbid psychiatric illnesses.

Temperament characteristics:

Recent research studies from Asia have actually extended the research by differentiating the genetic impacts and character profiles of patients with BD-I and BD-II. Considerable interactions in between genes and the novelty seeking attitude exist in BD-I than that seen in BD-II *(Lin et al., 2010)*. The interactions may explain the greater degrees of impulsivity and suicidal tendencies noted in BD-I than in BD-II *(Kim et al., 2015)*.

3.2. Prodrome and early stages of bipolar disorder

3.2.1. Research on the "soft" bipolar subtype:

Early detection of BD is considered necessary to enhance and reduce the morbidity treatment responsiveness *(McCraw et al., 2014; Nusslock and Frank, 2011)*. Increasing variety of Asian research studies concentrate on determining and handling the so-called 'soft' bipolar subtypes as specified by Akiskal and Pinto *(Akiskal and Pinto, 1999)*. The presence of brief durations of manic or hypomanic symptoms (2-3 days) in bipolar II disorder was considered as soft bipolar subtype *(Lee et al., 2009; Mak, 2009)*. The twelve-month occurrence of soft bipolar subtype is around 1.8% *(Lee et al., 2009)*. A family history of bipolar disorder, young age at onset and more of depressive reoccurrences were present in the soft bipolar subtypes *(Mak, 2009)*. Contrary findings do exist. In a Chinese research study with a bigger sample of patients with MDD (n=1487), around 20% of the sample had subthreshold manic symptoms indicative of the 'soft' bipolar type. The patients had an older age at beginning, less regular depressive episodes and less family history of psychiatric disorders *(Hu et al., 2012)*. Comorbid borderline character and a quick disappearance of depressive symptoms are likewise seen as indications of soft BD-II in persistent depressive disorder patients much like that reported from other areas of the World *(Akiskal et al., 1995; Henry et al., 1999; Utsumi et al., 2006)*. A current research study from this region found that 'soft' bipolar patients prosper in working memory and processing speed when compared to the BD-I and BD-II patients *(Lin et al., 2015)*. The research study furthers our understanding of BD that the 'soft' bipolar people might represent a various endophenotype in bipolar spectrum disorders.

3.2.2. Risk factors for Unipolar Depression (UD) to Bipolar Disorder (BD) conversion:

The international literature exposes that across the total period of depressive disease, every brand-new episode of anxiety begets a new and greater risk of establishing mania and eventually transform into bipolar affective disorder *(Angst et al., 2005)*. Studies from Asia have guided into trying to find the possible factors involved in the conversion of UD to BD. The occurrence of anti-depressant induced mania or hypomania, providing with mixed depressions, increased frequency of episodes in a year, and history of suicide efforts were related to heightened danger of conversion from unipolar anxiety to bipolar illness *(Inoue et al., 2015; Park et al., 2014)*.

3.3. Cross-national studies on course of BD:

Compared to studies carried out within a region, cross-national studies have the advantage of evaluating the geographic and ethnic distinctions in between two areas. One such research study examined the predominant recurrence polarity among 928 BD-I patients from five countries (Argentina, Spain, South Korea, Italy, and the United States). Patients from South Korea contributed 21.6% of the data (n=218). Compared to other continents, Asia (i.e., South Korea) had predominantly manic polarity in the course of BD-I. The manic PP was related to high chances of having index episode as mania and was frequently related to Substance Usage Disorder (SUD) comorbidity. The depressive PP was unusual, however they were connected with a greater threat of self-destructive behaviours *(Baldessarini et al., 2012b)*. Another cross-national study compared BD-I characteristics between patients from the United States (n=96) and Taiwan (n=46). Quarterly follow-up for eight years exposed that the United States patient population had more depressive reoccurrences, more AUD comorbidity and more psychotic symptomatology compared to the Asian counterpart, Taiwan. BD-I patients

from Taiwan relatively had actually spent less time in subsyndromal states, and more time in remission. The much better adherence rates and attitudes in looking for psychiatric health services in Asian patients were pointed out as reasons for much better remission rates in Taiwan compared to the US. The authors also reveal that the rate of reoccurrence was similar in both groups recommending that the course of BD ends up being worldwide similar over time *(Strakowski et al., 2007)*. From these research studies, one might acknowledge that there are specific distinctions in primary polarity, comorbid compound use disorders, subsyndromal states and treatment mindsets between BD patients from Asia and the rest of the World.

