Comorbidity

10

'Comorbidity' is a term introduced by Feinstein to refer to the coexistence of two essentially independent and distinct disorders. According to this early concept, there exists an 'index' or 'primary' disorder and a comorbid separate second disorder which potentially affects the selection of treatment and the prognosis of the index one (Feinstein 1970). Comorbidity may be due to chance or to ascertainment bias (Berkson's bias); however, the consistent pattern of comorbidity concerning several disorders (e.g. comorbid anxiety and depression) makes unlikely the suggestion it is happening by chance (Kessler et al. 2007). According to some authors, the conceptual overlapping especially between mood and anxiety disorders and the overlapping of symptoms might produce an 'artefactual comorbidity' (Maj 2005).

Most authors and textbooks clearly suggest that comorbidity, both with mental as well as with somatic diseases, is the rule rather than the exception in BD. Many go even further and suggest that the clinical picture of BD is grossly complicated because of comorbidity. In terms of official classification systems, this complex picture is reflected by the finding that most BD patients suffer from more than two distinct 'comorbid' mental disorders.

The literature is conclusive concerning the overall high rate of comorbidity and its adverse effect on overall outcome of the patients; however, it is rather inconclusive concerning certain diseases and specific rates. This is because of differences in study samples (e.g. inpatients, outpatients, epidemiological samples, registered and insured which by definition might suffer from a less severe form, etc.) and assessment methods. General population epidemiological studies often use trained lay interviewers, while clinical studies often utilize only highly experienced researchers. Thus, there is an unsolved riddle in place: Clinical samples are more reliably evaluated, but they might include patients with more severe form of the illness and higher comorbidity, while general population samples have problematic assessment, almost always with the use of structured interviews and thus an artificial inflation of rates, because of false allocation or multiple allocation of the same symptom.

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This chapter will deal with mental and medical comorbidity in adult BD patients with the exception of personality disorders, alcohol and substance abuse as well as behavioural addictions (e.g. gambling, Internet addiction, etc.). Also, this chapter will not cover the issue of comorbidity in children, adolescents and the elderly. These topics will be covered in especially dedicated chapters of this book. Treatment of comorbid disorders will be covered in the chapters specifically dedicated to treatment options.

In general, with the exception of substance use disorders, medical and psychiatric comorbidity is more common in females than in males (Arnold 2003). It is interesting that while bipolar males and females have similar rates of migraine headache (Mahmood et al. 1999), migraine is more frequent among females than males in community samples. Also, bipolar males are less likely than females to develop hypothyroidism as a consequence of lithium treatment (Kupka et al. 2002).

This chapter will also include detailed tables with lists of published papers concerning the rates of comorbid conditions in BD patients. Where possible, these tables will also include an estimation of the probable rate of the specific comorbid disorder after pooling all study samples together. This does not constitute a meta-analysis, but it can give a rough approximation of the average reported rate weighted by sample size and should be considered only as indicative. It should be noted that study samples often overlap and while in many instances this is obvious, in other instances it is very difficult to clarify even when concerning the same group of authors or the same institution. In this weighted averaging, the data from the general population, from non-bipolar medical patients' registries and from other nonmental patients control groups will be pooled together in a group named 'general population' which of course is not representative of the general population in epidemiological terms. Since this was in no way a formal meta-analysis, the author kept the privilege to exclude from pooling a small number of studies which were clearly outliers or of unknown composition or quality. Therefore, in several cases, the numbers shown as results of the pooling process do not correspond to the sum of all studies.

10.1 Psychiatric Comorbidity

In spite of the large theoretical debate on the true rates of comorbid conditions in BD, the everyday clinical reality is that of gross under-recognition and under-treatment of comorbidities (Simon et al. 2004a). This is because in everyday clinical practice the average psychiatrist is inclined to utilize a single comprehensive primary diagnosis and neglect the 'residual' symptomatology. This might lead not only to residual untreated symptoms, but also there is a danger that treating the 'primary' condition might worsen 'comorbidities'.

General population surveys suggest that almost all BD patients manifested at least a second mental disorder and almost two-thirds of patients reported that the

'comorbid' condition appeared first and BD followed (Kessler et al. 1997). Studies on clinical samples reported lower comorbidity rates.

Several studies suggested that from one-half to two-thirds of BD patients were suffering from one comorbid condition during lifetime (Subramaniam et al. 2013; Krishnan 2005; Leverich et al. 2003; Vieta et al. 2001; Tohen et al. 2003; Sasson et al. 2003; McElroy et al. 2001; Mantere et al. 2006; Strakowski et al. 1992; Dell'Osso et al. 2011) although unusually low rates have also been reported (Szadoczky et al. 1998). Additionally, 42 % of them manifested two, and 25 % manifested three comorbid psychiatric conditions (McElroy et al. 2001).

However, the prevalence of current (cross-sectional) comorbidity is significantly lower with around one-third of BD patients suffering from any psychiatric comorbidity (Mantere et al. 2006; Oreski et al. 2012; Vieta et al. 2001). The age of the sample seems to play a role since younger patients seem to manifest higher rates of current psychiatric comorbidity (Dell'Osso et al. 2011). Rates as high as almost 80 % have been reported (Bellani et al. 2012). It is important to note that when the official records are used in a retrospective way, only 18 % of hospitalized BD patients are reported to suffer from some additional mental disorder, and only approximately 3.5 % from two with any anxiety disorder present in only 1 % (Sorvaniemi and Hintikka 2005). These very low rates might reflect mainly the usual practice of clinicians to stick to a single major diagnosis in everyday clinical practice.

Mental comorbidity seems to relate with a more overall complicated clinical picture for BD, with younger age at onset (Moor et al. 2012) and worse long-term outcome, including increased suicidality and self-harm (Vieta et al. 2001; Moor et al. 2012; McElroy et al. 2001; Leverich et al. 2003; Young et al. 1993), poor adherence to treatment (Vieta et al. 2001) and less favourable response to lithium (Sasson et al. 2003; Young et al. 1993). However, at least one study does not support the relationship between comorbidity and outcome (Strakowski et al. 1992).

During manic and hypo-manic episodes, the overall psychiatric comorbidity is lower in comparison to depressive and mixed episodes (56.8 % vs. 82.9 %) (Mantere et al. 2006). Community studies suggest that the 'comorbid' condition appears first and BD follows (Kessler et al. 1997; Johnson et al. 2000), but studies on clinical samples suggest the opposite (Kupka et al. 2001).

Probably the most frequent comorbid condition is any anxiety disorder with substance abuse/dependence, impulse control disorders, eating disorders and attention deficit hyperactivity disorder (ADHD) following (Singh and Zarate 2006).

The reported rates concerning the presence of any comorbid mental disorder in BD patients are shown in detail in Table 10.1. The pooled rate suggests that two-thirds of BD patients are suffering from at least one comorbid mental disorder and the rate is similar to the respected which is reported for unipolar depression.

In the same Table (10.1), the rate of comorbid BD on other mental disorders is also shown.

