Long-Term Course

3

3.1 Predominant Polarity

Historically, the first note on polarity was made in the early 1960s when Leonhard reported that 17.9 % of patients had a manic and 25.6 % had a depressive predominant polarity, while the rest of the patients had similar occurrence of the two poles (Leonhard 1963). However, the concept was formulated by Jules Angst (1978).

Recently, the concept of predominant polarity has been introduced to further characterize the subtypes of bipolar disorders, especially in terms of long-term prognosis, and to assist clinicians in the long-term therapeutical design (Judd et al. 2003; Colom et al. 2006; Quitkin et al. 1986). Several attempts to develop an operationalized concept have been published (Rosa et al. 2008; Vieta et al. 2009; Pacchiarotti et al. 2013; Osher et al. 2000; Daban et al. 2006; Baldessarini et al. 2012b). Some authors suggested that having more lifetime episodes of a given polarity would be sufficient to determine the predominant polarity (Henry et al. 1999; Osher et al. 2000; Colom et al. 2006; Forty et al. 2009; Gonzalez-Pinto et al. 2010a). Eventually it has been suggested that a reliable definition of predominant polarity should demand that at least two-thirds of episodes belong to one of the poles (Colom et al. 2006). Further research confirmed the validity of this approach (Baldessarini et al. 2012b; Rosa et al. 2008; Vieta et al. 2009; Pacchiarotti et al. 2013; Nivoli et al. 2011b; Garcia-Lopez et al. 2009; Mazzarini et al. 2009). This definition has been accepted by the International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of the course and outcome in bipolar disorders (Tohen et al. 2009). Even before research had recognized it, naturalistic data suggest that predominant polarity seems to be a major factor in determining the long-term treatment of BD patients in clinical practice (Nivoli et al. 2012). In this frame, it had been proposed to be included as a course specifier in DSM-5 (Colom and Vieta 2009), but this did not happen.

Two types of bipolar predominant polarity have been described: the depressive and the manic. Currently there are not enough data to support the presence of a third type of predominant polarity on the basis of the presence of mixed episodes (Tohen

K.N. Fountoulakis, *Bipolar Disorder: An Evidence-Based Guide to Manic Depression*, DOI 10.1007/978-3-642-37216-2_3

et al. 2009). Patients with predominant depressive polarity tend to experience depressive episodes at a frequency of at least 2:1 in comparison to manic episodes, while patients with predominant manic polarity experience the opposite pattern.

Almost half of the BD patients manifest a predominant polarity (Rosa et al. 2008; Baldessarini et al. 2012b; Mazzarini et al. 2009; Vieta et al. 2009); however, it seems that this percentage depends on the method and the sample (especially the stage of the illness). Of those with predominant polarity present, the majority (two-thirds) are classified as having depressive polarity vs. one-third with a manic polarity (Rosa et al. 2008; Nivoli et al. 2011b; Gonzalez-Pinto et al. 2010a; Colom et al. 2006; Mazzarini et al. 2009; Vieta et al. 2009). Other studies report a 50–50 ratio (Gonzalez-Pinto et al. 2010b; Rosa et al. 2008). The studies that included BD-II patients report a higher prevalence of the depressive predominant polarity (Rosa et al. 2008; Colom et al. 2006; Goikolea et al. 2007; Popovic and Vieta 2013), while those which incorporated samples of exclusively type I BD patients report a higher prevalence of the manic predominant polarity (Osher et al. 2000; Baldessarini et al. 2012a, b; Pacchiarotti et al. 2013; Mazzarini et al. 2009). Also, the studies that included a broader spectrum of BD patients tended to report a higher prevalence of the depressive predominant polarity (Alessandra et al. 2013; Garcia-Lopez et al. 2009; Popovic and Vieta 2013). This difference in percentages is probably caused by differences in the quality of the samples between studies reflecting the fact that later in the long-term course of BD depression prevails (especially in a chronic form) while mania is attenuated. It is interesting that a study from Israel is the only one to have reported a clear predominance of the manic pole (Osher et al. 2000).

A list of studies which report rates of predominant polarity in BD patients is shown in Table 3.1. It is not possible to calculate a weighted average since many publications probably have overlapping samples.

It should be noted however that if the number of days spent in a specific type of episodes is used to define the predominant polarity instead of the number of episodes, then the vast majority of BD patients will be classified as predominantly depressed (Judd et al. 2003; Perlis et al. 2005).

Depressive predominant polarity is related to more frequent ECT, longer latency time to correct the diagnosis since the first episode was more frequently depressive or mixed, more suicide attempts, more Axis-II comorbidity, history of mixed states, ever married and female sex (Rosa et al. 2008; Baldessarini et al. 2012b; Gonzalez-Pinto et al. 2010a; Nivoli et al. 2011a). In patients with a depressive predominant polarity, the depressive are both the first mood episode (Baldessarini et al. 2012b; Popovic et al. 2013; Rosa et al. 2008; Forty et al. 2009; Etain et al. 2012; Colom et al. 2006) as well as the index mood episode (Colom et al. 2006; Baldessarini et al. 2012b). A mixed onset of illness is also associated with a depressive predominant polarity (Baldessarini et al. 2012b), and more mixed episodes are observed in patients with depressive predominant polarity (Baldessarini et al. 2012b; Colom et al. 2006; Pacchiarotti et al. 2011, 2013). Melancholic features are very frequent (Daban et al. 2006). These patients also have a lifetime history with higher number of stressful life events, more suicide attempts (Colom et al. 2006; Baldessarini et al. 2012b; Gonzalez-Pinto et al. 2010b; Rosa et al. 2008) and more family history of affective disorders (Gonzalez-Pinto et al. 2010b).

Table 3.1 List of papers reporting rates of predominant polarity in BD patients. It is not possible to calculate a weighted average since many publications probably have overlapping samples

Publication	Sample size *N*	DPP *N* (%)	MPP *N* (%)	Definition of PP	Comments
Daban et al. (2006)	300	128 (42.7 %)		>50 %	
Colom et al. (2006)	224	135 (60.3 %)	89 (39.7 %)	≥2/3	Pts with predominant polarity only
Osher et al. (2000)	71	12 (16.9 %)	39 (54.9 %)	>50 %	BD-I only
Goikolea et al. (2007)	325	65 (20.0 %)	48 (14.8 %)	≥2/3	Prospective 10-year follow-up
Rosa et al. (2008)	149	45 (30.2 %)	47 (31.5 %)	≥2/3	
Forty et al. (2009)	552	238 (43.1 %)	215 (38.9 %)	>50 %	BD-I only
Garcia-Lopez et al. (2009)	296	71 (23.9 %)	65 (21.9 %)	≥2/3	Prospective follow-up time: 1–4 years
Mazzarini et al. (2009)	124	22 (17.7 %)	47 (37.9 %)	≥2/3	BD-I only
Vieta et al. (2009)	788	269 (34.1 %)	98 (12.4 %)	≥2/3	BD-I only
González-Pinto et al. (2010a, b)	169	51 (30.1 %)	44 (26.0 %)	>50 %	Prospective BD-I
Koyuncu et al. (2010)	70	30 (42.9 %)	27 (38.6 %)	>50 %	
Nivoli et al. (2011a, b)	604	143 (23.7 %)	114 (18.9 %)	≥2/3	
Pacchiarotti et al. (2011)	134	28 (21.1 %)	50 (37.3 %)	≥2/3	BD-I
Baldessarini et al. (2012a, b)	928	199 (21.4 %)	290 (31.3 %)	≥2/3	BD-I
Pacchiarotti et al. (2013)	187	18 (9.6 %)	30 (16.0 %)	≥2/3	BD-I inpatients
Popovic et al. (2013); Nivoli et al. (2013)	604	143 (55.6 %)	114 (44.4 %)	≥2/3	

DPP depressive predominant polarity, *MPP* manic predominant polarity, *PP* predominant polarity, *>50 %* PP defined as higher rate of either pole, *≥2/3* PP defined as at least 2/3 of episodes belonging to a specific pole

On the contrary, the predominant manic polarity is associated with an earlier age at onset, initial manic episodes and psychotic episodes, more frequent psychotic symptoms, cognitive impairment, more drug abuse, higher education and more family psychiatric history studies (Baldessarini et al. 2012b; Popovic et al. 2013; Forty et al. 2009; Gonzalez-Pinto et al. 2010a; Colom et al. 2006; Daban et al. 2006; Martinez-Aran et al. 2004; Post et al. 2003). Also in the beginning the manic predominant polarity is related to more hospitalizations, although this seems to reverse later in the course of the illness (Gonzalez-Pinto et al. 2010b). One study suggested that the manic predominant polarity is associated with rapid cycling (Vieta et al. 2009); however, subsequent studies rejected this suggestion (Nivoli et al. 2013; Vieta et al. 2009; Baldessarini et al. 2012b; Rosa et al. 2008; Popovic et al. 2013). Similarly, there does not seem to be any relationship of polarity and seasonality (Goikolea et al. 2007; Colom et al. 2006; Popovic et al. 2013).

There does not seem to exist any differences between the two types of predominant polarity concerning the psychiatric comorbidity (Colom et al. 2006; Popovic et al. 2013; Baldessarini et al. 2012b; Nivoli et al. 2013; Murru et al. 2011; Koyuncu et al. 2010; Mazzarini et al. 2009). It is interesting to note that some authors reported that the depressive predominant polarity is associated with the female gender (Nivoli et al. 2011a; Baldessarini et al. 2012b) and the manic with male (Popovic et al. 2013) although other studies did not confirm this finding (Baldessarini et al. 2012b; Vieta et al. 2009; Colom et al. 2006; Osher et al. 2000; Rosa et al. 2008; Gonzalez-Pinto et al. 2010a; Mazzarini et al. 2009). The depressive predominant polarity group has been associated with a greater likelihood of having been married (Gonzalez-Pinto et al. 2010a; Baldessarini et al. 2012b).

There are no clear differences between the manic and depressive groups in the long-term alcohol abuse or other substance abuse although there seems to be a tendency for the manic group to do better, especially in the long term (Gonzalez-Pinto et al. 2010a, b). A history of substance abuse preceding the first episode has been reported to correlate with a manic predominant polarity (Colom et al. 2006; Popovic et al. 2013).

Disability does not seem to differ between the two groups either (Colom et al. 2006), although in general the predominantly depressive group has a worse prognosis (Gonzalez-Pinto et al. 2010b) including the response to treatment of the acute bipolar depression phase (Vieta et al. 2009). Probably, the depressive predominant polarity is associated with a higher number of suicide attempts (Baldessarini et al. 2012b; Colom et al. 2006; Gonzalez-Pinto et al. 2010a; Popovic et al. 2013; Mazzarini et al. 2009), but one study suggested that a 'mixed episode polarity' is considerably more related to suicidality (Baldessarini et al. 2012b).

3.2 Seasonality

Seasonality is a classic rhythmic disturbance in mood disorders. It is generally believed that autumn and winter are related to depression and spring and summer to mania. Some relationship of seasonality to atypical features of depression is also believed to exist, especially concerning the manifestation of fatigue in combination

with craving for carbohydrates and oversleeping in winter (Simonsen et al. 2011; Shin et al. 2005).

Somewhere between 15 % and 50 % of bipolar patients are reported to manifest some type of seasonal variation of symptomatology, with 25 % being the most probable percentage (Faedda et al. 1993; Goikolea et al. 2007; Hunt et al. 1992; Shand et al. 2011). Even a genetic marker has been proposed with genetic variants in the NF1A gene region predisposing to seasonal pattern of mania (Lee et al. 2012).

Two seasonal variations, which are opposing, have been described: fall–winter depression with or without spring–summer mania or hypomania and spring–summer depression with or without fall–winter mania or hypomania (Faedda et al. 1993). Most studies support the first subtype (Lee et al. 2007; Clarke et al. 1999; Murray et al. 2011; Partonen and Lonnqvist 1996; Peck 1990; Walter 1977; Parker and Walter 1982; Mulder et al. 1990), but some authors suggest that seasonality is purely idiosyncratic and no universal patterns can be traced across patients (Hunt et al. 1992; Bauer et al. 2009; Eastwood and Stiasny 1978).