3.4. Influence of various factors on course of BD:

3.4.1. Influence of Gender:

Women experienced more frequent reoccurrences of anxiety and mixed states, higher familial loading and suicidality *(Shim et al., 2015; Yang et al., 2013)*. Amongst BD patients, SUD comorbidity was most likely in men *(Ahmadi et al., 2001; Baek et al., 2014)*. Fascinating observations of the gender distinctions in seasonality exist in the Asian literature. The significant Asian studies are summed up in Table 2.

3.4.2. Influence of Substance Use Disorder (SUD):

The Asian research studies have kept in mind lower occurrence rates of SUD when compared to the Western literature *(Chopra et al., 2006; Karthick et al., 2015a; Munoli et al., 2014)*. Male gender *(Ahmadi et al., 2001; Hapangama et al., 2013)* and low socio-economic status *(Sedain, 2013)* were independently associated with increased rates of substance usage. Alcohol is the most frequently used substance in patients with BD *(Chopra et al., 2006; Hapangama et al., 2013; Munoli et al., 2014; Tamam and Ozpoyraz, 2002; Tsai et al., 1997)*. Table 3 stresses the high unfavorable impact exerted by SUD over the course and outcome of BD.

3.4.3. Influence of other psychiatric comorbidities:

3.4.3.1. Comorbid anxiety disorders:

Asian studies report a relatively lower prevalence rates of psychiatric comorbidities in bipolar disorder *(Altindag et al., 2006a)*. Obsessive Compulsive Disorder (OCD) and Panic Attack (PD) are the more commonly studied comorbid stress and anxiety disorders in bipolar patients *(Altindag et al., 2006a; Pashinian et al., 2006; Shashidhara et al., 2015)*. Comorbid anxiety disorders impart regular recurrences, bad treatment action, regular hospitalisations and result in significant functional special needs in patients with BD *(Altindag et al., 2006a; Koyuncu et al., 2014, 2010; Shashidhara et al., 2015)*.

3.4.3.2. Comorbid personality disorders:

Asian studies reveal that comorbid personality disorders are more prevalent in BD patients than the basic population and are associated with state of mind dysregulation *(Fan and Hassell, 2008)*. Personality disorder (PD) qualities coming from Cluster B and Cluster C are more frequent and they cause frequent suicide efforts *(Altindag et al., 2006b; Uçok et al., 1998)*.

3.4.3.3 BD and childhood behavioural disorders:

Bipolar patients have been noted to have functions of comorbid Attention Deficit Hyperactivity Disorder (ADHD). Conversely, teenagers with ADHD especially with features of Conduct disorder (CD) or Oppositional Defiant Disorder (ODD) showed higher threat of establishing BD *(Chen et al., 2013)*. The ADHD comorbidity causes an earlier age at beginning with frequent mood episodes, increase the vulnerability to developing comorbid stress and anxiety and substance use disorders and decrease the social functioning of the affected individuals *(Karaahmet et al., 2013; Sugaya et al., 2013; Tamam et al., 2008)*. Research studies expose that youth maltreatment and unfavorable life events can predispose to bipolar illness burdened with comorbid stress and anxiety disorders, leading on to worse course and outcome *(Li et al., 2014)*. The prominent findings from the Asian studies are summarized in Table 4.

3.4.4. Influence of adherence:

Poor adherence was associated with numerous re-hospitalizations and as a result an increased financial problem in the form of lost working days *(Hapangama et al., 2013; Khess et al., 1997; Tang et al., 2010)*. Low socio-economic strata and increased transport expenses in addition contribute to medication non-adherence due to problems in the accessibility and

price of mental healthcare *(Oflaz et al., 2015)*. In addition, various illness-related elements *(Chopra et al., 2006; Hapangama et al., 2013; Moon et al., 2012; Oflaz et al., 2015; Yen et al., 2005)*, and patient-related elements such as ignorance about side effects *(Bener et al., 2013)* and lapse of memory *(Subramanian et al., 2016; Taj et al., 2008)* are oft-quoted reasons for patient's poor adherence mindsets. Greater levels of education *(Ozerdem et al., 2001)*, sufficient social assistance *(Bener et al., 2013; Col et al., 2014)* and adequate health problem psychoeducation *(Col et al., 2014)* resulted in much better adherence rates. The findings from the Asian research studies are depicted in Table 5.