Table 10.1 Rates of any mental comorbidity in BD patients and of BD on top of other mental disorders

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any mental comorbidity in pts with BD						
Szadoczky et al. (1998)	149	MDD	443	57 (38.3 %)	315 (71.1 %)	Lifetime rate
Bellani et al. (2012)	205	MDD	105	161 (78.5 %)	47 (44.8 %)	Cross-sectional rate
Kessler et al. (1997)	29			29 (100 %)		BD-I patients, National Comorbidity Survey, lifetime rate
Pooled	383		548	247 (64.5 %)	362 (66.05 %)	

Study	Study population	*N*	*N*	Prevalence in study population	Comments
Prevalence of BD in PD with other mental disorders					
Bowen et al. (1994)	Panic disorder	108		BD depression 19.4 % BD hypomanic 3.7 %	Self-report questionnaires
Darby et al. (2011)	OCD			BD-I 5.3 % BD-II 10.7 %	
Goldstein and Levitt (2007)	Youth-onset anxiety disorder	1,571	41,522	BD-I 14.57 %	National Epidemiologic Study, lifetime
Judd et al. (1998)	GAD			BD 17 %	National Comorbidity Survey
Lensi et al. (1996)	OCD	263		BD-I 1.5 % BD-II 13 %	Lifetime rates, probably overlapping with Perugi et al. (1997)
MacKinnon et al. (1997)	Panic dis	41		BD 88 %	
Perugi et al. (1997)	OCD	315		BD-I 2 % BD-II 13.6 %	Lifetime rates, probably including Lensi et al. (1996)
Perugi et al. (1999)	Panic disorder	119		BD-I 0.8 % BD-II 5 %	

Perugi et al. (1999)	Social phobia	71		BD-I 0 % BD-II 21.1 %	
Perugi et al. (1999)	OCD	79		BD-I 3.8 % BD-II 17.7 %	Overlapping with previous studies
Perugi et al. (2001)	Social phobia	153		BD-II 9.1 %	Overlapping with previous studies
Savino et al. (1993)	Panic disorder	140		7.1 %	Lifetime rates
Schneier et al. (1992)	Social phobia	361			Epidemiological Catchment Area study, lifetime rates
Wittchen et al. (1994)	GAD	8,098		10.5 %	National Comorbidity Survey, lifetime rates

MDD major depressive disorder

10.1.1 Comorbid Anxiety

Anxiety is extremely common in psychiatric patients, either as isolated symptoms or as full-blown comorbid disorders. This 'comorbidity' is so frequent that symptoms of anxiety could be considered to be 'non-specific' and 'transnosological'. Kraepelin was the first to describe it as a core feature of BD, and he embedded it in the clinical subtypes he described. However, only during the last couple of decades, there was a huge increase in published papers on this specific topic (Provencher et al. 2012). Especially in the frame of mixed episodes or anxious and agitated depression, anxiety and psychic tension are core components of the clinical picture in almost half of acutely ill patients (Cassidy et al. 1998a, b). This is partially responsible for the varying prevalence rates among studies and the conflicting opinions between authors.

Any anxiety disorder is reported to be present in 42–93 % of patients during lifetime and in almost 11–70 % cross-sectionally (Young et al. 2013; Tamam and Ozpoyraz 2002; Altshuler et al. 2010; Zutshi et al. 2006; Simon et al. 2004b; Kawa et al. 2005; Kessler et al. 1997; Levander et al. 2007; Nakagawa et al. 2008; Goldstein and Levitt 2008; Schaffer et al. 2006; Otto et al. 2006; Nery-Fernandes et al. 2009; Mantere et al. 2006, 2010; Henry et al. 2003; Freeman et al. 2002; Dittmann et al. 2002; Das 2013; Cosoff and Hafner 1998; Ciapparelli et al. 2007; Bellani et al. 2012; McElroy et al. 2001; Boylan et al. 2004; Szadoczky et al. 1998; Weber et al. 2011; Azorin et al. 2009). Up to half of these BD patients with comorbid anxiety manifest at least two anxiety disorders (Henry et al. 2003).

Comorbid anxiety is probably related to predominant depressive polarity (Das 2013; Coryell et al. 2009), the presence of depressive symptoms during a manic episode (Post et al. 1989), the severity of manic symptoms and overall severity of the disease (Lee and Dunner 2008; Gonzalez-Pinto et al. 2012; Toniolo et al. 2009), worse outcome (Young et al. 1993; Lee and Dunner 2008; Keller 2006; Gaudiano and Miller 2005; Frank et al. 2002; Otto et al. 2006; Feske et al. 2000; Keck et al. 1998; Conus et al. 2006; El-Mallakh and Hollifield 2008; Tohen et al. 2007), longer recovery time from index mood episode and especially depression (Frank et al. 2002; Das 2013; Coryell et al. 2009; Otto et al. 2006), earlier relapse (Otto et al. 2006) and lower quality of life (Kauer-Sant'Anna et al. 2007). Generalized anxiety disorder (GAD) and social phobia have the worst impact, probably because they are chronic in nature and trait-like (Boylan et al. 2004). However, some authors suggest that no such a relationship exists (Henry et al. 2003). The relationship of comorbid anxiety with suicidality is questionable (Slama et al. 2004). Probably it is more frequent in BD-II than in BD-I patients (Dittmann et al. 2002), although rapid cycling and substance abuse might reverse this and dramatically increase anxiety rates in BD-I (Gao et al. 2008).

Concerning the rates of BD in anxiety patients, they vary from study to study depending mainly on the specific anxiety disorder and probably on the phase of the illness. It has been reported that up to 21 % of anxiety patients also suffer from BD (Yerevanian et al. 2001; Savino et al. 1993; Schneier et al. 1992; Wittchen et al. 1994; Lensi et al. 1996; Perugi et al. 1997, 1999; Bowen et al. 1994; Goldstein and Levitt 2007) and in these patients anxiety has a very early age at onset, often preceding the

onset of BD itself (Goldstein and Levitt 2007). The phase of the disorder plays an important role; rates of anxiety are very low in purely and euphoric manic patients, while multiple anxiety disorders are present in the majority of mixed or depressive (Gaudiano and Miller 2005; Dilsaver and Chen 2003; McElroy et al. 1995; Himmelhoch and Garfinkel 1986) and seem to correlate with rapid cycling (Boylan et al. 2004; MacKinnon et al. 2002, 2003a). The literature suggest a strong connection between anxiety and impulsivity in BD patients, probably because increased arousal and reduced cognitive efficiency associated with anxiety could result in less rational and more impulsive thinking (Taylor et al. 2008; Bellani et al. 2012).

It is reported that anxiety is more common in BD in comparison to unipolar depression (Bellani et al. 2012; Szadoczky et al. 1998; Yerevanian et al. 2001; Chen and Dilsaver 1995); however, this does not accurately reflect the accumulated data (Table 10.2). At least one study found close to 80 % of BD patients to manifest any anxiety disorder, and it also reported that unipolar patients manifested even higher rates (>90 %) (Pini et al. 1997).

The reported rates concerning the presence of any anxiety disorder in BD patients are shown in detail in Table 10.2. The pooled rate suggests that cross-sectionally 14 % of BD patients suffer from any anxiety disorder. This rate is three times higher to that reported for the control population but three to four times or more lower in comparison to that reported for patients with schizophrenia or unipolar depression. The pooled lifetime rate for any anxiety disorder for BD patients is 42 % and still lower but very close to that reported for unipolar depressive patients and again almost three times higher in comparison to the control population. The great discrepancy of cross-sectional and lifetime rates suggest an episodic character in the presence of anxiety disorders in BD patients, while on the contrary it seems that in unipolar patients anxiety runs a more chronic course.

10.1.1.1 Comorbid Generalized Anxiety Disorder (GAD)

GAD tends to be chronic and thus lifetime and cross-sectional rates are almost identical; however, the prevalence varies widely from below 2 % up to above 40 % (Schaffer et al. 2006; Tamam and Ozpoyraz 2002; Zutshi et al. 2006; Simon et al. 2004b; Kessler et al. 1997; Nakagawa et al. 2008; Goldstein and Levitt 2008; Rihmer et al. 2001; Azorin et al. 2009; Otto et al. 2006; Slama et al. 2004; Dell'Osso et al. 2011; Cosoff and Hafner 1998; Pini et al. 1997; Mantere et al. 2006; McElroy et al. 2001; Bellani et al. 2012; Young et al. 1993; Boylan et al. 2004; Coryell et al. 2009) (Szadoczky et al. 1998). It is important to note that the overall prevalence of comorbid anxiety is lower in BD-I in comparison to BD-II, which is higher and similar to that observed in unipolar major depression (Mantere et al. 2006). Comorbid GAD might relate to increased suicidality (Neves et al. 2009).

From a reverse angle, it has been reported that 8.6–17 % of GAD patients also suffer from BD (Wittchen et al. 1994; Yerevanian et al. 2001; Judd et al. 1998).