It is reported also that lithium levels in plasma peak in summer (Cusin et al. 2002; Wilting et al. 2007), especially in males (D'Mello et al. 1995), and this difference could be up to 25 % (Medhi et al. 2008). It seems this phenomenon is part of a larger seasonal variation in the metabolism of electrolytes (Mellerup and Mellerup 1984).

Although it has been reported that there are no demographic differences between BD patients with seasonality and those without (Goikolea et al. 2007), certain subtypes of BD patients are reported to manifest specific seasonality in aspects of symptoms, like younger patients having trouble with the law mainly between August and January (London and Taylor 1981). However, an opposite pattern concerning aggression has also been reported (D'Mello et al. 1995; Volpe et al. 2008), and suicidality might be more often in winter (Volpe et al. 2008). Also, seasonal BD patients are reported to be more often BD-II with depressive predominant polarity (Goikolea et al. 2007); however, the fact that BD-II patients tend to be chronically depressed often seems to attenuate any seasonal effect (Friedman et al. 2006).

It is well known that females experience premenstrual changes in mood and behaviour, and these changes might be more pronounced in mood disorder patients. BD female patients are reported to experience seasonal and premenstrual changes in mood and behaviour regardless of their mood episodes (Choi et al. 2011). Depression during autumn–winter is the most reported seasonality trend among females (Murray et al. 2011) with admission to hospital with mania being more frequent in late summer and early autumn (Symonds and Williams 1976). A seasonal trend is also reported for admissions for depression with the highest peak in November for women and in April for men (Morken et al. 2002). However, other reports suggest that women demonstrated a bimodal seasonal distribution, with peak admission rates in spring and fall, while among men, the admission rate peaked in the springtime (D'Mello et al. 1995). Premenstrual and mood symptoms are associated with each other and are more pronounced in BD-II in comparison to BD-I (Choi et al. 2011). A significant elevation of lithium plasma levels in summer was reported for

males alone (D'Mello et al. 1995); however, a more recent study suggested the same for females alone (Cusin et al. 2002). There are also negative reports on the relationship of gender with seasonality (Myers and Davies 1978; Walter 1977).

It is interesting that lithium might induce subsensitivity to light since it was reported to significantly raise the dark adaptation threshold which is a measure of night vision (Carney et al. 1988b). Of course, it is unlikely that lithium exerts its antimanic effect through this mechanism.

It has also been reported that exposure to natural light appears to have a substantial effect on well-being in twins with BD (Hakkarainen et al. 2003), while admission rates because of acute mania were reported to be higher in the sunnier months and in months with a greater average day length (Carney et al. 1988a).

Also such an exposure was reported to reduce hospital stay in bipolar depression (Benedetti et al. 2001), although another study reported no correlation of depressive symptoms to sunshine and cloudiness. That latter study reported a strong correlation of depression with temperature (Christensen et al. 2008).

Although there is one negative (Dauphinais et al. 2012) and one positive trial (Deltito et al. 1991) on the usefulness of light therapy against bipolar depression, there are also reports on mania or hypomania induced by light therapy (Kantor et al. 1991; Labbate et al. 1994; Pande 1985; Chan et al. 1994).

Concerning location, there are three major zones: the northern and the southern hemispheres and the tropics. There are no differences between the northern and southern hemispheres when taking into consideration the reversed seasonality. Comparing studies from the two hemispheres helps in controlling for confounding variables such as public holidays.

In the USA, admissions to hospital (irrespective of type of episode) are reported to peak in summer (Myers and Davies 1978) or in spring (D'Mello et al. 1995). Manic episodes seem to peak in early spring, with a nadir in late fall. Mixed episodes might peak in late summer with a nadir in November (Cassidy and Carroll 2002). In Norway admissions specifically for bipolar depression had the highest peak in November for women and for men in April (Morken et al. 2002). A study from Finland reported that there was no seasonal variation concerning admissions; however, the first admission for a depressive compared with a manic episode occurred significantly more often in the autumn (Partonen and Lonnqvist 1996). One study from Hungary (Rihmer 1980) and one from Greece (Frangos et al. 1980) reported that hospitalizations for mania might happen more often in spring and autumn and for depression mainly in summer and winter. In Israel admission rates were higher during spring and summer (Shapira et al. 2004). In Canada there was no statistically significant seasonal pattern of admissions, but for mixed state admissions peaked in the summer (Whitney et al. 1999). In the UK there was a peak of admissions for mania only concerning females during August–September (Symonds and Williams 1976), where an analysis of the Wales data suggested a peak during spring–summer (Walter 1977). The STEP-BD study provided some but rather unclear data concerning a greater prevalence of bipolar depression in northern vs. southern study sites. Seasonal peak prevalence rates of depression differ by region (Friedman et al. 2006).

Studies reporting data from countries located in the southern hemisphere reported a spring–summer peak of admissions for mania (Sayer et al. 1991; Jones et al. 1995; Mulder et al. 1990; Parker and Walter 1982), but there was significant variability and heterogeneity of the results.

Studies comparing data coming from different hemispheres suggest there is no difference between them and also that no real seasonality was present (Bauer et al. 2009; Silverstone et al. 1995). One of them suggested an autumn preponderance of depressive episodes in both hemispheres (Silverstone et al. 1995).

The studies reporting data from the tropical zone mostly do not suggest the presence of a seasonal trend (Abdul-Rahim et al. 1992; Daniels et al. 2000; Jain et al. 1992). One study from Taiwan suggested the presence of a typical seasonal pattern with winter depression and summer manias (Lee et al. 2007).

Meteorological conditions have been studied in order to identify possible causative factors responsible for a seasonal pattern in BD. Light was a probable candidate factor, and supersensitivity to light has been proposed as a trait marker for BD (Lewy et al. 1985). Data from Korea suggested that the mean monthly hours of sunshine and sunlight radiation correlated significantly with manic episodes (Lee et al. 2002). Two papers from Brazil correlate symptoms not with seasons but with climate variables, with sunshine, temperature, rainfall and humidity being more important for manic episodes (Volpe et al. 2010; Volpe and Del Porto 2006). Humidity, barometric pressure and atmospheric ionization were the factors identified in a study from the UK (Mawson and Smith 1981).

Taken together, the above studies suggest that there are some data suggesting a peak of episodes and hospital admissions because of mania during spring to autumn and because of depression during the cold period of the year, but this was not consistent across studies. It is even more interesting that the data from the southern hemisphere report similar seasonal distribution. This is supported also by the reports from the tropical zone, where a similar seasonality pattern seems to exist, while in that zone the climate changes are not great between seasons.

3.3 Rapid Cycling

Although as early as 1911, Eugen Bleuler described a 50-h cycle in a mood patient (Zis and Goodwin 1979), and Emil Kraepelin commented on the relationship between cycle length and illness progression in 1921 (Kraepelin 1921), the concept of rapid cycling appeared for the first time in the 1970s in a landmark paper by Dunner and Fieve (1974). These authors also gave a definition of rapid cycling which includes the occurrence of at least four major depressive, manic, hypomanic or mixed episodes during a 12-month period, and this approach stands until today. Since then, several authors have discussed and disputed this definition, and they also described subpopulations of patients with even higher frequency of episodes. In general, the classic rapid cycling includes cycles of weeks to months of duration. Ultrarapid cycling is reported when mood cycling has frequency of weeks to days and ultradian cycling when there is significant mood variation within a 24-h period

(Kramlinger and Post 1996). Other terms include 'ultra-ultrarapid' and 'ultradian rapid' and refer to weekly or daily cycling which is not uncommon in BD patients (Kramlinger and Post 1996). So far, however, the data are limited and do not permit definite conclusions on the clinical phenomenology and nature of these mood swings (Barrios et al. 2001; Kramlinger and Post 1996; Maggini et al. 2000; Tillman and Geller 2003).

It is extremely interesting that a retrospective study which analysed 570 patient records from the 1960s, 1970s and 1980s reported that very rapid mood fluctuations were absent among bipolar patients in 1960s but were evident in the 1970s and the 1980s (Wolpert et al. 1990). However, this is not entirely true. Apart from Eugen Bleuler's report, during the last couple of centuries, there were many case reports, mainly of a 48-h cycle (Bunney et al. 1965; Jenner et al. 1967).

Recognition of this condition might be difficult especially for clinicians without this nosological entity embedded in their mind. This is because the higher the frequency, the lower the possibility patients are free of symptoms for prolonged periods. Essentially rapid cycling patients might not ever achieve complete remission during the interepisode intervals, and this leads to significant disability, but also often leads to a personality-like clinical picture. The correct diagnosis might elude for prolonged periods of time the diagnosis of a personality disorder is often put, and as a consequence treatment is inappropriate. This might be one of the reasons rapid cycling was rarely put as a diagnosis before its 'official' recognition in the mid-1970s, while today up to one-tenth or one-third of inpatients might be diagnosed as manifesting it.

Even today much confusion still exists. For example, both classification systems classify ultrarapid cases within the mixed episode category rather than rapid cycling. Essentially ultrarapid cycling is the only way a full-blown manic/hypomanic together with a full depressive episode can coexist in the same patient during the same time period, as classification systems require. This is in sharp contrast to the Kraepelinian proposal concerning the three independent factors underlying mood episodes (mood, cognition and physical activity; see the 'mixed episodes' part of this book). Even when the correct diagnosis is put, treatment is complex and difficult and requires advanced skills from the side of the therapist (Bauer et al. 1994; Fountoulakis et al. 2012).

Taking into consideration the orientation of the US National Institute of Mental Health (NIMH) to develop neurobiologically based Research Domain Criteria (RDoC) (Insel et al. 2010) and thus integrating genetic, environment, biological and experiential components in the classification (Cuthbert and Insel 2013), RC could serve as a model. Eventually this approach will lead to 'personalized psychiatry', also known as 'stratified psychiatry' (Schumann et al. 2013). However, there are no sufficient data yet to specifically utilize RC in order to develop such an advanced classification approach (Valenti et al. 2012; Mahon et al. 2013; Rovai et al. 2013).

The exact proportion of bipolar patients manifesting a rapid cycling course is not known. In the first ever study, Dunner and Fieve (1974) reported a prevalence of 13 %. In accord with this, data from most subsequent studies suggest a 5–33.3 % cross-sectional prevalence (Azorin et al. 2008; Coryell et al. 1992; Cruz et al. 2008;

Garcia-Amador et al. 2009; Kukopulos et al. 1980; Nurnberger et al. 1988; Schneck et al. 2004, 2008; Lee et al. 2010) and a 25.8–43 % lifetime prevalence (Coryell et al. 2003; Dittmann et al. 2002; Hajek et al. 2008; Yildiz and Sachs 2004; Lee et al. 2010). However, both lower and higher rates have been reported by a significant number of papers. These rates are as low as 4 % (Avasthi et al. 1999), and the higher ones distribute smoothly up to more than 50 %. Depending on the site of the research and probably the study sample, methodology and definition, rates of 25.8 % (Coryell et al. 2003), 30 % for 'frequent mood episodes' (Wells et al. 2010), 40 % (Dittmann et al. 2002), 33.3 % for primary care and 26.9 % for tertiary care samples (Hajek et al. 2008), 43 % for tertiary care (Yildiz and Sachs 2004), 33.3 % for lifetime and 40 % for year prevalence (Lee et al. 2010) and 56 % in a convenient clinical sample (Cowdry et al. 1983) have been published. In the multinational WAVE-BD study, prevalence rates ranged from 6.6 % (Romania) to 28.7 % (Turkey) (Vieta et al. 2013a).

One analysis from the National Comorbidity Survey Replication (NCS-R) study suggested a prevalence of 44 % (MacKinnon et al. 2003a), while another calculation on the basis of the same data reported 33.3 % lifetime and 50 % year prevalence of rapid cycling (Nierenberg et al. 2010). Probably this last estimation is closer to the reality at least for the bipolar population as shaped during the most recent decade. It is also interesting to note that in convenient clinical samples under follow-up, there seems to be a gradual improvement which contaminates epidemiological data. In one study it has been found that 32 % of the patients were manifesting rapid cycling at entry but only 5 % after 1 year (Schneck et al. 2008).