3.4.5. Influence of sleep quality:

Compared to the international literature, fewer research studies from Asia have actually examined the function of sleep in course of bipolar disorder. Research studies reveal that the sleep quality can be impaired in bipolar patients even during clinical remission *(Karthick et al., 2015b; Wang et al., 2014)* recommending that sleep issues exist in bipolar affective disorder irrespective of the stage of health problem. Researchers have discovered that BD-I patients show specific pre-set body clocks ("chronotypes") associated with start and seasonality of mood episodes *(Ahn et al., 2008; Lee et al., 2011).* The observations are summarized in Table 6.

3.4.6. Influence of seasons:

Considerable literature exists in the Asian context concerning the impact of seasons on the course of bipolar illness. Gender and polarity of the index episode have a bearing in predicting the seasonality of relapse admissions *(Hochman et al., 2016; Rajkumar and Sarkar, 2015; Yang et al., 2013).* The appropriate findings from the Asian research studies are outlined in Table 7.

4. DISCUSSION

4.1. The course of bipolar disorder:

Studies from the West report that at least 50% patients experience subsyndromal symptoms *(Sala et al., 2009)* and depressive symptoms had predominated the subsyndromal phases causing substantial morbidity *(Judd et al., 2002)*. In contrast, manic episodes tend to remit earlier *(Yatham et al., 2009)*. On longitudinal observations, depressive episodes were three times more regular than hypomanic or manic phases *(Judd et al., 2003; Solomon et al., 2009)*. Mania is the primary polarity of the bulk of recurrences noted in Asian research studies. Further, numerous non-Western countries (particularly those in the tropical regions) report a greater occurrence of manic PP *(Lee and Yu, 1994; Makanjuola, 1985; Mehta, 2014)*. The observations are in sharp contrast from the West where potential research studies had the ability to document more depressive symptoms *(Bopp et al., 2010; Strength et al., 2015; Judd et al., 2002; Strakowski et al., 2007)*. Understandably, the retrospective design of the Asian studies might still represent any under-representation of depressive episodes in the illness course *(Aghanwa, 2001; Srinivasan et al., 1985)*. The idea of manic PP (rather than the strictly specified UPM) seems to be valid in the context of Asian research. Such findings should direct us to further genetic research to determine the qualities of manic PP in more detail *(Baldessarini et al., 2012a)*. A recent systematic review emphasizes that predominant polarity of studies on PP, which conveyed that PP can be thought about as a legitimate criterion to be included as a 'course specifier' *(Carvalho et al., 2014)*.

4.2. Soft bipolar disorder and bipolar prodrome:

Soft bipolar patients on the edge of diagnostic conversion frequently tend to be females and exhibit poor treatment action with antidepressants *(Koukopoulos et al., 2013)*. In the Americas, there is a mounting significance for detecting BD as early as possible even at the medical care level with the assistance of basic diagnostic tools *(Kaye, 2005)*. As most of people from this continent primarily have access to main levels of healthcare, it is extremely most likely that the under-diagnosis of BD can take place when unipolar depressives are evaluated in an unsystematic style. The under-diagnosis further can result in getting worse of health problem course and increased suicide-related mortality consequent to bipolar depression *(Cerimele et al., 2013; Culpepper, 2014)*. Active screening for the risk aspects for conversion from UD to BD will help to tease out bipolar patients from the mass of unipolar depressives *(Inoue et al., 2015; Park et al., 2014)*. One needs to be conscious of the diagnostic challenges faced in identifying soft bipolar patients, separating them from borderline personality and the ominous danger of over-diagnosing bipolarity *(Nusslock and Frank, 2011)*. Proper screening and longitudinal observations of patients with MDD are required to replicate the observations from Asian literature.

4.3. Influence of Gender:

Reports of higher frequencies of blended and depressive episode reoccurrences in women than males are akin to those observed in the international literature *(Azorin et al., 2013; Kessing et al., 2004; Nivoli et al., 2011; Robb et al., 1998)*. The increased vulnerability of the females to tension and environmental influences are highlighted by the results of seasonality on ladies with BD. Greater prevalence of SUD comorbidity in men compared to ladies resulting in a worse course of illness and bad result concord with the Western literature *(Kawa et al., 2005; Nivoli et al., 2011)*. Cultural impacts amongst the Asian countries allowing the males but ladies to take in and procure alcohol shall discuss the gender disparity. The observations call for proper gender-specific screening and addressing of these problems are necessary to decrease the morbidity due to BD.