The reported rates concerning the presence of GAD in BD patients are shown in detail in Table 10.3. The pooled rate suggests that cross-sectionally 11.2 % of BD patients suffer from GAD. This rate is twice as much as that reported for the control population but similar to that reported for patients with schizophrenia or unipolar depression. The pooled lifetime rate for GAD in BD patients is 17.6 %, and it is three

Table 10.2 Cross-sectional and lifetime rates of any anxiety disorder comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Bellani et al. (2012)	205	MDD	105	122 (59.5 %)	30 (28.6 %)	
Boylan et al. (2004)	138			77 (55.8 %)		
Cassidy et al. (1998b)	316			124 (39.2 %)		Acute mania, at least one anxiety symptom present at interview
Ciapparelli et al. (2007)	56	Schiz	98	23 (41.1 %)	72 (73.9 %)	BD with psychotic features
Cosoff and Hafner (1998)	20	Schiz	60	14 (70.0 %)	34 (56.7 %)	
Das (2013)	102			30 (29.4 %)		Acute mania
Mantere et al. (2006, 2010)	191	MDD	269	85 (44.5 %)	152 (56.5 %)	Acute phase BD, half pts depressed
McElroy et al. (2001)	288			86 (29.9 %)		STANLEY foundation data
Otto et al. (2006)	918			293 (31.9 %)		STEP-BD, >75 % BD-I, half in recovery, ~25 % depressed
Simon et al. (2004b)	360			123 (34.2 %)		BD-I
Simon et al. (2004b)	115			22 (19.1 %)		BD-II
Tamam and Ozpoyraz (2002)	70			36 (51.4 %)		BD-I
Weber et al. (2011)	27,054	All non-BD discharges	2,325,247	3,071 (11.4 %)	78,809 (3.4 %)	Hospital records
Zutshi et al. (2006)	80	Nonpsychiatric controls	50	40 (50.0 %)	7 (14.0 %)	Remitted BD pts
Pooled	*29,913*			*4,146 (13.9%)*		
		Schiz	*158*		*106 (67.1 %)*	
		MDD	*374*		*207 (55.4 %)*	
		Other controls	*2,325,297*		*78,816 (3.4 %)*	

Lifetime rates						
Altshuler et al. (2010)	711			277 (39.0 %)		STANLEY foundation data, >80 % BD-I
Azorin et al. (2009)	1,090			297 (27.2 %)		Acute mania, hospitalized pts
Das (2013)	102			72 (70.6 %)		Acute mania
Dittmann et al. (2002)	108			11 (10.4 %)		BD-I
Dittmann et al. (2002)	38			7 (18.4 %)		BD-II
Goldstein and Levitt (2008)	1,411			670 (47.5 %)		2001–2002 National Epidemiologic Survey
Henry et al. (2003)	318			75 (23.6 %)		75 % BD-I, half pts psychotic
Kawa et al. (2005)	211			90 (42.6 %)		
Kessler et al. (1994, 1997)	29			27 (93.1 %)		BD-I National Comorbidity Study, retrospective study, limited by recall bias
Levander et al. (2007)	350			163 (46.6 %)		STANLEY foundation data, 2/3 of patients with alcohol use lifetime
Mantere et al. (2006)	191	MDD	269	102 (53.40)	152 (56.5 %)	Acute phase BD
McElroy et al. (2001)	288			122 (42.0 %)		STANLEY foundation data
Nakagawa et al. (2008)	116			60 (51.7 %)		Depressed patients
Nery-Fernandes et al. (2009)	62			21 (33.7 %)		Euthymic patients
Pini et al. (1997)	24	MDD	38	19 (79.2 %)	35 (92.1 %)	Depressed patients
Schaffer et al. (2006)	852			441 (51.8 %)		Canadian Community Health Survey: mental health and well-being
Simon et al. (2004b)	360			190 (52.8 %)		BD-I
Simon et al. (2004b)	115			53 (46.1 %)		BD-II
Tamam and Ozpoyraz (2002)	70			43 (61.4 %)		BD-I

(continued)

Table 10.2 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Yerevanian et al. (2001)	35	MDD	98	13 (37.1 %)	47 (48.0 %)	Mostly BD-II
Young et al. (2013)	304			68 (22.4 %)		
Zutshi et al. (2006)	80	Nonpsychiatric controls	*50*	49 (61.3 %)	7 (14.0 %)	Remitted BD pts
Pooled	*6,865*			*2,870 (41.8 %)*		
		MDD	*405*		*234 (57.8 %)*	
		Nonpsychiatric controls	*50*		*7 (14.0 %)*	

MDD major depressive disorder, *Schiz* schizophrenia

Table 10.3 Cross-sectional and lifetime rates of generalized anxiety disorder comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional						
Bellani et al. (2012)	205	MDD	105	28 (13.7 %)	4 (3.8 %)	
Boylan et al. (2004)	138			43 (31.2 %)		
Cosoff and Hafner (1998)	20	Schiz	60	2 (10.0 %)	7 (11.7 %)	
Dell'Osso et al. (2011)	508			7 (1.4 %)		
Mantere et al. (2006)	191	MDD	269	29 (15.18)	37 (13.75)	Acute phase BD
McElroy et al. (2001)	288			8 (2.78)		STANLEY foundation data
Otto et al. (2006)	918			122 (13.3 %)		STEP-BD. >75 % BD-I, half pts in recovery, ~25 % depressed
Simon et al. (2004b)	360			46 (12.8 %)		BD-I
Simon et al. (2004b)	115			12 (10.4 %)		BD-II
Tamam and Ozpoyraz (2002)	70			9 (12.9 %)		
Zutshi et al. (2006)	80	Controls	50	19 (23.8 %)	3 (6 %)	Remitted BD pts
Pooled	*2,893*	*Controls*	*50*	*325 (11.2 %)*	*3 (6 %)*	
		MDD	*374*		*41 (11.0 %)*	
		Schiz	*60*		*7 (11.7 %)*	
Lifetime						
Azorin et al. (2009)	1,090			217 (19.9 %)		Acutely manic hospitalized pts
Coryell et al. (2009)	427			20 (4.68 %)		
Goldstein and Levitt (2008)	1,411			346 (24.5 %)		2001–2002 National Epidemiologic Survey
Kessler et al. (1997)	29			12 (41.4 %)		BD-I, National Comorbidity Study

(continued)

Table 10.3 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
McElroy et al. (2001)	288			8 (2.8 %)		STANLEY foundation data
Nakagawa et al. (2008)	116			2 (1.7 %)		Depressed pts
Pini et al. (1997)	24	MDD	38	8 (33.3 %)	14 (36.8 %)	Depressed pts
Rihmer et al. (2001)	95	MDD	443	10 (10.5 %)	62 (14.0 %)	BD-I, Hungarian epidemiological study
Rihmer et al. (2001)	24	MDD	443	5 (20.8 %)	62 (14.0 %)	BD-II, Hungarian epidemiological study
Simon et al. (2004b)	360			68 (18.9 %)		BD-I
Simon et al. (2004b)	115			19 (16.5 %)		BD-II
Slama et al. (2004)	180			7 (3.9 %)		Pts in remission
Szadoczky et al. (1998)	149	MDD	443	22 (14.4 %)	61 (13.7 %)	Epidemiological, rates weighted for sex
Tamam and Ozpoyraz (2002)	70			10 (14.3 %)		BD-I
Yerevanian et al. (2001)	35	MDD	98	3 (8.6 %)	22 (22.5 %)	Mostly BD-II
Young et al. (1993)	81			26 (32.1 %)		
Zutshi et al. (2006)	80	Controls	*50*	20 (25 %)	3 (6 %)	Remitted BD pts
Pooled	*4,574*			*803 (17.6 %)*		
		Controls	*50*		*3 (6 %)*	
		MDD	*1,022*		*159 (15.6 %)*	

MDD major depressive disorder, *Schiz* schizophrenia

times higher in comparison to that reported concerning the control population and similar to the rate reported for unipolar depressed patients. The small but obvious discrepancy of cross-sectional and lifetime rates suggests an admixture of an episodic and chronic character in the presence of GAD in BD and unipolar depressive patients.