As mentioned above, the relationship between cycle length and illness progression was discussed for the first time by Emil Kraepelin (1921). Later the shortening of the cycle by passing the years and accumulation of episodes has been documented (Roy-Byrne et al. 1985; Angst 1981). Although it has been proposed that there is a ceiling effect and the frequency of the cycle might stabilize after four to six episodes (Goodwin and Jamison 1990), the data from the Stanley Bipolar Treatment Network suggest that rapid cycling characteristics are continuously increasing without any indication of a ceiling effect (Kupka et al. 2003). More recent studies suggest that rapid cycling constitutes a worsening of BD and develops later in the course of illness (Calabrese et al. 2001) possibly following a sensitization process triggered by antidepressant use or thyroid dysfunction, in patients with a depression–mania-free interval course and cyclothymic temperament (Azorin et al. 2008). At least in some patients, rapid cyclicity, spontaneous or induced, once established, becomes for many years a stable rhythm linked more to endogenous and to a lesser degree to environmental factors (Koukopoulos et al. 2003). In contrast to the above, apart from episode frequency, there are no solid data to support rapid cycling patients as a specific subgroup and suggest that in many cases rapid cycling is a transient phenomenon and not the final and stable stage of the illness (Bauer et al. 2008; Coryell 2005; Coryell et al. 1992, 2003; Kilzieh and Akiskal 1999).

Depression seems to relate very closely to rapid cycling in a variety of ways. There is a bulk of data suggesting that in most patients, rapid cycling is developed from an index episode of depression (Wehr et al. 1988; Roy-Byrne et al. 1985;

Perugi et al. 2000), and patients with depressive onset of bipolar illness are at higher risk to develop a rapid cycling course later (Garcia-Amador et al. 2009; Azorin et al. 2008; Perugi et al. 2000). Additionally, it is reported that depression often dominates the long-term clinical picture (Coryell et al. 2003; Goldberg et al. 2004; Lee et al. 2010; Schneck et al. 2004), although a manic predominance has also been reported (Kupka et al. 2005). The reason behind this relationship between depression and rapid cycling is not well understood; however, treatment with antidepressants and female gender might act as mediators (Ernst and Goldberg 2004; Schneck et al. 2008). It is well known that women are more likely to manifest a predominant depressive polarity (Nivoli et al. 2011a; Baldessarini et al. 2012b; Rosa et al. 2008), which in turn increases the likelihood of antidepressant treatment, and this creates a complex relationship with no clear cause and effect (Kilzieh and Akiskal 1999).

A closer look on the available data suggests an even more complex picture. In rapid cycling patients, more frequent cycling between depression and hypomania within the index episode has been reported (Coryell et al. 1992), and salient manic features are often present during depressive episodes (Goldberg et al. 2004, 2009). This puts forward the question whether at least some of these episodes are essentially mixed, although they might not fulfil standard diagnostic criteria (Vieta and Valenti 2013a). Conflicting reports and suggestions on this issue have been published with one paper suggesting that patients with a mixed episode at onset are highly unlikely to develop rapid cycling (Perugi et al. 2000) and several (with authors overlapping) suggesting the opposite (Azorin et al. 2008, 2009, 2012; Perugi et al. 1997). The failure of the recently released DSM-5 to capture the essence of mixed depressive states (e.g. agitated depression) significantly adds to the diagnostic and therapeutic uncertainties (Koukopoulos and Sani 2013; Koukopoulos et al. 2013).

Labile emotion is very frequent in rapid cycling patients and often might take the form of a soft ultrarapid pattern (Coryell et al. 1992). In this later case when the cycle lasts less than 24 h, the majority of switches (two-thirds) occur between morning and evening, and they usually follow a pattern from depression into mania/hypomania or euthymia, while only the remaining one-third follows the opposite direction. Likewise, switches that occur following the evening to the next morning pattern are correspondingly opposite (Feldman-Naim et al. 1997; Wilk and Hegerl 2010). On the other hand when the cycle lasts more than 24 h, the previously mentioned parameters (time of the day plus polarity of the episode) do not follow a systematic pattern anymore (Wilk and Hegerl 2010).

Although there is a general impression that rapid cycling is related to BD-II (Baek et al. 2011; Calabrese et al. 2001; Hajek et al. 2008; Kilzieh and Akiskal 1999; Baldessarini et al. 2000; Bauer et al. 1994; Coryell et al. 1992; Kukopulos et al. 1980; Perugi et al. 2000), the data from the Stanley Bipolar Treatment Network suggest that on the contrary it is weakly related to BD-I subtype (Kupka et al. 2003, 2005), and other studies suggest there is no preference (Garcia-Amador et al. 2009; Mackin 2005; Maj et al. 1994).

The literature on the clinical correlates of rapid cycling is rather consistent and suggests it is related to a greater number of total episodes and greater number of hospitalizations (Avasthi et al. 1999; Bauer et al. 1994; Coryell 2005; Kupka et al.

2005), with no symptom-free intervals between episodes and cyclothymic temperament (Azorin et al. 2008), worst long-term course (Mackin 2005; Coryell 2005; Kilzieh and Akiskal 1999), higher overall comorbidity (MacKinnon et al. 2003a, b; Hajek et al. 2008; Lee et al. 2010) and more severe disability (Hajek et al. 2005; Lee et al. 2010; Schneck et al. 2004; Wells et al. 2010), although there is one study suggesting no relationship to increased comorbidity (Wells et al. 2010). Most data reported so far agree that rapid cycling patients manifest onset of their illness at a younger age (Azorin et al. 2008; Bowden et al. 1999; Ernst and Goldberg 2004; Hajek et al. 2008; Lee et al. 2010; Lin et al. 2006; MacKinnon et al. 2003a; Schneck et al. 2004; Wells et al. 2010; Fountoulakis 2012) even before the age of 17 (Coryell et al. 2003). Two papers report later age at onset for rapid cycling patients (Baldessarini et al. 2000; Serretti et al. 2002) and some others no difference in age of onset (Bauer et al. 1994; Coryell et al. 1992; Kukopulos et al. 1980; Maj et al. 1994; Perugi et al. 2000; Schneck et al. 2008). In children and adolescents BD very often follows a rapid or ultrarapid course (Geller et al. 1998; Findling et al. 2001), and this might mean that there is great heterogeneity concerning the age-of-onset effect in the development of rapid cycling. One paper reports that the duration of illness is not longer in rapid cyclers, thus disputing the earlier onset of bipolar illness suggestion (Yildiz and Sachs 2004).

Alcohol and drug abuse are consistently reported to be more frequent in this group (Cruz et al. 2008; Kupka et al. 2003, 2005; MacKinnon et al. 2003a). One paper suggests the more frequent presence of history of childhood physical or sexual abuse (Kupka et al. 2005). Rapid cycling patients also manifest more suicide attempts (Azorin et al. 2008, 2010; Coryell et al. 2003; Cruz et al. 2008; Goldberg et al. 2004; Hajek et al. 2008), but this might be because of more frequent and more severe attempts in the same percentage of persons in comparison to non-rapid cyclers (Garcia-Amador et al. 2009). A limited number of papers suggest such a correlation with suicidality does not exist (Kilzieh and Akiskal 1999; MacKinnon et al. 2003a; Wells et al. 2010).

Overall, close relationship to depression could be the cause of all of the above. But also, at least partially the above characteristics could be explained by the fact that probably because of earlier onset of bipolar illness, rapid cycling patients manifest longer duration of illness in comparison to the same age patients without rapid cycling, and this overloads them in a variety of ways (Azorin et al. 2008; Avasthi et al. 1999; Maj et al. 1994; Berk et al. 2011; Vieta et al. 2013b).

Emotional lability and soft ultrarapid cycling within rapid cycling are not uncommon (Coryell et al. 1992). In cases of ultrarapid cycling with cycle length less than 24 h, two-thirds of switches occurring between morning and evening are from depression into mania/hypomania or euthymia and one-third in the opposite direction. Similarly, switches occurring between evening and the next morning are, respectively, opposite (Feldman-Naim et al. 1997; Wilk and Hegerl 2010). When the cycle length is greater than 24 h, the time of the day and the polarity of the episode seem to be random (Wilk and Hegerl 2010).

More severe forms of premenstrual tension syndrome, when present, might accelerate cycling in female BD patients (Price and DiMarzio 1986). In

retrospective studies of rapid cycling, the presence of severe premenstrual syndrome might constitute a confounding variable (Dias et al. 2011). It is reported that rapid cycling is found more often during the menopause (Dunner and Fieve 1974); however, most data do not support any relationship between the female reproducing cycle and phase and rapid cycling (Bauer et al. 1994; Leibenluft et al. 1999).

The outcome of rapid cycling BD is variable. It is well known that a subgroup of mood patients becomes 'sensitized', after repeated mood episodes, and the threshold for the manifestation of new episodes becomes progressively lower leading to more frequent relapses. Eventually the episodes are triggered spontaneously. This 'kindling' phenomenon is considered to be analogous to that observed in epilepsy (Post et al. 1986; Post 1992). Some authors suggest that rapid cycling is the result of a 'kindling' mechanism which results in shorter cycles and higher frequency of episodes after the experiencing of repeated episodes (Cutler and Post 1982; Goldberg and Harrow 1994; Post 1992; Zis and Goodwin 1979); however, there are some data against such an assumption, suggesting no relationship of rapid cycling to number of previous episodes (Turvey et al. 1999; Hammen and Gitlin 1997).

It is reported that one-third of patients manifest complete remission for at least the past year, 40 % continue being rapid cyclers with severe episodes, while 14 % remain rapid cycling but with attenuated episodes. A significant proportion of patients (13 %) might become long cyclers (Koukopoulos et al. 2003). However, as already mentioned before, in many cases rapid cycling is a transient phenomenon rather than the final and stable stage of the illness (Bauer et al. 2008; Coryell 2005; Coryell et al. 1992, 2003; Kilzieh and Akiskal 1999). Maybe patients with an initial cycle pattern of depression–mania/hypomania-free interval have a worse outcome, while patients with an initial cycle pattern of mania/hypomania–depression-free interval might do better (Koukopoulos et al. 2003). This pattern was not observed in other studies, and it is a matter of debate (Bauer et al. 1994; Coryell et al. 1992; Maj et al. 1994).

A robust finding in the literature is that females constitute the majority of patients with rapid cycling (Arnold 2003; Bauer et al. 1994; Cruz et al. 2008; Schneck et al. 2004; Tondo and Baldessarini 1998; Wehr et al. 1988; Yildiz and Sachs 2004), with their proportion to be reported as high as 92 % (Wehr et al. 1988). However, the most realistic estimations suggest that it averages around 72 % (Bauer et al. 1994). The true risk is somewhat different and is reported to be inconsistently higher among women (29.6 %) than among men (16.5 %) (Tondo and Baldessarini 1998). This was confirmed by a recent meta-analysis (Kupka et al. 2003). Only one study has reported a higher prevalence in males (Joffe et al. 1988), and some other reported equal rates between males and females (Maj et al. 1994; Baldassano et al. 2005; Serretti et al. 2002; Joffe et al. 1988). In one of them the study populations suffered from a too large proportion of males (Baldassano et al. 2005). In another study, the proportion of women was greater than the proportion of men only among patients with eight or more episodes per year (Kupka et al. 2005).