4.4. Influence of SUD comorbidity:

Patients with BD have the tendency to utilize substances for recreational purposes and their changing effects on mood *(Lorberg et al., 2010)*. Research studies from the rest of the World reveal that the prevalence of SUD comorbidity in BD range from 35% to 70% *(Clodfelter Jr and McDowell, 2001; Gao et al., 2010; Goldberg et al., 1995; Oquendo et al., 2010; Quello et al., 2005; Strakowski et al., 2000)*. The lower frequency rates in Asia might be described by the cultural influences prohibiting using compounds in the majority of its nations. Globally, alcohol and marijuana were frequently utilized by BD patients *(Cerullo and Strakowski, 2007; Gaudiano et al., 2008; Lagerberg et al., 2010)*. Alcohol, due to its accessibility and cost is still the most common compound used in the Asian context *(Sedain, 2013; Tsai et al., 1997).* SUD intensifies the disease course and the diagnosis of BD by causing regular mood reoccurrences and making episodes less open to treatment *(Clodfelter Jr and McDowell, 2001; Ostacher et al., 2010; Strakowski et al., 2000)*. SUD comorbidity impairs the adherence patterns *(Gao et al., 2010; Lagerberg et al., 2010; McIntyre et al., 2008)*, increases suicide risk *(Goldstein et al., 2008)* and vitiates the overall functioning *(Lagerberg et al., 2010)*. Asian studies (as shown in Table 3) repeat the above findings and accentuate the unhealthy impacts of SUD comorbidity. The dealing with clinicians ought to be cognizant of such associations, and a holistic approach is recommended when tackling both the illness and SUD issues together.

4.5. Influence of other psychiatric comorbidities:

The western literature reports that comorbid anxiety disorders can be present in about 60% of patients with BD leading to increased morbidity, reduced working and a greater danger of suicide efforts *(Sala et al., 2012; Vieta et al., 2001)*. Lower occurrence rates reported in Asian research studies could be the outcome of studying hospital-based patient population and the lack of largescale community-based studies in most of the establishing nations in Asia. Because co-morbid PDs impair the recovery process in BD, efficient screening efforts are required for proper management *(Dunayevich et al., 2000; Fan and Hassell, 2008)*. Research on character pathology has exposed that both Cluster B and C traits prevail than Cluster A *(George et al., 2003)*. Asian studies concur with the international literature that childhood maltreatment and emotional overlook in youth are reported to have strong associations with BD in adults *(Romero et al., 2009; Sala et al., 2014; Watson et al., 2014)*. The findings expose that psychiatric comorbidities in BD can start to take place at the early stages of the life and tend to aggravate the illness course through various mechanisms. Clinicians would be needed to designate specific focus on the comorbidities while managing patients with BD to achieve a total recovery from the health problem.

4.6. Influence of adherence:

Adherence to medications is thought about as one of the essential elements to prevent regressions in bipolar illness *(Keck et al., 1998; Sajatovic et al., 2009; Teter et al., 2011; Yatham et al., 2009)*. When accompanied by poor adherence, the cost of managing the bipolar illness increases in plethoras *(Durrenberger et al., 1999)*. Cross-national research studies reveal that compared to the West, Asians were more likely to perceive the treatment as crucial and had adequate household support to guarantee adherence to treatment *(Strakowski et al., 2007).* A plethora of aspects exists in the Asian context which contributes to bad adherence in BD. Some of them are a low socioeconomic background, the patient's mindsets to acceptance of drugs and the role of the doctor 'as an individual who shares requisite info to his/her patient and ensures adherence'. A positive healing relationship, adequate social assistance and a economical and available health care system can improve the adherence to appropriate requirements.

4.7. Influence of sleep quality:

Internationally, research studies have exposed that circadian rhythm disturbances speed up regular mood episodes *(Eidelman et al., 2010; Gruber et al., 2011; Harvey, 2011; Putnins et al., 2012; Suppes et al., 2000; Wehr et al., 1983)*.