10.1.1.2 Comorbid Panic Disorder

In BD patients, panic disorder is reported to have a cross-sectional prevalence of 2.3–62.5 % and a lifetime prevalence of 2.9–56.5 % (Vieta et al. 2001; Schaffer et al. 2006; Young et al. 1993, 2013; Tamam and Ozpoyraz 2002; Altshuler et al. 2010; Zutshi et al. 2006; Simon et al. 2004b; Kawa et al. 2005; Kessler et al. 1994, 1997; Levander et al. 2007; Nakagawa et al. 2008; Goldstein and Levitt 2008; Rihmer et al. 2001; Azorin et al. 2009; Pini et al. 1997, 2003; Otto et al. 2006; Okan Ibiloglu and Caykoylu 2011; Mula et al. 2008a; Henry et al. 2003; Dilsaver et al. 1997, 2008; Slama et al. 2004; Dell'Osso et al. 2011; Craig et al. 2002; Cosoff and Hafner 1998; Ciapparelli et al. 2007; Mantere et al. 2006; McElroy et al. 2001; Robins and Regier 1991; Chen and Dilsaver 1995; Bellani et al. 2012; Boylan et al. 2004; Coryell et al. 2009; Szadoczky et al. 1998). The phase of the disorder plays an important role; panic is virtually absent in purely manic patients and present in more than 80 % of mixed or depressive patients (Dilsaver and Chen 2003). Comorbid panic disorder is related to worse outcome of BD with younger age at onset (Schurhoff et al. 2000), more depressive episodes and possibly higher suicidality (Frank et al. 2002; Kilbane et al. 2009; Neves et al. 2009). Reversely, panic attacks constitute a risk factor for the future development of BD (Kinley et al. 2011; Goodwin and Hamilton 2002) and panic disorder when comorbid with BD has an earlier onset and greater severity (Goodwin and Hoven 2002).

Patients with panic disorder have rates of BD ranging from 6 to 88 % (Savino et al. 1993; Bowen et al. 1994; Perugi et al. 1997, 1999; MacKinnon et al. 1997; Yerevanian et al. 2001), and switching to mania or hypomania during treatment of panic disorder with antidepressants has been reported (Pecknold and Fleury 1986; Sholomskas 1990).

The reported rates concerning the presence of panic disorder in BD patients are shown in detail in Table 10.4. The pooled rate suggests that cross-sectionally 15.4 % of BD patients suffer from panic disorder. This rate is more than ten times the rate expected for the general population but similar to that reported for patients with schizophrenia or unipolar depression. The pooled lifetime rate for panic disorder in BD patients is 16.9 %, and it is again more than ten times higher in comparison to that reported concerning the control population and similar to that reported for unipolar depressive patients. The negligible difference between cross-sectional and lifetime prevalence suggests that panic disorder probably presents with a chronic rather than episodic course in BD and unipolar depressive patients.

10.1.1.3 Comorbid Simple (Specific) Phobia

Simple (specific) phobia is also comorbid with BD, and cross-sectional comorbid rates are reported to vary from 1.6 to 22.9 % (Boylan et al. 2004; Cosoff and Hafner 1998; Strakowski et al. 1992; Tamam and Ozpoyraz 2002; Vieta et al. 2001).

Table 10.4 Cross-sectional and lifetime rates of panic disorder comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Bellani et al. (2012)	205	MDD	105	60 (29.3 %)	10 (9.8 %)	
Boylan et al. (2004)	138			37 (26.8 %)		
Ciapparelli et al. (2007)	56	Schiz	98	13 (23.2 %)	24 (24.5 %)	BD with psychotic features
Coryell et al. (2009)	427			107 (25.5 %)		
Cosoff and Hafner (1998)	20	Schiz	60	3 (15.0 %)	3 (5.0 %)	
Dell'Osso et al. (2011)	508			32 (6.3 %)		
Dilsaver and Chen (2003)	25			1 (4.0 %)		Pure manic, >90 % of pts with psychotic features
Dilsaver and Chen (2003)	19			16 (84.2 %)		Depressive mania, >90 % of pts with psychotic features
Dilsaver et al. (1997)	53			33 (62.3 %)		Bipolar depression
Dilsaver et al. (1997)	32			1 (2.3 %)		Pure mania
Dilsaver et al. (1997)	44			20 (62.5 %)		Depressive mania
Mantere et al. (2006)	191	MDD	269	46 (24.1)	45 (16.7 %)	Acute phase BD pts
McElroy et al. (2001)	288			27 (9.4 %)		STANLEY foundation data
Okan Ibiloglu and Caykoylu (2011)	50			30 (60.0 %)		BD-I
Okan Ibiloglu and Caykoylu (2011)	46			22 (47.8 %)		BD-II
Otto et al. (2006)	918			78 (8.5 %)		STEP-BD, >75 % BD-I, half pts in recovery, ~25 % depressed
Pini et al. (2003)	151			35 (23.2 %)		
Simon et al. (2004b)	360			33 (9.2 %)		BD-I
Simon et al. (2004b)	115			5 (4.4 %)		BD-II
Strakowski et al. (1992)	41			2 (4.9 %)		First-episode manic/mixed inpatients
Tamam and Ozpoyraz (2002)	70			4 (5.7 %)		BD-I

Vieta et al. (2001)	129			3 (2.3 %)		BD-I, pts in remission
Zutshi et al. (2006)	80	Controls	50	4 (5.0 %)	0 (0 %)	Remitted BD
Pooled	*3,966*			*612 (15.4 %)*		
		MDD	*374*		*55 (14.7 %)*	
		Schiz	*158*		*27 (17.1 %)*	
		Controls	*50*		*0 (0.0 %)*	
Lifetime rates						
Altshuler et al. (2010)	711			122 (17.2 %)		>80 % BD-I, STANLEY foundation data
Azorin et al. (2009)	1,090			56 (5.1 %)		Acutely manic hospitalized pts
Chen and Dilsaver (1995; Robins and Regier (1991)	168	Gen pop	18,571	35 (20.8 %)	149 (0.8 %)	Epidemiological Catchment Area
Chen and Dilsaver (1995; Robins and Regier (1991)	168	MDD	557	35 (20.8 %)	56 (10.0 %)	Epidemiological Catchment Area
Coryell et al. (2009)	427			17 (4.0 %)		
Craig et al. (2002)	138	MDD with psychosis	87	4 (2.9 %)	7 (8.0 %)	BD with psychosis
Dilsaver et al. (2008)	69	MDD	118	39 (56.5 %)	27 (22.9 %)	Data from Latinos
Goldstein and Levitt (2008)	1,411			381 (27.0 %)		2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions
Henry et al. (2003)	318			52 (16.4 %)		75 % BD-I, half psychotic, currently or lifetime
Kawa et al. (2005)	211			44 (20.8 %)		
Kessler et al. (1994)	130			43 (33.1 %)		BD-I Epidemiological Catchment Area
Kessler et al. (1997)	29			10 (34.5 %)		BD-I National Comorbidity Survey
Levander et al. (2007)	350			72 (20.6 %)		STANLEY foundation data, 2/3 with alcohol use
McElroy et al. (2001)	288			58 (20.1 %)		STANLEY foundation data
Mula et al. (2008a)	70	MDD	60	10 (14.3 %)	24 (40 %)	BD-I

(continued)