This correlation between rapid cycling and female gender might stem from a variety of factors, including the menstrual cycle and the higher risk of hypothyroidism in females. Also there is a circular correlation of female gender with a number

Table 3.2 Prevalence of rapid cycling in BD patients

Publication	Prevalence	Sample size *N*	Rapid cycling *N* (%)	Comments
Kukopulos et al. (1980)	Current	434	86 (20 %)	
Nurnberger et al. (1988)	Current	195	29 (15 %)	
Coryell et al. (1992)	Current	919	46 (5 %)	
Schneck et al. (2004)	Current	456	91 (20 %)	STEP-BD
Azorin et al. (2008)	Current	1,090	86 (9 %)	
Cruz et al. (2008)	Current	3,089	535 (17.3 %)	EMBLEM
Garcia-Amador et al. (2009)	Current	305	55 (18 %)	
Coryell et al. (2003)	Lifetime	345	89 (25.8 %)	13.7 (±6.1) years follow-up
Dittmann et al. (2002)	Lifetime	152	41 (27 %)	2.5 years follow-up
Hajek et al. (2008)	Lifetime	240	80 (33.3 %)	Primary care sample
Yildiz and Sachs (2004)	Lifetime	197	84 (43 %)	Tertiary care sample
Schneck et al. (2008)	Current	1,742	562 (32 %)	STEP-BD
Total current		**8,230**	**1,490 (18.10 %)**	
Total lifetime		**934**	**294 (31.48 %)**	

of factors, including depression and cyclothymic temperament (Kilzieh and Akiskal 1999) as well as a more deleterious effect of antidepressant treatment in females specifically (Yildiz and Sachs 2003). The role of the bipolar type seems controversial since the gender effect was reported to be stronger in the BD-I type (Schneck et al. 2004; Yildiz and Sachs 2004), although BD-II is strongly related to female gender. Overall the mean weighted by sample size, annual/current prevalence rate is 18.10 %, while the lifetime prevalence is estimated to be 31.48 % (Table 3.2).

A variety of medical conditions might cause rapid cycling BD in previously mentally healthy individuals. These include subarachnoid haemorrhage (Blackwell 1991), closed head injury (Zwil et al. 1993) or focal temporal pole damage (Murai and Fujimoto 2003). Other conditions related to rapid cycling include homocystinuria (Awara et al. 2012), mild immune activation which seems to normalize with lithium treatment (Rapaport et al. 1999) and the effect of environmental temperature and its changes (Boker et al. 2008). One study correlated rapid cycling in BD-II to changes in the ventromedial prefrontal cortex (Narita et al. 2011).

The first report on the possible relationship between hypothyroidism and rapid cycling appeared in 1979 and was an observation that patients receiving lithium and thyroid substitution therapy were more prone to become rapid cyclers (Cho et al. 1979).

Today, hypothyroidism is considered by many authors to correlate with rapid cycling with around half of rapid cycling patients manifesting it (Cowdry et al. 1983; Bauer et al. 1990; Bauer and Whybrow 1990; Azorin et al. 2008; Kusalic 1992).

However, there are a number of methodological considerations including the medication status, recruitment bias, definition of hypothyroidism as well as the comparison groups. Also several authors report that no such a correlation exists (Joffe et al. 1988; Post et al. 1997; Maj et al. 1994; Bartalena et al. 1990; Coryell et al. 1992; Kupka et al. 2002; Oomen et al. 1996; Wehr et al. 1988), and this is supported by a meta-analysis (Kupka et al. 2003). On this basis thyroid augmentation is not recommended for the treatment of rapid cycling BD patients (Kilzieh and Akiskal 1999) although there are some but limited data in support of its efficacy (Kusalic 1992).

Although previous treatment with lithium was considered to be the cause of hypothyroidism in many cases, there seems to be at least some rapid cycling patients for whom this explanation is not valid (Bauer and Whybrow 1990; Fountoulakis et al. 2013; Bauer et al. 1990). However, the relationship between lithium treatment, female gender, hypothyroidism and rapid cycling (Bauer and Whybrow 1990; Cowdry et al. 1983; Fountoulakis et al. 2008; Bauer et al. 1990) seems to be more complex, since even in euthyroid rapid cycling patients but not in controls, short-term lithium treatment might cause grade III hypothyroidism (Gyulai et al. 2003). Also an association between the occurrence of thyroperoxidase antibodies and a history of rapid cycling has been reported (Oomen et al. 1996). However, another study disputed the presence of even this latent hypothyroidism (Joffe et al. 1988).

Conclusively, there are not sufficient data to support a direct link between rapid cycling and hypothyroidism. More research is needed especially in patients who have never received lithium.

It is widely accepted among clinicians that treatment of antidepressants, apart from the induction of the manic pole, might also cause cycle acceleration. However, this has not been solidly proven. The first case report of a possible antidepressant-induced rapid cycling appeared in 1956 and concerned the monoamine oxidase inhibitor iproniazid (Crane 1956). For the first time this issue was put forward systematically in the seminal paper of Wehr and Goodwin (1979). Since then many studies addressed this question both retrospectively and prospectively. A major problem is that many authors mix induction of the opposite pole by antidepressants with induction of rapid cycling and carry observations from switching to rapid cycling. The conclusions based on such an approach could not be considered to be valid, but often constitute the basis of discussions and reviews.

The classical picture is that rapid cycling may be precipitated by the use of antidepressants in more than 70 % of cases and maintained after their continuation (Wehr et al. 1988). More recent studies reported rates of antidepressant-induced rapid cycling range between 3 % and 50 % (Goodwin and Jamison 1990; Wehr et al. 1988; Yatham et al. 2003), and this wide range is probably because of methodological problems. It is suggested that such an induction happens mostly within the first year of antidepressant initiation (Altshuler et al. 1995). However, the data are rather inconclusive. The data from long-term retrospective studies are conflicting (Wolpert et al. 1990; Angst 1985; Lewis and Winokur 1982, 1987, 1989). All shorter-duration retrospective studies suggest an association between rapid cycling and antidepressant use (Kukopulos et al. 1980; Wehr et al. 1988; Altshuler et al. 1995), while one such study limited this association to female patients only (Yildiz and Sachs 2003).

On the contrary only two prospective studies suggest the presence of such an association (Wehr and Goodwin 1979; Koukopoulos et al. 2003), while three others were negative (Bauer et al. 2005, 2006; Coryell et al. 2003). The clinical profile of those rapid cycling patients supposedly induced by antidepressants is not reported to differ from the rest of rapid cycling population (Bauer et al. 1994) although females (Yildiz and Sachs 2003) and especially female BD-II patients might be overrepresented (Altshuler et al. 1995).

The conclusion of major reviews is that such an association is not supported by the data or it is overvalued (Kilzieh and Akiskal 1999; Coryell 2005; Grunze 2008; Mattes 2006). Also it has been proposed that the relationship of antidepressants with rapid cycling, female gender and possibly BD-II merely probably reflects the predominance of depression in rapid cyclers and consequently the predominance of antidepressant treatment (Coryell et al. 1992; Vieta and Valenti 2013b). Currently there are no data suggesting that other classes of agents (e.g. antipsychotics or antiepileptics) might induce rapid cycling.

Family studies suggest that patients with rapid cycling do not differ from the rest in terms of family load for mood disorders. Although there are some reports suggesting that they might have a stronger family loading of BD (Avasthi et al. 1999; Wehr et al. 1988) and maybe more frequently a relative with rapid cycling (MacKinnon et al. 2003a) and a close relationship to the presence of panic disorder, substance abuse and suicidality in the family (MacKinnon et al. 2003a, b; Vieta et al. 2004), these findings were usually not statistically significant, and essentially most of the data are clearly negative (Bauer et al. 1994; Coryell et al. 1992; Kilzieh and Akiskal 1999; Lish et al. 1993; Nurnberger et al. 1988; Fountoulakis and Akiskal 2008). A meta-analysis confirmed a lack of familial load for rapid cycling bipolar patients (Kupka et al. 2003).

In terms of specific genes, the Val66Met polymorphism (Green et al. 2006; Muller et al. 2006); the SNPs hCV11592756, rs2049045 and GT(n) (Muller et al. 2006) of the brain-derived neurotrophic factor (BDNF); the low activity allele variation in the COMT gene (Kirov et al. 1998; Papolos et al. 1998); the 5-HT transporter gene (Rousseva et al. 2003) and the haplotype GGAC of the circadian gene CRY2 (Sjoholm et al. 2010) have been associated with rapid cycling BD. One study concerning the low activity allele of the COMT gene was negative (Geller and Cook 2000). As a general conclusion from genetic studies, one can say that they are too few, with small study populations, and results need clarification and replication. In the future, it is important to control for a number of confounding factors like exposure to antidepressants, temperament, etc. In this frame, an interesting hypothesis suggests that temperament might act as the determining endophenotype while rapid cycling serves as an intermediate phenotype (Sayin et al. 2007; Mackinnon and Pies 2006; Insel and Cuthbert 2009).

Conclusively, rapid cycling is still an uncharted area. Around one-third of BD patients will experience rapid cycling at some time in their lives. A number of factors, including predominance of depression, treatment with antidepressants, female gender, refractoriness to lithium and hypothyroidism, seem to involve in the aetiopathogenesis or to shape the clinical manifestations and the long-term outcome. The

most proper definition of rapid cycling is still not available, since many patients manifest emotional lability which often takes the form of ultra or ultra-ultrarapid cycling, but they are often diagnosed as suffering from mixed episodes or personality disorders according to contemporary classification systems. It is highly likely that rapid cycling represents a worsening of the underlying disorder, which, in turn, leads towards a significant deterioration of clinical outcomes, more severe disability and increased suicidality. There are convincing data that rapid cycling represents a transitory period rather than a stable condition once it manifests. During those rapid cycling periods, patients are difficult to diagnose and to treat especially when the clinical picture resembles a personality disorder (Mackinnon and Pies 2006). Future research should clarify whether rapid cycling represents an exacerbation of emotional endophenotypes (e.g. affective temperaments) linked to disorders associated with affective dysregulation, such as BD.

References

Abdul-Rahim FA, Al-Sabai A, Al-Hamad AR, Bamgboye E (1992) The seasonality of mania: preliminary findings. Ann Saudi Med 12(5):472–475. doi:12-472 [pii]

Alessandra MA, Colom F, Pacchiarotti I, Murru A, Scott J, Valenti M, Mazzarini L, Mar Bonnin CD, Jose SM, Serretti A, Vieta E (2013) Treatment strategies according to clinical features in a naturalistic cohort study of bipolar patients: a principal component analysis of lifetime pharmacological and biophysic treatment options. Eur Neuropsychopharmacol 23(4):263–275

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L (1995) Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 152(8):1130–1138

Angst J (1978) The course of affective disorders. II. Typology of bipolar manic-depressive illness. Arch Psychiatr Nervenkr 226(1):65–73

Angst J (1981) Unsolved problems in the indications for lithium prophylaxis in affective and schizoaffective disorders. Bibliogr Psychiatry (161):32–44

Angst J (1985) Switch from depression to mania–a record study over decades between 1920 and 1982. Psychopathology 18(2–3):140–154

Arnold LM (2003) Gender differences in bipolar disorder. Psychiatr Clin North Am 26(3):595–620

Avasthi A, Sharma A, Malhotra S, Gupta N, Kulhara P (1999) Rapid cycling affective disorder: a descriptive study from North India. J Affect Disord 54(1–2):67–73. doi:S0165-0327(98)00135-9 [pii]

Awara MA, Zahid S, Elnenaei MO (2012) Rapid cycling bipolar affective disorder and recurrent strokes secondary to high blood homocysteine. J Ment Health. doi:10.3109/09638237.2012.670884

Azorin JM, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrenon S, Akiskal HS (2008) Factors associated with rapid cycling in bipolar I manic patients: findings from a French national study. CNS Spectr 13(9):780–787

Azorin JM, Aubrun E, Bertsch J, Reed C, Gerard S, Lukasiewicz M (2009) Mixed states vs. pure mania in the French sample of the EMBLEM study: results at baseline and 24 months – European mania in bipolar longitudinal evaluation of medication. BMC Psychiatry 9:33. doi:10.1186/1471-244X-9-33, 1471-244X-9-33 [pii]

Azorin JM, Kaladjian A, Besnier N, Adida M, Hantouche E, Lancrenon S, Akiskal H (2010) Suicidal behaviour in a French Cohort of major depressive patients: characteristics of attempters and nonattempters. J Affect Disord 123(1–3):87–94. doi:10.1016/j.jad.2009.09.004, S0165-0327(09)00422-4 [pii]