Current research studies have shed light in the neurobiological association between sleep and bipolar disorder. The studies reveal that the sleep disturbances exist not just throughout mood episodes however likewise in the interepisode periods causing substantial disability of functioning *(Giglio et al., 2009; Talbot et al., 2012)*. Different pathophysiological processes are associated with the dysregulation specifically changes in melatonin levels, variations of clock genes and chronotypes *(Abreu and Bragança, 2015; Robillard et al., 2013)*. Studies also state that the disturbances in sleep cycles and the seasonal changes in state of mind might share a common neurobiological etiology *(Brambilla et al., 2012)*. The greater latency for sleep and 'night choice for wakefulness', and the existence of sleep disruption even throughout remission states as argued by the Asian studies are some of the commonalities discovered in the remainder of the World *(Seleem et al., 2015)*. Though the cause remains unknown, the striking association in between the sleep disruptions and mood disorders should make one comprehend they are neurobiologically associated. The sleep problems need to be resolved with independent attention in follow-up sees of bipolar patients.

4.8. Influence of the seasons:

Seasonality typically describes the annual rainfalls of state of mind episodes which prevail in about 20-25% of the BD population *(Kim et al., 2011)*. Just like the Asian nations *(Lee et al., 2002; Rajkumar and Sarkar, 2015)* other tropical areas like Latin America also report increased reoccurrence rates for mania in the spring season *(Volpe et al., 2010)*. The geographical vulnerability of the equatorial and the tropical zones such as Asia is postulated to cause prolonged summers and a longer exposure to sunlight compared with the rest of the World. Such vulnerability has actually been indicated in increased frequency of manic episodes in those areas compared to regular depressive episodes reported somewhere else *(Bauer et al., 2014; Kohno et al., 2012; Lee et al., 2002; Narayanaswamy et al., 2014; Osher et al., 2000)*. When BD-II with seasonal course pattern is considered, the greater number of depressive reoccurrences remains in line with similar research studies reported elsewhere *(Geoffroy et al., 2014; Goikolea et al., 2007)*. The details gathered may help clinicians in preparing for and actively evaluating for mood episodes in susceptible patients during specific seasons. When required without losing important time, it may also inform the patient and caretakers in this area to keep an eye on the state of mind status and look for psychiatric help.

4.9. Limitations:

The possible impacts of numerous factors associated with the health problem course particularly, the age, age of beginning, socio-economic status and the family history might not be discussed due to a scarceness of research studies in Asia making direct analyses for such variables. The review does not include findings relating to course patterns of childhood BD which can differ entirely from adult BD along the lines of disease course, comorbidities and the factors influencing the disease course. We have not consisted of the impacts of treatment on the course of bipolar disorder due to the highly comprehensive and variable treatment modalities recommended for bipolar disorder.

5. CONCLUSION

When some of the observations concurred with the existing international literature on the course of BD, particular findings emerged differently which represented the native functions of BD disease course in Asia. The manic episodes predominate the course of bipolar illness in Asia as obvious from native and cross-national research studies. A particular subtype of recurrent health problem specifically Reoccurring Unipolar Mania is extremely prevalent in some parts albeit its diagnostic validity has to be established by carrying out prospective studies.

The course of BD-II is overloaded with prolonged depressive episodes, comorbid anxiety disorders, and seasonal worsening of depression. Amidst contrasting proof, blossoming research in 'soft' bipolarity has determined that a family history of bipolar disorder, young age at start and frequent depressive recurrences are predictive of the 'soft' bipolar functions in susceptible patients.

Asian studies have actually also discovered that an incident of anti-depressant caused mania or hypomania, combined depressions, increased episode-cycles, and suicidal behaviours were associated with higher threat of a transformation from unipolar anxiety to bipolar illness.

Cognizance of the bd and gender-specific subtype-specific seasonal influences will help the family and the clinicians to determine the high-risk populations and avoid several recurrences. Though the prevalence of BD is equivalent in either gender, women suffer more frequent depressive recurrences and display greater suicidal behaviours when compared with males. Guys were more likely to have comorbid compound use disorders complicating the health problem course by

intensifying the psychopathology, begetting several recurrences, regular hospitalisations and poor practical outcomes. Apart from SUD, comorbid anxiety disorders, personality disorders and childhood behavioural disorders seem to aggravate the health problem course, treatment response and practical recovery of the patient.