Table 10.4 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Mula et al. (2008a)	51	MDD	60	16 (31.4 %)	24 (40 %)	BD-II
Nakagawa et al. (2008)	116			37 (31.9 %)		BD depression
Pini et al. (1997)	24	MDD	38	9 (37.5 %)	12 (31.6 %)	BD depression
Rihmer et al. (2001)	95	MDD	443	7 (7.4 %)	55 (12.4 %)	BD-I pts, Hungarian epidemiological study
Rihmer et al. (2001)	24	MDD	443	3 (12.5 %)	55 (12.4 %)	BD-II pts, Hungarian epidemiological study
Schaffer et al. (2006)	852			164 (19.3 %)		Canadian Community Health Survey: mental health and well-being
Simon et al. (2004b)	360			66 (18.3 %)		BD-I
Simon et al. (2004b)	115			16 (13.9 %)		BD-II
Slama et al. (2004)	302			24 (7.9 %)		Pts in remission
Szadoczky et al. (1998)	149	MDD	443	16 (10.6 %)	55 (12.4 %)	Epidemiological study
Tamam and Ozpoyraz (2002)	70			7 (10.0 %)		BD-I
Yerevanian et al. (2001)	35	MDD	98	2 (5.7 %)	18 (18.4 %)	Most pts BD-II
Young et al. (1993)	81			26 (32.1 %)		
Young et al. (2013)	304			21 (6.9 %)		
Zutshi et al. (2006)	80	Controls	50	6 (7.5 %)	0 (0.0 %)	Remitted BD
Pooled	*8,068*			*1,363 (16.9 %)*		
		MDD	*1,401*		*199 (14.2 %)*	
		Controls	*18,621*		*149 (0.8 %)*	

MDD major depressive disorder, *Schiz* schizophrenia

Lifetime rates vary from 3 % to 65.5 % (Szadoczky et al. 1998; Yerevanian et al. 2001; Coryell et al. 2009; Pini et al. 1997; Kessler et al. 1997; Slama et al. 2004; Rihmer et al. 2001; Nakagawa et al. 2008; Kawa et al. 2005; Tamam and Ozpoyraz 2002; Levander et al. 2007; Altshuler et al. 2010).

The reported rates concerning the presence of simple (specific) phobia in BD patients are shown in detail in Table 10.5. The pooled rate suggests that cross-sectionally 9 % of BD patients suffer from simple phobia. This rate is double in comparison to that reported for patients with schizophrenia. The pooled lifetime rate for simple phobia in BD patients is 10.4 %, and thus it is similar to the cross-sectional rate, suggesting a chronic course for simple phobias in BD patients. The lifetime prevalence of simple phobia in unipolar depression is around 30 % higher in comparison to BD.

10.1.1.4 Comorbid Social Anxiety Disorder (Social Phobia)

Social phobia as comorbid condition in BD patients seems also to run a chronic course with cross-sectional rate ranging from 1.6 to 29 % and a lifetime ranging from 2.5 to 53.6 % (Vieta et al. 2001; Schaffer et al. 2006; Tamam and Ozpoyraz 2002; Altshuler et al. 2010; Zutshi et al. 2006; Simon et al. 2004b; Kawa et al. 2005; Levander et al. 2007; Nakagawa et al. 2008; Goldstein and Levitt 2008; Rihmer et al. 2001; Azorin et al. 2009; Pini et al. 2006; Otto et al. 2006; Okan Ibiloglu and Caykoylu 2011; Slama et al. 2004; Dilsaver et al. 2008; Kessler et al. 1994; Cosoff and Hafner 1998; Ciapparelli et al. 2007; McElroy et al. 2001; Bellani et al. 2012; Boylan et al. 2004; Szadoczky et al. 1998). In the ECA study, almost half of BD patients also had social anxiety disorder (Kessler et al. 1994), and in half of them, social phobia appeared more than a decade earlier than BD (Kessler et al. 1999). The phase of the disorder plays an important role; social phobia is virtually absent in purely manic patients and present in two-thirds of mixed or depressive (Dilsaver and Chen 2003). Peculiarly, one group of authors didn't find any such symptoms in depressed BD patients (Pini et al. 1997). In spite of the fact that social phobia is correlated to functional impairment, increased suicidality and overall severity and outcome, its presence is often neglected, and it is not adequately treated, even when not comorbid with major mood disorders (Olfson et al. 2000; Bisserbe et al. 1996; Weiller et al. 1996). However, when comorbid with BD, its treatment is problematic since the appropriate treatment is antidepressants, and it seems that almost 80 % of patients who respond also switch to hypomania (Himmelhoch 1998).

It is reported that on average, 9.1 % of patients with social phobia also manifest BD during lifetime (Perugi et al. 2001). Depending on the clinical state of the study sample, up to 20 % of social phobia patients suffer from BD-II, but BD-I seems to be rare or even absent (Perugi et al. 1999).

The reported rates concerning the presence of social phobia in BD patients are shown in detail in Table 10.6. The pooled rate suggests that cross-sectionally 13.9 % of BD patients suffer from social phobia. This rate is almost double in comparison to that reported in the control group and similar to that of unipolar depression but somewhat lower to that observed in patients with schizophrenia. The pooled lifetime rate for social phobia in BD patients is 18.8 %, and thus it is only marginally

Table 10.5 Cross-sectional and lifetime rates of simple (specific) phobia comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Boylan et al. (2004)	138			14 (10.1 %)		
Cosoff and Hafner (1998)	20	Schiz	60	2 (10 %)	3 (5 %)	
Strakowski et al. (1992)	41			2 (4.9 %)		First-episode manic/mixed inpatients
Tamam and Ozpoyraz (2002)	70			16 (22.9 %)		BD-I
Vieta et al. (2001)	129			2 (1.6 %)		BD-I pts in remission
Pooled	*398*			*36 (9.0 %)*		
		Schiz	*60*		*3 (5 %)*	
Lifetime rates						
Szadoczky et al. (1998)	149			19 (12.9 %)		Epidemiological study
Yerevanian et al. (2001)	35	MDD	98	6 (17.1 %)	25 (25.5 %)	Mostly BD-II pts
Coryell et al. (2009)	427			23 (5.38 %)		
Pini et al. (1997)	24	MDD	38	1 (5.3 %)	2 (5.7 %)	BD depression
Kessler et al. (1997)	29			19 (65.5 %)		BD-I pts National Comorbidity Study
Slama et al. (2004)	300			9 (3 %)		Pts in remission
Rihmer et al. (2001)	95	MDD	443	9 (9.5 %)	51 (11.5 %)	BD-I Hungarian epidemiological study
Rihmer et al. (2001)	24	MDD	443	4 (16.7 %)	51 (11.5 %)	BD-II Hungarian epidemiological study
Nakagawa et al. (2008)	116			12 (10.3 %)		BD depression
Kawa et al. (2005)	211			33 (15.6 %)		
Tamam and Ozpoyraz (2002)	70			18 (25.7 %)		BD-I pts
Levander et al. (2007)	350			47 (13.4 %)		STANLEY foundation data, 2/3 of pts with alcohol use
Altshuler et al. (2010)	711			63 (8,9 %)		>80 % BD-I pts, STANLEY foundation data
Pooled	*2,541*			*263 (10.4 %)*		
		MDD	*579*		*78 (13.5 %)*	

MDD major depressive disorder, *Schiz* schizophrenia

Table 10.6 Cross-sectional and lifetime rates of social phobia comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Bellani et al. (2012)	205	MDD	105	30 (14.6 %)	8 (7.6 %)	
Boylan et al. (2004)	138			24 (	17.4 %)	
Ciapparelli et al. (2007)	56	Schiz	98	6 (10.7 %)	19 (19.4 %)	BD with psychotic features
Cosoff and Hafner (1998)	20	Schiz	60	1 (5.0 %)	10 (16.7 %)	
Dilsaver and Chen (2003)	25			0 (0.0 %)		Pure manic, >90 % pts with psychotic features
Dilsaver and Chen (2003)	19			13 (68.4 %)		Depressive mania, >90 % pts with psychotic features
Mantere et al. (2006)	191	MDD	269	34 (17.8 %)	53 (19.7 %)	Acute BD pts
McElroy et al. (2001)	288			36 (12.5 %)		STANLEY foundation data
Okan Ibiloglu and Caykoylu (2011)	50			8 (16.0 %)		BD-I
Okan Ibiloglu and Caykoylu (2011)	46			7 (15.2 %)		BD-II
Otto et al. (2006)	918			122 (13.3 %)		STEP-BD, >75 % BD-I, half pts in recovery, ~25 % depressed
Simon et al. (2004b)	360			50 (13.9 %)		BD-I
Simon et al. (2004b)	115			10 (8.7 %)		BD-II
Tamam and Ozpoyraz (2002)	70			12 (17.1 %)		BD-I
Vieta et al. (2001)	129			2 (1.6 %)		BD-I patients in remission
Zutshi et al. (2006)	80	Controls	50	23 (28.8 %)	4 (8.0 %)	Remitted BD
Pooled	*2,710*			*378 (13.9 %)*		
		MDD	*374*		*61 (16.3 %)*	
		Schiz	*158*		*29 (18.4 %)*	
		Controls	*50*		*4 (8.0 %)*	