Azorin JM, Kaladjian A, Adida M, Fakra E, Belzeaux R, Hantouche E, Lancrenon S (2012) Self-assessment and characteristics of mixed depression in the French national EPIDEP study. J Affect Disord 143(1–3):109–117. doi:10.1016/j.jad.2012.05.036, S0165-0327(12)00391-6 [pii]

Baek JH, Park DY, Choi J, Kim JS, Choi JS, Ha K, Kwon JS, Lee D, Hong KS (2011) Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord 131(1–3):59–67. doi:10.1016/j.jad.2010.11.020, S0165-0327(10)00717-2 [pii]

Baldassano CF, Marangell LB, Gyulai L, Ghaemi SN, Joffe H, Kim DR, Sagduyu K, Truman CJ, Wisniewski SR, Sachs GS, Cohen LS (2005) Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. Bipolar Disord 7(5):465–470. doi:10.1111/j.1399-5618.2005.00237.x, BDI237 [pii]

Baldessarini RJ, Tondo L, Floris G, Hennen J (2000) Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and II disorder patients. J Affect Disord 61(1–2):13–22. doi:S0165-0327(99)00196-2 [pii]

Baldessarini RJ, Salvatore P, Khalsa HM, Imaz-Etxeberria H, Gonzalez-Pinto A, Tohen M (2012a) Episode cycles with increasing recurrences in first-episode bipolar-I disorder patients. J Affect Disord 136(1–2):149–154. doi:10.1016/j.jad.2011.08.037

Baldessarini RJ, Undurraga J, Vazquez GH, Tondo L, Salvatore P, Ha K, Khalsa HM, Lepri B, Ha TH, Chang JS, Tohen M, Vieta E (2012b) Predominant recurrence polarity among 928 adult international bipolarIdisorderpatients.ActaPsychiatrScand125(4):293–302.doi:10.1111/j.1600-0447.2011.01818.x

Barrios C, Chaudhry TA, Goodnick PJ (2001) Rapid cycling bipolar disorder. Expert Opin Pharmacother 2(12):1963–1973. doi:10.1517/14656566.2.12.1963

Bartalena L, Pellegrini L, Meschi M, Antonangeli L, Bogazzi F, Dell'Osso L, Pinchera A, Placidi GF (1990) Evaluation of thyroid function in patients with rapid-cycling and non-rapid-cycling bipolar disorder. Psychiatry Res 34(1):13–17. doi:0165-1781(90)90054-9 [pii]

Bauer MS, Whybrow PC (1990) Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch Gen Psychiatry 47(5):435–440

Bauer MS, Whybrow PC, Winokur A (1990) Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism. Arch Gen Psychiatry 47(5):427–432

Bauer MS, Calabrese J, Dunner DL, Post R, Whybrow PC, Gyulai L, Tay LK, Younkin SR, Bynum D, Lavori P et al (1994) Multisite data reanalysis of the validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. Am J Psychiatry 151(4):506–515

Bauer M, Rasgon N, Grof P, Altshuler L, Gyulai L, Lapp M, Glenn T, Whybrow PC (2005) Mood changes related to antidepressants: a longitudinal study of patients with bipolar disorder in a naturalistic setting. Psychiatry Res 133(1):73–80. doi:10.1016/j.psychres.2004.08.006, S0165-1781(04)00219-7 [pii]

Bauer M, Rasgon N, Grof P, Glenn T, Lapp M, Marsh W, Munoz R, Suwalska A, Baethge C, Bschor T, Alda M, Whybrow PC (2006) Do antidepressants influence mood patterns? A naturalistic study in bipolar disorder. Eur Psychiatry 21(4):262–269. doi:10.1016/j.eurpsy.2006.04.009, S0924-9338(06)00091-5 [pii]

Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R (2008) Rapid cycling bipolar disorder – diagnostic concepts. Bipolar Disord 10(1 Pt 2):153–162. doi:10.1111/j.1399-5618.2007.00560.x, BDI560 [pii]

Bauer M, Glenn T, Grof P, Rasgon NL, Marsh W, Sagduyu K, Alda M, Murray G, Quiroz D, Malliaris Y, Sasse J, Pilhatsch M, Whybrow PC (2009) Relationship among latitude, climate, season and self-reported mood in bipolar disorder. J Affect Disord 116(1–2):152–157. doi:10.1016/j.jad.2008.11.013, S0165-0327(08)00469-2 [pii]

Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E (2001) Morning sunlight reduces length of hospitalization in bipolar depression. J Affect Disord 62(3):221–223. doi:S016503270000149X [pii]

Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yucel M, Gama CS, Dodd S, Dean B, Magalhaes PV, Amminger P, McGorry P, Malhi GS (2011) Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 35(3):804–817. doi:10.1016/j.neubiorev.2010.10.001, S0149-7634(10)00154-5 [pii]

Blackwell MJ (1991) Rapid-cycling manic-depressive illness following subarachnoid haemorrhage. Br J Psychiatry 159:279–280

Boker SM, Leibenluft E, Deboeck PR, Virk G, Postolache TT (2008) Mood oscillations and coupling between mood and weather in patients with rapid cycling bipolar disorder. Int J Child Health Hum Dev 1(2):181–203

Bowden CL, Calabrese JR, McElroy SL, Rhodes LJ, Keck PE Jr, Cookson J, Anderson J, Bolden-Watson C, Ascher J, Monaghan E, Zhou J (1999) The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. Biol Psychiatry 45(8):953–958. doi:S000632239900013X [pii]

Bunney WE Jr, Hartmann EL, Mason JW (1965) Study of a patient with 48-hour manic-depressive cycles. II. Strong positive correlation between endocrine factors and manic defense patterns. Arch Gen Psychiatry 12:619–625

Calabrese JR, Shelton MD, Rapport DJ, Kujawa M, Kimmel SE, Caban S (2001) Current research on rapid cycling bipolar disorder and its treatment. J Affect Disord 67(1–3):241–255. doi:S016503279800161X [pii]

Carney PA, Fitzgerald CT, Monaghan CE (1988a) Influence of climate on the prevalence of mania. Br J Psychiatry 152:820–823

Carney PA, Seggie J, Vojtechovsky M, Parker J, Grof E, Grof P (1988b) Bipolar patients taking lithium have increased dark adaptation threshold compared with controls. Pharmacopsychiatry 21(3):117–120. doi:10.1055/s-2007-1014661

Cassidy F, Carroll BJ (2002) Seasonal variation of mixed and pure episodes of bipolar disorder. J Affect Disord 68(1):25–31. doi:S0165032700003256 [pii]

Chan PK, Lam RW, Perry KF (1994) Mania precipitated by light therapy for patients with SAD. J Clin Psychiatry 55(10):454

Cho JT, Bone S, Dunner DL, Colt E, Fieve RR (1979) The effect of lithium treatment on thyroid function in patients with primary affective disorder. Am J Psychiatry 136(1):115–116

Choi J, Baek JH, Noh J, Kim JS, Choi JS, Ha K, Kwon JS, Hong KS (2011) Association of seasonality and premenstrual symptoms in bipolar I and bipolar II disorders. J Affect Disord 129(1–3):313–316. doi:10.1016/j.jad.2010.07.030, S0165-0327(10)00512-4 [pii]

Christensen EM, Larsen JK, Gjerris A, Peacock L, Jacobi M, Hassenbalch E (2008) Climatic factors and bipolar affective disorder. Nord J Psychiatry 62(1):55–58. doi:10.1080/08039480801970049, 791409081 [pii]

Clarke M, Moran P, Keogh F, Morris M, Kinsella A, Larkin C, Walsh D, O'Callaghan E (1999) Seasonal influences on admissions for affective disorder and schizophrenia in Ireland: a comparison of first and readmissions. Eur Psychiatry 14(5):251–255. doi:S0924-9338(99)00174-1 [pii]

Colom F, Vieta E (2009) The road to DSM-V. Bipolar disorder episode and course specifiers. Psychopathology 42(4):209–218. doi:10.1159/000218518, 000218518 [pii]

Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J (2006) Clinical and therapeutic implications of predominant polarity in bipolar disorder. J Affect Disord 93(1–3):13–17

Coryell W (2005) Rapid cycling bipolar disorder: clinical characteristics and treatment options. CNS Drugs 19(7):557–569. doi:1971 [pii]

Coryell W, Endicott J, Keller M (1992) Rapidly cycling affective disorder. Demographics, diagnosis, family history, and course. Arch Gen Psychiatry 49(2):126–131

Coryell W, Solomon D, Turvey C, Keller M, Leon AC, Endicott J, Schettler P, Judd L, Mueller T (2003) The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 60(9):914–920. doi:10.1001/archpsyc.60.9.914, 60/9/914 [pii]

Cowdry RW, Wehr TA, Zis AP, Goodwin FK (1983) Thyroid abnormalities associated with rapid-cycling bipolar illness. Arch Gen Psychiatry 40(4):414–420

Crane GE (1956) The psychiatric side-effects of iproniazid. Am J Psychiatry 112(7):494–501

Cruz N, Vieta E, Comes M, Haro JM, Reed C, Bertsch J (2008) Rapid-cycling bipolar I disorder: course and treatment outcome of a large sample across Europe. J Psychiatr Res 42(13):1068–1075. doi:10.1016/j.jpsychires.2007.12.004, S0022-3956(07)00212-9 [pii]

Cusin C, Serretti A, Mandelli L, Lucca A, Smeraldi E (2002) Seasonal variations of lithium plasma levels. Psychiatry Res 111(1):35–41. doi:S0165178102001300 [pii]

Cuthbert BN, Insel TR (2013) Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med 11:126. doi:10.1186/1741-7015-11-126

Cutler NR, Post RM (1982) Life course of illness in untreated manic-depressive patients. Compr Psychiatry 23(2):101–115. doi:0010-440X(82)90055-4 [pii]

D'Mello DA, McNeil JA, Msibi B (1995) Seasons and bipolar disorder. Ann Clin Psychiatry 7(1):11–18

Daban C, Colom F, Sanchez-Moreno J, Garcia-Amador M, Vieta E (2006) Clinical correlates of first-episode polarity in bipolar disorder. Compr Psychiatry 47(6):433–437. doi:10.1016/j.comppsych.2006.03.009, S0010-440X(06)00051-4 [pii]

Daniels BA, Kirkby KC, Mitchell P, Hay D, Mowry B (2000) Seasonal variation in hospital admission for bipolar disorder, depression and schizophrenia in Tasmania. Acta Psychiatr Scand 102(1):38–43

Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE (2012) Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. Psychiatry Res 196(1):57–61. doi:10.1016/j.psychres.2012.01.015, S0165-1781(12)00045-5 [pii]

Deltito JA, Moline M, Pollak C, Martin LY, Maremmani I (1991) Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. J Affect Disord 23(4):231–237

Dias RS, Lafer B, Russo C, Del Debbio A, Nierenberg AA, Sachs GS, Joffe H (2011) Longitudinal follow-up of bipolar disorder in women with premenstrual exacerbation: findings from STEP-BD. Am J Psychiatry 168(4):386–394. doi:10.1176/appi.ajp.2010.09121816, appi.ajp.2010.09121816 [pii]

Dittmann S, Biedermann NC, Grunze H, Hummel B, Scharer LO, Kleindienst N, Forsthoff A, Matzner N, Walser S, Walden J (2002) The Stanley Foundation Bipolar Network: results of the naturalistic follow-up study after 2.5 years of follow-up in the German centres. Neuropsychobiology 46(Suppl 1):2–9. doi:68018 68018 [pii]

Dunner DL, Fieve RR (1974) Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 30(2):229–233

Eastwood MR, Stiasny S (1978) Psychiatric disorder, hospital admission, and season. Arch Gen Psychiatry 35(6):769–771

Ernst CL, Goldberg JF (2004) Clinical features related to age at onset in bipolar disorder. J Affect Disord 82(1):21–27. doi:10.1016/j.jad.2003.10.002, S0165032703002581 [pii]