Many illness-related elements such as rapid cycling, SUD comorbidity, absence of insight, and cyclothymic character are known to be related to bad adherence to treatment. Other contributing factors such as low financial support, low education levels, and logistic difficulties in seeking health care may need reliable modifications in the current psychological health shipment system. Clinicians need to resolve tangible factors such as ignorance about sideeffects and lapse of memory in taking medications to make sure sufficient levels of adherence. Asian research studies on sleep and course of BD, though couple of, have reiterated that sleep disruption exists regardless of the phase of the disease even throughout remission. Such research studies have also identified that an 'eveningness' chronotype causes greater vulnerability for seasonal exacerbations of BD. The Asian nations, the majority of them located in the middle of the equatorial and tropical latitudes, are exposed to substantial impacts of the seasons. Manic and depressive episodes most regularly take place throughout the summer season and winter respectively. Future research study needs to be able to develop massive potential research studies to verify the prevailing BD course patterns and yield appropriate information about the prevalence and effect of different subtypes of BD. Active screening efforts are essential, specifically in the medical care setting, for a prompt diagnosis and to consequently avoid illness morbidity. Concurrent effective interventions to deal with the psychiatric comorbidities are indispensable for a thorough recoupment from the bipolar illness. There lies much scope for evaluating the neurobiological foundations adding to the endemic nature of the health problem course and the aspects influencing the health problem development.

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APPENDIX - A

- **Tables:**

Table 1: Studies on predominant polarity of bipolar disorder in Asia

Author , Year	Country	Method/ Setting	Sample characteristic	Findings
Srinivasan et al.,1985	INDIA	South India; compared demography and phenomenology between UPM and BPM	UPM=12, BPM=17	UPM has early age at onset, no significant differences in phenomenology; mild depressions are unnoticed and underreported; UPM not a valid diagnosis
Khanna et al., 1992	INDIA	Course of bipolar disorder in eastern India	N=95	Most are unipolar mania; especially in those who had index manic episode
Osher et al., 2000	ISRAEL	Chart review of BD in southern Israel	N=71	Mania-predominant course was found as opposed to depression-predominant course seen in Europe

Aghanwa 2001	FIJI	Compared course characteristics between UPM and BPM	UPM =51; BPM=31	High rates of Recurrent unipolar mania; although its demographic and clinical characteristics do not clearly distinguish it from manic-depression.
Chopra et al., 2006	INDIA	Assessed Naturalistic course of bipolar in rural community; follow-up of 8.5 years	N=34	72% had mania predominant course
Baldessarini et al., 2012b	MULTI SITE (5 CONTI NENTS INCLU DING ASIA)	Assessed predominant recurrence polarity among 928 BD-I patients	N=928 (n=218 from South Korea)	The Asian country Korea has predominantly manic polarity in total illness; categorization of PP was stable; first episode was mania;
Ramdurg and Kumar, 2013	INDIA	Study of socio-demographic profile, phenomenology, course and outcome of bipolar disorder in Indian population	N= 100	Predominant polarity of majority of episodes is mania(n=64)

N-Sample size, BD-Bipolar Disorder, UPM-Unipolar Mania, BPM-Bipolar Mania,

PP-Predominant Polarity, NIMH-LCM-National Institute of Mental Health-Life Chart Methodology

Table 2: Influence of gender on course of bipolar disorder in Asia:

Author, Year	Country	Setting / Method	Sample size	Salient findings
Osher et al., 2000	KOREA	Chart review of BD patients	N=71	No gender differences in course characteristics
Ahmadi et al., 2001	IRAN	Prevalence of SUD in psychiatric inpatients	N= 205, (BD=37.5%)	SUD comorbidity more prevalent in men (63%)
Lee et al., 2002	KOREA	Effects of season and climate on the first manic episode of bipolar affective disorder in Korea	N=152	Mean monthly hours of sunshine and sunlight radiation had significant positive correlation with onset of manic episodes; predominantly in females
Yang et al., 2013	TAIWAN	Effect of gender on seasonality	BD=9619	Female admissions were associated with seasonal depressive episodes and male admissions for seasonal manic episodes
Baek et al., 2014	KOREA	Cross-sectional study assessed axis I comorbidity in BD	BD-I= 222, BD-II=194 in remission	Prevalence of AUD : 16.8%; mostlyin males
Shim et al., 2015	KOREA	Retrospective chart review of BD-I with mixed episodes	N=171	Females were more likely to have mixed episodes, high familial loading, high suicidality