(continued)

Table 10.6 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Lifetime rates						
Altshuler et al. (2010)	711			80 (11.3 %)		>80 % BD-I pts, STANLEY foundation data
Azorin et al. (2009)	1,090			27 (2.5 %)		Acutely hospitalized manic pts
Dilsaver et al. (2008)	69	MDD	118	37 (53.6 %)	20 (16.9 %)	Latino pts
Goldstein and Levitt (2008)	1,411			320 (22.7 %)		2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions
Kawa et al. (2005)	211			40 (18.9 %)		
Kessler et al. (1994)	130			61 (47.2 %)		BD-I Epidemiological Catchment Area
Kessler et al. (1997, 1999)	29	MDD	1,080	13 (44.8 %)	296 (26.5 %)	BD-I pts National Comorbidity Study
Levander et al. (2007)	350			65 (18.6 %)		STANLEY foundation data, 2/3 pts with alcohol use
McElroy et al. (2001)	288			47 (16.3 %)		STANLEY foundation data
Nakagawa et al. (2008)	116			13 (11.2 %)		Bipolar depression
Pini et al. (1997)	24	MDD	38	0 (0.0 %)	4 (10.5 %)	BD depression
Pini et al. (2006)	189			24 (12.7 %)		
Rihmer et al. (2001)	95	MDD	443	4 (4.2 %)	78 (17.6 %)	BD-I Hungarian epidemiological study
Rihmer et al. (2001)	24	MDD	443	3 (12.5 %)	78 (17.6 %)	BD-II Hungarian epidemiological study
Schaffer et al. (2006)	852			338 (39.7 %)		Canadian Community Health Survey: mental health and well-being
Simon et al. (2004b)	360			83 (23.1 %)		BD-I
Simon et al. (2004b)	115			21 (18.3 %)		BD-II
Slama et al. (2004)	302			24 (7.9 %)		Pts in remission

Szadoczky et al. (1998)	149	MDD	443	12 (7.8 %)	78 (17.6 %)	Epidemiological
Tamam and Ozpoyraz (2002)	70			14 (20.0 %)		BD-I
Zutshi et al. (2006)	80	Controls	50	24 (30.0 %)	4 (8.0 %)	Remitted BD pts
Pooled	*6,665*			*1,250 (18.8 %)*		
		MDD	*1,729*		*398 (23.0 %)*	
		Controls	*50*		*4 (8.0 %)*	

MDD major depressive disorder, *Schiz* schizophrenia

higher in comparison to the cross-sectional rate, suggesting a chronic course for social phobia in BD patients. It is more than double the rate observed in the control population. The lifetime prevalence of simple phobia in unipolar depression is around 23 %, and it is higher in comparison to BD.

10.1.1.5 Comorbid Post-traumatic Stress Disorder (PTSD)

PTSD is very frequent in BD patients with a cross-sectional rate between 0.9 and 21 % (Bellani et al. 2012; Boylan et al. 2004; Mantere et al. 2006; McElroy et al. 2001; Okan Ibiloglu and Caykoylu 2011; Otto et al. 2006; Simon et al. 2004b; Tamam and Ozpoyraz 2002; Keck et al. 1995; Neria et al. 2002; Strakowski et al. 1998) and a lifetime rate between 2 and 62.3 % (Freeman et al. 2002; Altshuler et al. 2010; Azorin et al. 2009; Dilsaver et al. 2008; Kessler et al. 1994, 1997; Levander et al. 2007; McElroy et al. 2001; Mueser et al. 2004; Nakagawa et al. 2008; Simon et al. 2004b; Tamam and Ozpoyraz 2002; Yerevanian et al. 2001).

The nature of this comorbidity is unknown; however, BD patients are vulnerable to develop PTSD both because they are at a higher risk to experience a traumatic situation mainly because of impulsivity and poor judgement but also because they are more likely to develop PTSD after experiencing a traumatic event. During periods of mania or hyperthymia, BD patients manifest a high resiliency to traumatic events, although during these specific periods most traumatic events are caused and experienced. This resiliency rapidly disappears after the resolution of the hyperthymic state. Especially during periods of depression, BD patients are extremely vulnerable to traumatic events. In turn, the presence of PTSD might worsen the overall course of BD since it disrupts sleep patterns and increases the overall stress. PTSD comorbidity is related to worse outcome, more substance abuse, low quality of life and more disability as well as higher suicidality (Simon et al. 2004b).

The reported rates concerning the presence of PTSD in BD patients are shown in detail in Table 10.7. The pooled rate suggests that cross-sectionally 7.8 % of BD patients suffer from PTSD. This rate is almost double in comparison to that reported in unipolar depression. The pooled lifetime rate for PTSD in BD patients is 11.7 %, and thus it is significantly higher in comparison to the cross-sectional rate, suggesting an episodic course for PTSD in BD patients. The lifetime prevalence of PTSD in unipolar depression is around 22 %, and it is double of that reported concerning BD.

Significantly lower in comparison to 16 % reported by an older meta-analysis on seven studies alone which did not distinguish between studies reporting cross-sectional and lifetime rates (Otto et al. 2004).

10.1.2 Comorbid Obsessive–Compulsive Disorder (OCD)

Comorbid OCD in BD patients is reported to have a prevalence ranging from 1.6 to 35 % cross-sectionally (Vieta et al. 2001; Pashinian et al. 2006; Krishnan 2005; Cosoff and Hafner 1998; Boylan et al. 2004; Kruger et al. 1995, 2000; Otto et al. 2006; Tamam and Ozpoyraz 2002; Dell'Osso et al. 2011; Ciapparelli et al. 2007;

Table 10.7 Cross-sectional and lifetime rates of PTSD comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Bellani et al. (2012)	205	MDD	105	37 (18.0 %)	11 (10.5 %)	
Boylan et al. (2004)	138			20 (14.5 %)		
Keck et al. (1995)	71			12 (16.9 %)		Manic/mixed inpatients
Mantere et al. (2006)	191	MDD	269	20 (10.5 %)	2 (0.7 %)	Acute BD pts
McElroy et al. (2001)	288			12 (4.2 %)		STANLEY foundation data
Neria et al. (2002)	102			11 (10.8 %)		First admission pts
Okan Ibiloglu and Caykoylu (2011)	50			5 (10.0 %)		BD-I pts
Okan Ibiloglu and Caykoylu (2011)	46			3 (6.5 %)		BD-II pts
Otto et al. (2006)	918			44 (4.8 %)		STEP-BD. >75 % BD-I, half pts in recovery, ~25 % depressed
Simon et al. (2004b)	360			23 (6.4 %)		BD-I pts
Simon et al. (2004b)	115			1 (0.9 %)		BD-II pts
Strakowski et al. (1998)	77			16 (20.8 %)		Manic/mixed first-episode inpatients
Tamam and Ozpoyraz (2002)	70			0 (0.0 %)		BD-I pts
Pooled	*2,631*			*204 (7.8 %)*		
		MDD	*374*		*13 (3.5 %)*	
Lifetime rates						
Altshuler et al. (2010)	711			56 (7.9 %)		>80 % BD-I STANLEY foundation data
Azorin et al. (2009)	1,090			22 (2.0 %)		Acutely manic hospitalized pts
Dilsaver et al. (2008)	69	MDD	118	43 (62.3 %)	28 (23.8 %)	Latinos
Kessler et al. (1994)	130			50 (38.8 %)		BD-I pts Epidemiological Catchment Area

(continued)