Etain B, Lajnef M, Bellivier F, Mathieu F, Raust A, Cochet B, Gard S, M'Bailara K, Kahn JP, Elgrabli O, Cohen R, Jamain S, Vieta E, Leboyer M, Henry C (2012) Clinical expression of bipolar disorder type I as a function of age and polarity at onset: convergent findings in samples from France and the United States. J Clin Psychiatry 73(4):e561–e566

Faedda GL, Tondo L, Teicher MH, Baldessarini RJ, Gelbard HA, Floris GF (1993) Seasonal mood disorders. Patterns of seasonal recurrence in mania and depression. Arch Gen Psychiatry 50(1):17–23

Feldman-Naim S, Turner EH, Leibenluft E (1997) Diurnal variation in the direction of mood switches in patients with rapid-cycling bipolar disorder. J Clin Psychiatry 58(2):79–84

Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR (2001) Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 3(4):202–210. doi:bdi030405 [pii]

Forty L, Jones L, Jones I, Smith DJ, Caesar S, Fraser C, Gordon-Smith K, Hyde S, Craddock N (2009) Polarity at illness onset in bipolar I disorder and clinical course of illness. Bipolar Disord 11(1):82–88

Fountoulakis KN (2012) Introduction–bipolar illness: current understanding and future perspectives. CNS Neurosci Ther 18(3):193. doi:10.1111/j.1755-5949.2012.00298.x

Fountoulakis KN, Akiskal HS (2008) Focus on bipolar illness. CNS Spectr 13(9):762

Fountoulakis KN, Vieta E, Bouras C, Notaridis G, Giannakopoulos P, Kaprinis G, Akiskal H (2008) A systematic review of existing data on long-term lithium therapy: neuroprotective or neurotoxic? Int J Neuropsychopharmacol 11(2):269–287. doi:10.1017/S1461145707007821

Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN (2012) Treatment of mixed bipolar states. Int J Neuropsychopharmacol 15(7):1015–1026. doi:10.1017/S1461145711001817

Fountoulakis KN, Kontis D, Gonda X, Yatham LN (2013) A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. Bipolar Disord 15(2):115–137. doi:10.1111/bdi.12045

Frangos E, Athanassenas G, Tsitourides S, Psilolignos P, Robos A, Katsanou N, Bulgaris C (1980) Seasonality of the episodes of recurrent affective psychoses. Possible prophylactic interventions. J Affect Disord 2(4):239–247

Friedman E, Gyulai L, Bhargava M, Landen M, Wisniewski S, Foris J, Ostacher M, Medina R, Thase M (2006) Seasonal changes in clinical status in bipolar disorder: a prospective study in 1000 STEP-BD patients. Acta Psychiatr Scand 113(6):510–517. doi:10.1111/j.1600-0447.2005.00701.x, ACP701 [pii]

Garcia-Amador M, Colom F, Valenti M, Horga G, Vieta E (2009) Suicide risk in rapid cycling bipolar patients. J Affect Disord 117(1–2):74–78. doi:10.1016/j.jad.2008.12.005, S0165-0327(08)00481-3 [pii]

Garcia-Lopez A, De Dios-Perrino C, Ezquiaga E (2009) Polarity of the first episode and predominant polarity in a cohort of bipolar outpatients. Eur Neuropsychopharmacol 19:S571

Geller B, Cook EH Jr (2000) Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. Biol Psychiatry 47(7):605–609. doi:S0006-3223(99)00251-6 [pii]

Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, Heath J (1998) Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 37(2):171–178

Goikolea JM, Colom F, Martinez-Aran A, Sanchez-Moreno J, Giordano A, Bulbena A, Vieta E (2007) Clinical and prognostic implications of seasonal pattern in bipolar disorder: a 10-year follow-up of 302 patients. Psychol Med 37(11):1595–1599. doi:10.1017/S0033291707000864, S0033291707000864 [pii]

Goldberg JF, Harrow M (1994) Kindling in bipolar disorders: a longitudinal follow-up study. Biol Psychiatry 35(1):70–72

Goldberg JF, Wankmuller MM, Sutherland KH (2004) Depression with versus without manic features in rapid-cycling bipolar disorder. J Nerv Ment Dis 192(9):602–606. doi:00005053-200409000-00004 [pii]

Goldberg JF, Brooks JO 3rd, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, Miklowitz DJ, Ketter TA, Sachs GS, Thase ME (2009) Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry 70(2):155–162. doi:ej08m04301 [pii]

Gonzalez-Pinto A, Alberich S, Barbeito S, Alonso M, Vieta E, Martinez-Aran A, Saenz M, Lopez P (2010a) Different profile of substance abuse in relation to predominant polarity in bipolar disorder. The Vitoria long-term follow-up study. J Affect Disord 124(3):250–255

Gonzalez-Pinto A, Alberich S, Barbeito S, Alonso M, Vieta E, Martinez-Aran A, Saenz M, Lopez P (2010b) Different profile of substance abuse in relation to predominant polarity in bipolar disorder: the Vitoria long-term follow-up study. J Affect Disord 124(3):250–255. doi:10.1016/j.jad.2009.11.005, S0165-0327(09)00498-4 [pii]

Goodwin F, Jamison K (1990) Manic-depressive illness. Oxford University Press, New York

Green EK, Raybould R, Macgregor S, Hyde S, Young AH, O'Donovan MC, Owen MJ, Kirov G, Jones L, Jones I, Craddock N (2006) Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. Br J Psychiatry 188:21–25. doi:10.1192/bjp.BD.105.009969, 188/1/21 [pii]

Grunze HC (2008) Switching, induction of rapid cycling, and increased suicidality with antidepressants in bipolar patients: fact or overinterpretation? CNS Spectr 13(9):790–795

Gyulai L, Bauer M, Bauer MS, Garcia-Espana F, Cnaan A, Whybrow PC (2003) Thyroid hypofunction in patients with rapid-cycling bipolar disorder after lithium challenge. Biol Psychiatry 53(10):899–905. doi:S0006322302015731 [pii]

Hajek T, Slaney C, Garnham J, Ruzickova M, Passmore M, Alda M (2005) Clinical correlates of current level of functioning in primary care-treated bipolar patients. Bipolar Disord 7(3):286–291. doi:10.1111/j.1399-5618.2005.00182.x, BDI182 [pii]

Hajek T, Hahn M, Slaney C, Garnham J, Green J, Ruzickova M, Zvolsky P, Alda M (2008) Rapid cycling bipolar disorders in primary and tertiary care treated patients. Bipolar Disord 10(4):495–502. doi:10.1111/j.1399-5618.2008.00587.x, BDI587 [pii]

Hakkarainen R, Johansson C, Kieseppa T, Partonen T, Koskenvuo M, Kaprio J, Lonnqvist J (2003) Seasonal changes, sleep length and circadian preference among twins with bipolar disorder. BMC Psychiatry 3:6. doi:10.1186/1471-244X-3-6

Hammen C, Gitlin M (1997) Stress reactivity in bipolar patients and its relation to prior history of disorder. Am J Psychiatry 154(6):856–857

Henry C, Lacoste J, Bellivier F, Verdoux H, Bourgeois ML, Leboyer M (1999) Temperament in bipolar illness: impact on prognosis. J Affect Disord 56(2–3):103–108

Hunt N, Sayer H, Silverstone T (1992) Season and manic relapse. Acta Psychiatr Scand 85(2):123–126

Insel TR, Cuthbert BN (2009) Endophenotypes: bridging genomic complexity and disorder heterogeneity. Biol Psychiatry 66(11):988–989. doi:10.1016/j.biopsych.2009.10.008, S0006-3223(09)01208-6 [pii]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 167(7):748–751. doi:10.1176/appi.ajp.2010.09091379

Jain S, Kaliaperumal VG, Chatterji S, Rao S, Murthy RS (1992) Climate and admissions for mania in the tropics. J Affect Disord 26(4):247–250

Jenner FA, Gjessing LR, Cox JR, Davies-Jones A, Hullin RP, Hanna SM (1967) A manic depressive psychotic with a persistent forty-eight hour cycle. Br J Psychiatry 113(501):895–910

Joffe RT, Kutcher S, MacDonald C (1988) Thyroid function and bipolar affective disorder. Psychiatry Res 25(2):117–121. doi:0165-1781(88)90042-X [pii]

Jones I, Hornsby H, Hay D (1995) Seasonality of mania: a Tasmanian study. Aust N Z J Psychiatry 29(3):449–453

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 60(3):261–269. doi:yoa20225 [pii]

Kantor DA, Browne M, Ravindran A, Horn E (1991) Manic-like response to phototherapy. Can J Psychiatry 36(9):697–698

Kilzieh N, Akiskal HS (1999) Rapid-cycling bipolar disorder. An overview of research and clinical experience. Psychiatr Clin North Am 22(3):585–607

Kirov G, Murphy KC, Arranz MJ, Jones I, McCandles F, Kunugi H, Murray RM, McGuffin P, Collier DA, Owen MJ, Craddock N (1998) Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. Mol Psychiatry 3(4):342–345

Koukopoulos A, Sani G (2013) DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand. doi:10.1111/acps.12140

Koukopoulos A, Sani G, Koukopoulos AE, Minnai GP, Girardi P, Pani L, Albert MJ, Reginaldi D (2003) Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients. J Affect Disord 73(1–2):75–85. doi:S016503270200321X [pii]

Koukopoulos A, Sani G, Ghaemi SN (2013) Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). Br J Psychiatry 203(1):3–5. doi:10.1192/bjp.BD.112.124404, 203/1/3 [pii]

Koyuncu A, Tukel R, Ozyildirim I, Meteris H, Yazici O (2010) Impact of obsessive-compulsive disorder comorbidity on the sociodemographic and clinical features of patients with bipolar disorder. Compr Psychiatry 51(3):293–297

Kraepelin E (1921) Manic-depressive insanity and paranoia. Livingstone, Edinburgh

Kramlinger KG, Post RM (1996) Ultra-rapid and ultradian cycling in bipolar affective illness. Br J Psychiatry 168(3):314–323

Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L (1980) Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol 13(4):156–167. doi:10.1055/s-2007-1019628

Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD, Frye MA, Keck PE Jr, Leverich GS, Rush AJ, Suppes T, Pollio C, Drexhage HA (2002) High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry 51(4):305–311. doi:S0006322301012173 [pii]

Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA (2003) Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry 64(12): 1483–1494

Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PE Jr, Frye MA, Denicoff KD, Grunze H, Leverich GS, McElroy SL, Walden J, Nolen WA (2005) Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. Am J Psychiatry 162(7):1273–1280. doi:10.1176/appi.ajp.162.7.1273, 162/7/1273 [pii]

Kusalic M (1992) Grade II and grade III hypothyroidism in rapid-cycling bipolar patients. Neuropsychobiology 25(4):177–181. doi:118833 [pii] 118833

Labbate LA, Lafer B, Thibault A, Sachs GS (1994) Side effects induced by bright light treatment for seasonal affective disorder. J Clin Psychiatry 55(5):189–191

Lee HJ, Kim L, Joe SH, Suh KY (2002) Effects of season and climate on the first manic episode of bipolar affective disorder in Korea. Psychiatry Res 113(1–2):151–159. doi:S0165178102002378 [pii]

Lee HC, Tsai SY, Lin HC (2007) Seasonal variations in bipolar disorder admissions and the association with climate: a population-based study. J Affect Disord 97(1–3):61–69. doi:10.1016/j.jad.2006.06.026, S0165-0327(06)00293-X [pii]

Lee S, Tsang A, Kessler RC, Jin R, Sampson N, Andrade L, Karam EG, Mora ME, Merikangas K, Nakane Y, Popovici DG, Posada-Villa J, Sagar R, Wells JE, Zarkov Z, Petukhova M (2010) Rapid-cycling bipolar disorder: cross-national community study. Br J Psychiatry 196(3):217–225. doi:10.1192/bjp.BD.109.067843, 196/3/217 [pii]