N-Sample size, BD-Bipolar Disorder, SUD- Substance Use Disorder, AUD-Alcohol Use Disorder

Table 3: Influence of substance use comorbidity on course of bipolar disorder in Asia:

Author, Year	Country	Method / Setting	Sample size	Findings
Khess et al., 1997	INDIA	Four year follow- up of first episode manic patients	N=32	Comorbid ADS increased the rates of recurrence
Tsai et al., 1997	CHINA	Assessed long- term psychosocial outcome using GAF in Bipolar pts using alcohol	N=157	Alcohol most common substance to be used; it worsens outcome in BD
Ahmadi et al., 2001	IRAN	Prevalence of substance use in psychiatric inpatients	N=205 (37.5% were BD)	SUD comorbidity commonly seen in males (63%)
Karam et al., 2002	LEBANON	Retrospectively assessed prevalence of substance abuse/dependence in psychiatric inpatients covering 13 years in a general hospital psychiatric unit	N=222	Prevalence of SUD in BD-I was 42%
Tamam and Ozpoyraz, 2002	TURKEY	Assessed comorbidity in BD-I remitted pts	N=70	ADS comorbidity seen in 61.4%;led to more severe psychopathology
Singh et al., 2005	INDIA	Assessed QOL in euthymic bipolar pts who had comorbid substance dependence	N=40	BD and comorbid AUD pts experienced lower QOL;QOL worsens with severity of AUD
Chopra et al., 2006	INDIA	F/u of bipolar pts for 8.5 years, assessed comorbid SUD prevalence	N=34	26% of sample had alcohol dependence

N-Sample size, SUD-Substance Use Disorder, ADS-Alcohol Dependence Syndrome,

BD-Bipolar Disorder, AUD-Alcohol Use Disorder, GAF-Global Assessment of Functioning, QOL-Quality of Life, PP-Predominant Polarity

Table 4: Effect of other psychiatric comorbidities on course of bipolar disorder in Asia:

Author, Year	Country	Study	Sample size	Results
Uçok et al., 1998	TURKEY	Evaluated comorbidity of Personality disorders in Bipolar disorder	N=90	Obsessive- compulsive, paranoid, histrionic, and borderline personality disorders were significantly more prevalent in bipolar patients; Suicide attempts were more frequent in such patients
Altindag et al., 2006	TURKEY	Studied prevalence and clinical correlates of comorbid Anxiety disorder in BD-I	N=70	19 (27%) of BD-I had comorbid AD. Most common is OCD and specific phobia, followed by panic disorder. AD comorbidity is associated with frequent hospitalisations, psychotic symptoms and suicide attempts
Tsai et al., 2012	TAIWAN	Checked usefulness of empirically derived subgroups of BD-I	N=306	3% anxiety comorbidity; 12% SUD comorbidity. Those who had anxiety comorbidity were female predominant with early age at onset.
Tamam et al., 2008	TURKEY	Assessed comorbidity of adult ADHD and BD	N=159 (BD)	26 (16.3%) had comorbid adult ADHD; also had other comorbidities like Panic disorder, SUD, etc. ADHD comorbidity affects course of BD and impairs social adjustment of patients

Koyuncu et al., 2010	TURKEY	Studied impact of OCD on demographic and clinical features of BD	N=214 [BD-I=185; BD-II=13; BD-NOS=16]	OCD was more prevalent in BD-NOS group; OCD rendered the course of BD chronic. No other differences in clinical or socio-demographic parameters
Karakus and Tamam, 2011	TURKEY	Assessed prevalence and correlates of comorbid Impulse Control Disorders (ICDs) in BD-I in remission states	N=124	Prevalence of ICD=27%; MC was pathologic skin picking. Intermittent explosive disorder, trichotillomania are also common. SUD comorbidity, suicide attempts and frequent depressive episodes should warn the clinician to suspect ICD comorbidity in BD
Chang et al., 2012	TAIWAN	Assessed anxiety disorder comorbidity rate in Han Chinese in Taiwan	N=325 [BD-I=120; BD-II=205]	BD-II patients are twice likely to report comorbid anxiety disorders