Table 10.7 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Kessler et al. (1997)	29			11 (37.9 %)		BD-I pts National Comorbidity Study
Levander et al. (2007)	350			36 (10.3 %)		STANLEY foundation data, 2/3 with alcohol use
McElroy et al. (2001)	288			19 (6.6 %)		STANLEY foundation data
Mueser et al. (2004)	141	MDD	78	55 (39.0 %)	35 (44.9 %)	
Nakagawa et al. (2008)	116			24 (20.7 %)		Depressed pts
Simon et al. (2004b)	360			67 (18.8 %)		BD-I pts
Simon et al. (2004b)	115			14 (12.2 %)		BD-II pts
Tamam and Ozpoyraz (2002)	70			10 (14.3 %)		BD-I pts
Yerevanian et al. (2001)	35	MDD	98	3 (8.6 %)	3 (3.0 %)	Mostly BD-II pts
Pooled	*3,504*			*410 (11.7 %)*		
		MDD	*294*		*66 (22.4 %)*	

MDD major depressive disorder, *Schiz* schizophrenia, *Gen pop* general population

Okan Ibiloglu and Caykoylu 2011; Koyuncu et al. 2010; Simon et al. 2004b) and 1.5–62.3 % life time (Yerevanian et al. 2001; Tamam and Ozpoyraz 2002; Pini et al. 1997, 2003; Krishnan 2005; Simon et al. 2004b; Altshuler et al. 2010; Azorin et al. 2009; Zutshi et al. 2006; Magalhaes et al. 2010; Szadoczky et al. 1998; Dilsaver et al. 2008; Coryell et al. 2009; Craig et al. 2002; Slama et al. 2004; Henry et al. 2003; Nakagawa et al. 2008; Levander et al. 2007; Chen and Dilsaver 1995; Kawa et al. 2005). Probably, depending on the composition of the study sample, the frequency of OCD is lower in BD in comparison to unipolar depression (Kruger et al. 1995).

Reversely, BD is observed in 10.3–16 % of OCD patients with the majority of these cases (up to two-thirds) being BD-II (Perugi et al. 1997; Timpano et al. 2012; Darby et al. 2011; Hantouche et al. 2002; Maina et al. 2007). However, some rates reported are so low that they suggest BD is not more frequent in OCD than in controls (Nestadt et al. 2009). This might be probably to the fact that the distribution of bipolarity among OCD patients is not homogenous with only female OCD patients manifesting also BD (Grabe et al. 2001). When spectrums instead of distinct disorders are concerned, a significant overlap between the bipolar spectrum and the obsessive spectrum is observed (Angst et al. 2005).

An illness chart, generally suggests that OCD has an early onset and precedes BD onset in half to two-thirds of patients, while in the vast majority the course is chronic and fluctuating (Zutshi et al. 2007; Issler et al. 2005). The similarity between cross-sectional and lifetime rates is in support of the idea that OCD is a chronic condition when comorbid with BD; however, this might not be entirely true since OC symptoms improve significantly during periods of acute mania (Zutshi et al. 2007), and this improvement is so great that often no cases of OCD are detected during periods of acute mania (Magalhaes et al. 2010). Other authors argue that an episodic course appears to be typical of OCD when comorbid with BD (Perugi et al. 1997, 2002; Zutshi et al. 2007; Tukel et al. 2006; Strakowski et al. 1998). According to these suggestions, bipolarity has a pathoplastic effect on OCD (Strakowski et al. 1998; Mahasuar et al. 2011), and probably, in neurobiology, the OC symptoms are neurobiologically related more to BD mechanisms rather than to OCD (Zutshi et al. 2007). There seems that OC symptoms cycle in phase with BD symptomatology, and the rule is that in the absence of mood symptoms OC symptoms also disappear (Strakowski et al. 1998). It is important to mention that switching to mania or hypomania during treatment of OCD with antidepressants has been reported (White et al. 1986; Steiner 1991; Vieta and Bernardo 1992; Rihmer et al. 1996; Perugi et al. 2002).

Comorbid OCD and BD are related with a more gradual onset of OC symptoms (Perugi et al. 1997); higher rate of depressive episodes (Perugi et al. 1997, 2002; Zutshi et al. 2007; Mahasuar et al. 2011); higher general anxiety (Perugi et al. 2002; Zutshi et al. 2007; Tukel et al. 2006); better insight (Tukel et al. 2006); more frequent history of suicide attempts (Magalhaes et al. 2010; Mahasuar et al. 2011; Kruger et al. 2000), rapid cycling and alcohol, nicotine, coffee and substance dependence (Perugi et al. 2002; Magalhaes et al. 2010); and more frequent hospitalizations (Mahasuar et al. 2011) as well as greater overall severity of the clinical picture

and global disability (Mahasuar et al. 2011; Tukel et al. 2006) although OC symptoms might be less severe (Zutshi et al. 2007). In BD patients with comorbid OC, there are reports suggesting a higher frequency of narcissistic and antisocial personality disorders (Maina et al. 2007) and a high family loading for mood disorders (Zutshi et al. 2007). OC symptoms are characterized by a significantly higher rate of sexual, religious and symmetry/exactness obsessions, more ordering/arranging compulsions and a significantly lower rate of checking rituals (Perugi et al. 1997, 2002; Tukel et al. 2006). There is only one study which reports that there was no difference between BD patients with and without comorbid OCD concerning age, sex, education, marital status, polarity, age of BD onset, presence of psychotic symptoms, presence of rapid cycling, history of suicide attempts, first episode type and predominant episode type (Koyuncu et al. 2010).

The reported rates concerning the presence of OCD in BD patients are shown in detail in Table 10.7. The pooled rate suggests that cross-sectionally 8.2 % of BD patients suffer from OCD. This rate is similar to that reported in the unipolar depression group and almost half of that reported in patients with schizophrenia. The pooled lifetime rate for OCD in BD patients is 8.8 % and identical to the cross-sectional rate, suggesting a chronic course for OCD in BD patients. It is more three times higher than the rate observed in the control population and similar to that reported in unipolar depressive patients (Table 10.8).

10.1.3 Comorbid Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is usually considered to be a paediatric disorder; however, its characteristics often persist for the whole life span. It is considered to constitute either an early sign or a risk factor for the development of other mental disorders.

The research on comorbidity of BD with ADHD started after the results of epidemiological studies in children and adolescents which suggested a high comorbid appearance (Biederman et al. 1996). The current book focuses mainly on adult BD, and in this frame the comorbidity of ADHD with BD will be discussed for adult patients only, except for those issues whose understanding demands to consider also paediatric ADHD.

First, it is important to point out that diagnosing ADHD in adults can be a challenge. Hyperactivity and externalizing behaviours tend to decrease with age (Nierenberg et al. 2005), while the high comorbidity with major depression, BD, anxiety disorders and alcohol and substance abuse obscures the clinical picture (Fischer et al. 2007; Kessler et al. 2006). At least 80 % of adults with ADHD suffer from a second mental disorder, with one-fourth to one-third suffering from depression (Fischer et al. 2007; Biederman et al. 1993). Thus, ADHD is frequently not diagnosed, and it has been reported that only one in ten adults ADHD is diagnosed and appropriately treated (Faraone and Antshel 2008).

Specifically, concerning the coexistence with BD, it is believed that patients with comorbid ADHD/BD are under-diagnosed and under-treated (Klassen et al. 2010).