Lee HJ, Woo HG, Greenwood TA, Kripke DF, Kelsoe JR (2012) A genome-wide association study of seasonal pattern mania identifies NF1A as a possible susceptibility gene for bipolar disorder. J Affect Disord. doi:10.1016/j.jad.2012.07.032, S0165-0327(12)00563-0 [pii]

Leibenluft E, Ashman SB, Feldman-Naim S, Yonkers KA (1999) Lack of relationship between menstrual cycle phase and mood in a sample of women with rapid cycling bipolar disorder. Biol Psychiatry 46(4):577–580. doi:S0006-3223(99)00023-2 [pii]

Leonhard K (1963) Die prapsychotische Temperamente bei den monopolaren und bipolaren phasischen Psychosen. Psychiatry Neurol (Basel) 146:105–115

Lewis JL, Winokur G (1982) The induction of mania. A natural history study with controls. Arch Gen Psychiatry 39(3):303–306

Lewis JL, Winokur G (1987) The induction of mania: a natural history study with controls. Psychopharmacol Bull 23(1):74–78

Lewis J, Winokur G (1989) Induction of mania by antidepressants. Am J Psychiatry 146(1):126–128

Lewy AJ, Nurnberger JI Jr, Wehr TA, Pack D, Becker LE, Powell RL, Newsome DA (1985) Supersensitivity to light: possible trait marker for manic-depressive illness. Am J Psychiatry 142(6):725–727

Lin PI, McInnis MG, Potash JB, Willour V, MacKinnon DF, DePaulo JR, Zandi PP (2006) Clinical correlates and familial aggregation of age at onset in bipolar disorder. Am J Psychiatry 163(2):240–246. doi:10.1176/appi.ajp.163.2.240, 163/2/240 [pii]

Lish JD, Gyulai L, Resnick SM, Kirtland A, Amsterdam JD, Whybrow PC, Price RA (1993) A family history study of rapid-cycling bipolar disorder. Psychiatry Res 48(1):37–46

London WP, Taylor BM (1981) Seasonality of bipolar disorders in a forensic setting. Psychiatry Res 5(2):139–145. doi:0165-1781(81)90044-5 [pii]

Mackin P (2005) Rapid cycling is equivalently prevalent in bipolar I and bipolar II disorder, and is associated with female gender and greater severity of illness. Evid Based Ment Health 8(2):52. doi:8/2/52 [pii]

Mackinnon DF, Pies R (2006) Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord 8(1):1–14. doi:10.1111/j.1399-5618.2006.00283.x, BDI283 [pii]

MacKinnon DF, Zandi PP, Gershon E, Nurnberger JI Jr, Reich T, DePaulo JR (2003a) Rapid switching of mood in families with multiple cases of bipolar disorder. Arch Gen Psychiatry 60(9):921–928. doi:10.1001/archpsyc.60.9.921, 60/9/921 [pii]

MacKinnon DF, Zandi PP, Gershon ES, Nurnberger JI Jr, DePaulo JR Jr (2003b) Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. Am J Psychiatry 160(9):1696–1698

Maggini C, Salvatore P, Gerhard A, Migone P (2000) Psychopathology of stable and unstable mixed states: a historical view. Compr Psychiatry 41(2):77–82. doi:S0010-440X(00)90136-6 [pii]

Mahon K, Perez-Rodriguez MM, Gunawardane N, Burdick KE (2013) Dimensional endophenotypes in bipolar disorder: affective dysregulation and psychosis proneness. J Affect Disord 151(2):695–701. doi:10.1016/j.jad.2013.08.003

Maj M, Magliano L, Pirozzi R, Marasco C, Guarneri M (1994) Validity of rapid cycling as a course specifier for bipolar disorder. Am J Psychiatry 151(7):1015–1019

Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M (2004) Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 161(2):262–270

Mattes JA (2006) Antidepressant-induced rapid cycling: another perspective. Ann Clin Psychiatry 18(3):195–199. doi:10.1080/10401230600801242, U40528M04X554240 [pii]

Mawson D, Smith A (1981) Relative humidity and manic admissions in the London area. Br J Psychiatry 138:134–138

Mazzarini L, Pacchiarotti I, Colom F, Sani G, Kotzalidis GD, Rosa AR, Sanna L, De Rossi P, Girardi N, Bonnin CM, Sanchez-Moreno J, Vazquez GH, Gasto C, Tatarelli R, Vieta E (2009) Predominant polarity and temperament in bipolar and unipolar affective disorders. J Affect Disord 119(1–3):28–33. doi:10.1016/j.jad.2009.03.016, S0165-0327(09)00129-3 [pii]

Medhi B, Prakash O, Jose VM, Pradhan B, Chakrabarty S, Pandhi P (2008) Seasonal variation in plasma levels of lithium in the Indian population: is there a need to modify the dose? Singapore Med J 49(9):724–727

Mellerup B, Mellerup ET (1984) Seasonal variation in urinary excretion of calcium, magnesium and phosphate in manic-melancholic patients. Chronobiol Int 1(1):81–86

Morken G, Lilleeng S, Linaker OM (2002) Seasonal variation in suicides and in admissions to hospital for mania and depression. J Affect Disord 69(1–3):39–45. doi:S0165032700003736 [pii]

Mulder RT, Cosgriff JP, Smith AM, Joyce PR (1990) Seasonality of mania in New Zealand. Aust N Z J Psychiatry 24(2):187–190

Muller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL (2006) Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. Br J Psychiatry 189:317–323. doi:10.1192/bjp.BD.105.010587, 189/4/317 [pii]

Murai T, Fujimoto S (2003) Rapid cycling bipolar disorder after left temporal polar damage. Brain Inj 17(4):355–358. doi:9UD2D4QQE15824D8 [pii]

Murray G, Lam RW, Beaulieu S, Sharma V, Cervantes P, Parikh SV, Yatham LN (2011) Do symptoms of bipolar disorder exhibit seasonal variation? A multisite prospective investigation. Bipolar Disord 13(7–8):687–695. doi:10.1111/j.1399-5618.2011.00959.x

Murru A, Nivoli AMA, Pacchiarotti I, Popovic D, Vieta E, Colom F (2011) Clinical, functional and therapeutic implications of comorbid personality disorders in a sample of bipolar patients. Eur Neuropsychopharmacol 21:S432–S433

Myers DH, Davies P (1978) The seasonal incidence of mania and its relationship to climatic variables. Psychol Med 8(3):433–440

Narita K, Suda M, Takei Y, Aoyama Y, Majima T, Kameyama M, Kosaka H, Amanuma M, Fukuda M, Mikuni M (2011) Volume reduction of ventromedial prefrontal cortex in bipolar II patients with rapid cycling: a voxel-based morphometric study. Prog Neuropsychopharmacol Biol Psychiatry 35(2):439–445. doi:10.1016/j.pnpBD.2010.11.030, S0278-5846(10)00461-6 [pii]

Nierenberg AA, Akiskal HS, Angst J, Hirschfeld RM, Merikangas KR, Petukhova M, Kessler RC (2010) Bipolar disorder with frequent mood episodes in the national comorbidity survey replication (NCS-R). Mol Psychiatry 15(11):1075–1087. doi:10.1038/mp.2009.61, mp200961 [pii]

Nivoli AM, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, Bonnin CM, Grande I, Sanchez-Moreno J, Vieta E, Colom F (2011a) Gender differences in a cohort study of 604

bipolar patients: the role of predominant polarity. J Affect Disord 133(3):443–449. doi:10.1016/j.jad.2011.04.055, S0165-0327(11)00222-9 [pii]
Nivoli AMA, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, Bonnin CM, Grande I, Sanchez-Moreno J, Vieta E, Colom F (2011b) Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. J Affect Disord 133(3):443–449
Nivoli AM, Colom F, Pacchiarotti I, Murru A, Scott J, Valenti M, Mazzarini L, Del Mar Bonnin C, Sanchez-Moreno J, Serretti A, Vieta E (2012) Treatment strategies according to clinical features in a naturalistic cohort study of bipolar patients: a principal component analysis of lifetime pharmacological and biophysic treatment options. Eur Neuropsychopharmacol. doi:10.1016/j.euroneuro.2012.07.015, S0924-977X(12)00197-6 [pii]
Nivoli AMA, Colom F, Pacchiarotti I, Murru A, Scott J, Valenti M, Mazzarini L, Mar Bonnin CD, Jose SM, Serretti A, Vieta E (2013) Treatment strategies according to clinical features in a naturalistic cohort study of bipolar patients: a principal component analysis of lifetime pharmacological and biophysic treatment options. Eur Neuropsychopharmacol 23(4):263–275
Nurnberger J Jr, Guroff JJ, Hamovit J, Berrettini W, Gershon E (1988) A family study of rapid-cycling bipolar illness. J Affect Disord 15(1):87–91
Oomen HA, Schipperijn AJ, Drexhage HA (1996) The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. Clin Endocrinol (Oxf) 45(2):215–223
Osher Y, Yaroslavsky Y, el-Rom R, Belmaker RH (2000) Predominant polarity of bipolar patients in Israel. World J Biol Psychiatry 1(4):187–189
Pacchiarotti I, Mazzarini L, Kotzalidis GD, Valenti M, Nivoli AM, Sani G, Torrent C, Murru A, Sanchez-Moreno J, Patrizi B, Girardi P, Vieta E, Colom F (2011) Mania and depression. Mixed, not stirred. J Affect Disord 133(1–2):105–113. doi:10.1016/j.jad.2011.03.037
Pacchiarotti I, Nivoli AMA, Mazzarini L, Kotzalidis GD, Sani G, Koukopoulos A, Scott J, Strejilevich S, Sanchez-Moreno J, Murru A, Valenti M, Girardi P, Vieta E, Colom F (2013) The symptom structure of bipolar acute episodes: in search for the mixing link. J Affect Disord 149(1–3):56–66
Pande AC (1985) Light-induced hypomania. Am J Psychiatry 142(9):1126
Papolos DF, Veit S, Faedda GL, Saito T, Lachman HM (1998) Ultra-ultra rapid cycling bipolar disorder is associated with the low activity catecholamine-O-methyltransferase allele. Mol Psychiatry 3(4):346–349
Parker G, Walter S (1982) Seasonal variation in depressive disorders and suicidal deaths in New South Wales. Br J Psychiatry 140:626–632
Partonen T, Lonnqvist J (1996) Seasonal variation in bipolar disorder. Br J Psychiatry 169(5):641–646
Peck DF (1990) Climatic variables and admissions for mania: a reanalysis. J Affect Disord 20(4):249–250
Perlis RH, Delbello MP, Miyahara S, Wisniewski SR, Sachs GS, Nierenberg AA (2005) Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. Biol Psychiatry 58(7):549–553. doi:10.1016/j.biopsych.2005.07.029, S0006-3223(05)00918-2 [pii]
Perugi G, Akiskal HS, Micheli C, Musetti L, Paiano A, Quilici C, Rossi L, Cassano GB (1997) Clinical subtypes of bipolar mixed states: validating a broader European definition in 143 cases. J Affect Disord 43(3):169–180. doi:S0165-0327(97)01446-8 [pii]
Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L (2000) Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 41(1):13–18. doi:S0010-440X(00)90125-1 [pii]
Popovic D, Vieta E (2013) Clinical implications of polarity index of drugs in maintenance treatment of bipolar disorder: a naturalistic study. Eur Neuropsychopharmacol 23:S68–S69
Popovic D, Torrent C, Goikolea JM, Cruz N, Sanchez-Moreno J, Gonzalez-Pinto A, Vieta E (2013) Clinical implications of predominant polarity and the polarity index in bipolar disorder: a naturalistic study. Acta Psychiatr Scand 129(5):366–374

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 149(8):999–1010

Post RM, Rubinow DR, Ballenger JC (1986) Conditioning and sensitisation in the longitudinal course of affective illness. Br J Psychiatry 149:191–201

Post RM, Kramlinger KG, Joffe RT, Roy-Byrne PP, Rosoff A, Frye MA, Huggins T (1997) Rapid cycling bipolar affective disorder: lack of relation to hypothyroidism. Psychiatry Res 72(1): 1–7. doi:S0165-1781(97)00076-0 [pii]

Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA (2003) Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 64(6):680–690; quiz 738–789

Price WA, DiMarzio L (1986) Premenstrual tension syndrome in rapid-cycling bipolar affective disorder. J Clin Psychiatry 47(8):415–417

Quitkin FM, Rabkin JG, Prien RF (1986) Bipolar disorder: are there manic-prone and depressive-prone forms? J Clin Psychopharmacol 6(3):167–172

Rapaport MH, Guylai L, Whybrow P (1999) Immune parameters in rapid cycling bipolar patients before and after lithium treatment. J Psychiatr Res 33(4):335–340. doi:S0022-3956(99)00007-2 [pii]

Rihmer Z (1980) Season of birth and season of hospital admission in bipolar depressed female patients. Psychiatry Res 3(3):247–251

Rosa AR, Andreazza AC, Kunz M, Gomes F, Santin A, Sanchez-Moreno J, Reinares M, Colom F, Vieta E, Kapczinski F (2008) Predominant polarity in bipolar disorder: diagnostic implications. J Affect Disord 107(1–3):45–51. doi:10.1016/j.jad.2007.07.021, S0165-0327(07)00274-1 [pii]

Rousseva A, Henry C, van den Bulke D, Fournier G, Laplanche JL, Leboyer M, Bellivier F, Aubry JM, Baud P, Boucherie M, Buresi C, Ferrero F, Malafosse A (2003) Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. Pharmacogenomics J 3(2):101–104. doi:10.1038/sj.tpj.6500156, 6500156 [pii]

Rovai L, Maremmani AG, Rugani F, Bacciardi S, Pacini M, Dell'osso L, Akiskal HS, Maremmani I (2013) Do Akiskal & Mallya's affective temperaments belong to the domain of pathology or to that of normality? Eur Rev Med Pharmacol Sci 17(15):2065–2079

Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D (1985) The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 317:1–34

Sayer HK, Marshall S, Mellsop GW (1991) Mania and seasonality in the southern hemisphere. J Affect Disord 23(3):151–156. doi:0165-0327(91)90027-P [pii]

Sayin A, Kuruoglu AC, Yazici Gulec M, Aslan S (2007) Relation of temperament and character properties with clinical presentation of bipolar disorder. Compr Psychiatry 48(5):446–451. doi:10.1016/j.comppsych.2007.04.004, S0010-440X(07)00052-1 [pii]

Schneck CD, Miklowitz DJ, Calabrese JR, Allen MH, Thomas MR, Wisniewski SR, Miyahara S, Shelton MD, Ketter TA, Goldberg JF, Bowden CL, Sachs GS (2004) Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the Systematic Treatment Enhancement Program. Am J Psychiatry 161(10):1902–1908. doi:10.1176/appi.ajp.161.10.1902, 161/10/1902 [pii]

Schneck CD, Miklowitz DJ, Miyahara S, Araga M, Wisniewski S, Gyulai L, Allen MH, Thase ME, Sachs GS (2008) The prospective course of rapid-cycling bipolar disorder: findings from the STEP-BD. Am J Psychiatry 165(3):370–377

Schumann G, Binder EB, Holte A, de Kloet ER, Oedegaard KJ, Robbins TW, Walker-Tilley TR, Bitter I, Brown VJ, Buitelaar J, Ciccocioppo R, Cools R, Escera C, Fleischhacker W, Flor H, Frith CD, Heinz A, Johnsen E, Kirschbaum C, Klingberg T, Lesch KP, Lewis S, Maier W, Mann K, Martinot JL, Meyer-Lindenberg A, Muller CP, Muller WE, Nutt DJ, Persico A, Perugi G, Pessiglione M, Preuss UW, Roiser JP, Rossini PM, Rybakowski JK, Sandi C, Stephan KE, Undurraga J, Vieta E, van der Wee N, Wykes T, Haro JM, Wittchen HU (2013) Stratified

medicine for mental disorders. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. doi:10.1016/j.euroneuro.2013.09.010
Serretti A, Mandelli L, Lattuada E, Smeraldi E (2002) Rapid cycling mood disorder: clinical and demographic features. Compr Psychiatry 43(5):336–343. doi:S0010440X02000111 [pii]
Shand AJ, Scott NW, Anderson SM, Eagles JM (2011) The seasonality of bipolar affective disorder: comparison with a primary care sample using the seasonal pattern assessment questionnaire. J Affect Disord 132(1–2):289–292. doi:10.1016/j.jad.2011.02.015, S0165-0327(11)00069-3 [pii]
Shapira A, Shiloh R, Potchter O, Hermesh H, Popper M, Weizman A (2004) Admission rates of bipolar depressed patients increase during spring/summer and correlate with maximal environmental temperature. Bipolar Disord 6(1):90–93. doi:081 [pii]
Shin K, Schaffer A, Levitt AJ, Boyle MH (2005) Seasonality in a community sample of bipolar, unipolar and control subjects. J Affect Disord 86(1):19–25. doi:10.1016/j.jad.2004.11.010, S0165-0327(04)00438-0 [pii]
Silverstone T, Romans S, Hunt N, McPherson H (1995) Is there a seasonal pattern of relapse in bipolar affective disorders? A dual northern and southern hemisphere cohort study. Br J Psychiatry 167(1):58–60
Simonsen H, Shand AJ, Scott NW, Eagles JM (2011) Seasonal symptoms in bipolar and primary care patients. J Affect Disord 132:200–208. doi:10.1016/j.jad.2011.02.018, S0165-0327(11)00072-3 [pii]
Sjoholm LK, Backlund L, Cheteh EH, Ek IR, Frisen L, Schalling M, Osby U, Lavebratt C, Nikamo P (2010) CRY2 is associated with rapid cycling in bipolar disorder patients. PLoS One 5(9):e12632. doi:10.1371/journal.pone.0012632, e12632 [pii]
Symonds RL, Williams P (1976) Seasonal variation in the incidence of mania. Br J Psychiatry 129:45–48
Tillman R, Geller B (2003) Definitions of rapid, ultrarapid, and ultradian cycling and of episode duration in pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. J Child Adolesc Psychopharmacol 13(3):267–271. doi:10.1089/104454603322572598
Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, Malhi GS, Calabrese JR, Nolen WA, Vieta E, Kapczinski F, Goodwin GM, Suppes T, Sachs GS, Chengappa KR, Grunze H, Mitchell PB, Kanba S, Berk M (2009) The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 11(5):453–473. doi:10.1111/j.1399-5618.2009.00726.x, BDI726 [pii]
Tondo L, Baldessarini RJ (1998) Rapid cycling in women and men with bipolar manic-depressive disorders. Am J Psychiatry 155(10):1434–1436
Turvey CL, Coryell WH, Solomon DA, Leon AC, Endicott J, Keller MB, Akiskal H (1999) Long-term prognosis of bipolar I disorder. Acta Psychiatr Scand 99(2):110–119
Valenti M, Pacchiarotti I, Bonnin CM, Rosa AR, Popovic D, Nivoli AM, Goikolea JM, Murru A, Undurraga J, Colom F, Vieta E (2012) Risk factors for antidepressant-related switch to mania. J Clin Psychiatry 73(2):e271–e276. doi:10.4088/JCP.11m07166
Vieta E, Valenti M (2013a) Mixed states in DSM-5: implications for clinical care, education, and research. J Affect Disord 148(1):28–36. doi:10.1016/j.jad.2013.03.007, S0165-0327(13)00232-2 [pii]
Vieta E, Valenti M (2013b) Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. CNS Drugs 27(7):515–529. doi:10.1007/s40263-013-0073-y
Vieta E, Calabrese JR, Hennen J, Colom F, Martinez-Aran A, Sanchez-Moreno J, Yatham LN, Tohen M, Baldessarini RJ (2004) Comparison of rapid-cycling and non-rapid-cycling bipolar I manic patients during treatment with olanzapine: analysis of pooled data. J Clin Psychiatry 65(10):1420–1428
Vieta E, Berk M, Wang W, Colom F, Tohen M, Baldessarini RJ (2009) Predominant previous polarity as an outcome predictor in a controlled treatment trial for depression in bipolar I disorder patients. J Affect Disord 119(1–3):22–27. doi:10.1016/j.jad.2009.02.028, S0165-0327(09)00097-4 [pii]
Vieta E, Langosch JM, Figueira ML, Souery D, Blasco-Colmenares E, Medina E, Moreno-Manzanaro M, Gonzalez MA, Bellivier F (2013a) Clinical management and burden of bipolar disorder: results from a multinational longitudinal study (WAVE-bd). Int J Neuropsychopharmacol 16(8):1719–1732. doi:10.1017/S1461145713000278

Vieta E, Popovic D, Rosa AR, Sole B, Grande I, Frey BN, Martinez-Aran A, Sanchez-Moreno J, Balanza-Martinez V, Tabares-Seisdedos R, Kapczinski F (2013b) The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur Psychiatry J Assoc Eur Psychiatr 28(1):21–29. doi:10.1016/j.eurpsy.2011.11.007

Volpe FM, Del Porto JA (2006) Seasonality of admissions for mania in a psychiatric hospital of Belo Horizonte, Brazil. J Affect Disord 94(1–3):243–248. doi:10.1016/j.jad.2006.03.025, S0165-0327(06)00173-X [pii]

Volpe FM, Tavares A, Del Porto JA (2008) Seasonality of three dimensions of mania: psychosis, aggression and suicidality. J Affect Disord 108(1–2):95–100. doi:10.1016/j.jad.2007.09.014, S0165-0327(07)00343-6 [pii]

Volpe FM, da Silva EM, dos Santos TN, de Freitas DE (2010) Further evidence of seasonality of mania in the tropics. J Affect Disord 124(1–2):178–182. doi:10.1016/j.jad.2009.11.001, S0165-0327(09)00486-8 [pii]

Walter SD (1977) Seasonality of mania: a reappraisal. Br J Psychiatry 131:345–350

Wehr TA, Goodwin FK (1979) Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 36(5):555–559

Wehr TA, Sack DA, Rosenthal NE, Cowdry RW (1988) Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 145(2):179–184

Wells JE, McGee MA, Scott KM, Oakley Browne MA (2010) Bipolar disorder with frequent mood episodes in the New Zealand Mental Health Survey. J Affect Disord 126(1–2):65–74. doi:10.1016/j.jad.2010.02.136, S0165-0327(10)00274-0 [pii]

Whitney DK, Sharma V, Kueneman K (1999) Seasonality of manic depressive illness in Canada. J Affect Disord 55(2–3):99–105

Wilk K, Hegerl U (2010) Time of mood switches in ultra-rapid cycling disorder: a brief review. Psychiatry Res 180(1):1–4. doi:10.1016/j.psychres.2009.08.011, S0165-1781(09)00318-7 [pii]

Wilting I, Fase S, Martens EP, Heerdink ER, Nolen WA, Egberts AC (2007) The impact of environmental temperature on lithium serum levels. Bipolar Disord 9(6):603–608. doi:10.1111/j.1399-5618.2007.00438.x, BDI438 [pii]

Wolpert EA, Goldberg JF, Harrow M (1990) Rapid cycling in unipolar and bipolar affective disorders. Am J Psychiatry 147(6):725–728

Yatham LN, Calabrese JR, Kusumakar V (2003) Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. Bipolar Disord 5(2):85–97. doi:019 [pii]

Yildiz A, Sachs GS (2003) Do antidepressants induce rapid cycling? A gender-specific association. J Clin Psychiatry 64(7):814–818

Yildiz A, Sachs GS (2004) Characteristics of rapid cycling bipolar-I patients in a bipolar speciality clinic. J Affect Disord 79(1–3):247–251. doi:10.1016/S0165-0327(02)00350-6, S0165032702003506 [pii]

Zis AP, Goodwin FK (1979) Major affective disorder as a recurrent illness: a critical review. Arch Gen Psychiatry 36(8 Spec No):835–839

Zwil AS, McAllister TW, Cohen I, Halpern LR (1993) Ultra-rapid cycling bipolar affective disorder following a closed-head injury. Brain Inj 7(2):147–152