BD-Bipolar Disorder, BD-NOS-BD-Not Otherwise Specified, AD-Anxiety Disorders, OCD-Obsessive-Compulsive Disorder, ADHD-Attention Deficit Hyperactivity Disorder, CD-Conduct Disorder, ODD-Oppositional Defiant Disorder, SUD-Substance Use Disorders, PD-Panic Disorder, SAD-Social Anxiety Disorder, PTSD-Post-Traumatic Stress Disorder

Table 5: Effect of adherence on course of bipolar disorder in Asia:

Author / Year	Country	Method / Setting	Sample size	Salient findings
Khess et al., 1997	INDIA	Four-year follow-up of first-episode manic patients	N=32	Poor compliance to treatment is associated with readmissions
Overdamp et al., 2001	TURKEY	Life chart review of BD patients	N=108	Family support along with good adherence improves functioning and outcome
Yen et al., 2005	TAIWAN	Relationships between insight and adherence in schizophrenic and bipolar subjects	BD= 65	Poor insight leads to poor adherence
Chopra et al., 2006	INDIA	Naturalistic follow-up of BD patients for 8.5 years	N=34	Poor adherence associated with rapid cycling
Strakowski et al., 2007	Cross- national (US vs. Taiwan)	Prospective follow-up of BD-I patients after first manic episode	Cincinnati=96, Taipei=46	Taiwan patients exhibited better adherence patterns
Taj et al., 2008	PAKISTAN	Questionnaire based cross-sectional study of factors associated with non-adherence in bipolar patients in a tertiary care hospital	N=23	Sedation, forgetting medications, higher cost of medications, poor psychoeducation are causes of non-adherence
Tang et al., 2010	TAIWAN	Assessed one-year post-hospital medical costs in bipolar patients using National Health Insurance database	Covered the years 2006-2007	Annual medical costs due to relapses were 7.6 times higher than the per capita insurance

N-Sample size, BD-Bipolar Disorder

Table 6: Effect of sleep on course of bipolar disorder in Asia:

Author, Year	Country	Method / Setting	Sample Size	Findings
Ahn et al., 2008	KOREA	Compared chronotype distribution between bipolar I disorder and schizophrenia using Composite Scale of Morningness (CSM)	BD-I=92, Schizophrenia=113, Controls =95	BD-I pts showed a significantly greater preference for 'eveningness' chronotype (including delayed sleep timing) than control individuals
Lee et al., 2011	KOREA	Assessed sleep quality and association with seasonality of affective symptoms in Delayed Sleep Phase Syndrome (DSPS) patients	DSPS=327, Controls=331;	DSPS and SAD may share a pathophysiological mechanism causing delayed circadian phase leading to seasonal worsening of mood disorders
Wang et al., 2014	TAIWAN	Assessed Sleep complaints and memory in psychotropic drug- free euthymic patients with bipolar disorder.	N=22 ; Controls=44	Quality of sleep and memory function of the euthymic and drug- free BD patients were significantly poorer than those of the controls

N-Sample size, BD-Bipolar Disorder, DSPS-Delayed Sleep Phase Syndrome, SAD-Seasonal Affective Disorder

Table 7: Effect of seasons on course of bipolar disorder in Asia:

Author, Year	Country	Method/Setting	Sample characteristic	Findings
Yang et al., 2013	TAIWAN	Examined effects of age, sex, index admission, and predominant polarity on bipolar disorder seasonality in a nationwide population	BD=9619	1.Polarity of index episode determined seasonality of relapses 2.Females expressed seasonality for depressive recurrences and males for manic recurrences 3.Depressive PP exhibited greater seasonality 4. Young adults had greater seasonality than middle-aged patients.
Lee et al., 2002	TAIWAN	Retrospective study; assessed seasonal variations in bipolar disorder admissions and the association with climate	N=15,060	Certain seasons were associated with particular types of admissions. Spring/Summer for mania, early winter for depression, early spring for mixed episodes.
Rajkumar and Sarkar, 2015	INDIA	Retrospective review of seasonality of admissions for Mania in BD;	covered four years (2010-2013)	Peak admissions for mania during late autumn and spring seasons; male sex and age >25 years were associated with such seasonality

N-Sample size, BD-Bipolar Disorder, PP-Predominant Polarity