Table 10.8 Cross-sectional and lifetime rates of OCD comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cross-sectional rates						
Bellani et al. (2012)	205	MDD	105	28 (13.7 %)	2 (1.9 %)	
Boylan et al. (2004)	138			12 (8.7 %)		
Ciapparelli et al. (2007)	56	Schiz	98	10 (17.8 %)	20 (20.4 %)	BD with psychotic features
Cosoff and Hafner (1998)	20	Schiz	60	6 (30 %)	8 (13.3 %)	
Dell'Osso et al. (2011)	508			21 (4.1 %)		
Kruger et al. (1995)	37	MDD	105	13 (35.1 %)	37 (35.2 %)	BD-I inpatients
Mantere et al. (2006)	191	MDD	269	4 (2.1 %)	18 (6.7 %)	Acute BD pts
McElroy et al. (2001)	288			22 (7.6 %)		STANLEY
Okan Ibiloglu and Caykoylu (2011)	50			3 (6.0 %)		BD-I
Okan Ibiloglu and Caykoylu (2011)	46			7 (15.2 %)		BD-II
Otto et al. (2006)	918			62 (6.8 %)		STEP-BD. >75 % BD-I, half in recovery, ~25 % depressed
Simon et al. (2004b)	360			24 (67 %)		BD-I
Simon et al. (2004b)	115			3 (2.6 %)		BD-II
Strakowski et al. (1992)	41			3 (7.3 %)		First-episode manic/mixed inpatients
Tamam and Ozpoyraz (2002)	70			23 (32.9 %)		BD-I
Zutshi et al. (2006)	80	Controls	50	20 (25 %)	1 (2 %)	Remitted BD
Koyuncu et al. (2010)	185			22 (11.9 %)		
Koyuncu et al. (2010)	13			3 (23.1 %)		
Kruger et al. (2000)	143			10 (7 %)		
Pashinian et al. (2006)	56			1 (1.8 %)		

(continued)

Table 10.8 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Vieta et al. (2001)	129			2 (1.6 %)		BD-I first manic episode patients
Pooled	*3,649*			*299 (8.2 %)*		BD-I patients in remission
		MDD	*479*		*57 (11.9 %)*	
		Schiz	*158*		*28 (17.7 %)*	
		Controls	*50*		*1 (2.0 %)*	
Lifetime rates						
Altshuler et al. (2010)	711			68 (9.6 %)		>80 % BD-I Stanley
Azorin et al. (2009)	1,090			16 (1.5 %)		Manic acutely hospitalized
Chen and Dilsaver (1995)	168			35 (20.8 %)		ECA
Coryell et al. (2009)	427			11 (2.6 %)		Lifetime
Craig et al. (2002)	138	MDD with psychosis	87	3 (2.2 %)	5 (5.8 %)	BD with psychosis
Dilsaver et al. (2008)	69	MDD	118	43 (62.3 %)	22 (18.6 %)	Latinos
Henry et al. (2003)	318			9 (2.8 %)		75 % BD-I, half psychotic currently or lifetime
Kawa et al. (2005)	211			17 (8 %)		
Levander et al. (2007)	350			48 (13.7 %)		Stanley, 2/3 with alcohol use
McElroy et al. (2001)	288			27 (9.38)		STANLEY
Nakagawa et al. (2008)	116			8 (6,9 %)		Depressed
Pini et al. (1997)	24	MDD	38	5 (20.1 %)	5 (13.2 %)	BD depression
Robins and Regier (1991)	168	Gen pop	18,571	35 (20.8 %)	483 (2.6 %)	ECA
Simon et al. (2004b)	360			39 (10,8 %)		BD-I
Simon et al. (2004b)	115			8 (7.0 %)		BD-II

Slama et al. (2004)	301			9 (3.0 %)		Pts in remission
Szadoczky et al. (1998)	149	MDD	443	5 (3.4 %)	29 (6.5 %)	Epidemiological
Tamam and Ozpoyraz (2002)	70			27 (38.6 %)		BD-I
Yerevanian et al. (2001)	35	MDD	98	5 (14.3 %)	6 (6.1 %)	Lifetime, mostly BD-II
Zutshi et al. (2006)	80	Controls	50	28 (35.0 %)	1 (2.0 %)	Remitted BD
Magalhaes et al. (2010)	259			32 (12.4 %)		
Pooled	*5,447*			*478 (8.8 %)*		
		MDD	*784*		*67 (8.5 %)*	
		Gen pop	*18,621*		*484 (2.6 %)*	

MDD major depressive disorder, *Schiz* schizophrenia, *Gen pop* general population

This comorbidity is complex and of unclear nature (Sachs et al. 2000), but also sometimes there is an artificial inflation of comorbidity because of overlapping symptomatology (Pataki and Carlson 2013). This overlapping between the clinical pictures of BD and ADHD constitutes a significant problem in everyday clinical practice. It is important to have in mind that periodicity, decreased need for sleep, psychotic symptoms, hallucinations and inflated self-esteem are not elements of the clinical picture of ADHD and can be used in the differential diagnosis (Wingo and Ghaemi 2007; Kent and Craddock 2003). Essentially, the problem of differential diagnosis lies in the differentiation between severe ADHD with mood lability and mania/hypomania (Barkley and Fischer 2010). The only paper which studied the use or exclusion of overlapping symptoms reported that although the majority of patients kept the same diagnosis irrespective of criteria used, a significant minority, maybe up to 20–30 % of patients did not (Milberger et al. 1995). To make things even more complex, two-thirds of patients with comorbid ADHD and BD suffer also from an anxiety disorder (Tamam et al. 2008).

The literature suggests that the prevalence of ADHD in adult BD patients ranges from 3.2 to 30 % (Sachs et al. 2000; Wingo and Ghaemi 2007; Perugi et al. 2013; Nierenberg et al. 2005; McIntyre et al. 2010b; Weber et al. 2011; Sentissi et al. 2008; Tamam et al. 2006, 2008; Merikangas et al. 2011; Kessler et al. 2006). The studies do not differentiate between cross-sectional and lifetime rates. In adult subjects with childhood ADHD which did not persist into adulthood, the rate of BD was higher and equal to 10–34.1 % (Tamam et al. 2006, 2008; Winokur et al. 1993; Carlson et al. 2002; Sachs et al. 2000; Bernardi et al. 2010). A significant proportion of BD patients (up to 25 %) has received treatment with stimulants in the past because of the presence of ADHD or refractory depression, but it is interesting that less than half of them received also a concurrent mood stabilizer (Wingo and Ghaemi 2008). This supports the hypothesis that the wide use of stimulants in North America for the treatment of children with ADHD might induce an earlier-onset BD (DelBello et al. 2001); however, this hypothesis has not been confirmed, and even a protective effect for stimulants has been reported (Tillman and Geller 2006).

Reversely up to 5.1–47 % of adult ADHD patients suffer from BD (Park et al. 2011; Secnik et al. 2005; Wilens et al. 2003; McGough et al. 2005; Faraone et al. 2006b) and approximately 28 % of ADHD children will manifest BD-I during early adulthood (Tillman and Geller 2006). The range of rates for adult ADHD patients alone is narrower and much lower and equal to 1.5–4.4 % (Biederman and Faraone 2005; Faraone et al. 2006a; Kessler et al. 2006).

Comorbid ADHD is associated with earlier age at illness onset (Sachs et al. 2000; Nierenberg et al. 2005; McIntyre et al. 2010b; Tamam et al. 2006), more frequent mixed episodes vs. pure manic (Perugi et al. 2013), more frequent early onset of substance abuse (in up to 90 % of patients) (Wilens et al. 1997), a higher number of psychiatric comorbidities (Wilens et al. 2009; McIntyre et al. 2010b), decreased quality of life (McIntyre et al. 2010b) and worse course of bipolar disorder and greater burden of other psychiatric comorbid conditions (Klassen et al. 2010; Perugi et al. 2013; Pataki and Carlson 2013; Nierenberg et al. 2005; Bernardi et al. 2010; Ruggero et al. 2010; Carlson et al. 2012; Ryden et al. 2009). Two conflicting reports

on the type of BD exist. The first suggested that the vast majority of patients with this specific comorbidity (almost 90 %) belong to the BD-II type (Wilens et al. 2003), while the second one suggested they are more often BD-I (Nierenberg et al. 2005).

Family studies are equivocal. One review suggested there is no relationship between BD and ADHD (Duffy 2012), while another review concluded the opposite (Skirrow et al. 2012). There are studies which suggest that there is a strong connection between ADHD and BD and the comorbid condition runs in families, with over 20 % of offspring or BD parents manifesting ADHD. These particular studies included BD patients with a more severe form of the disorder and high comorbidity, and therefore their conclusions might not be generalizable (Chang et al. 2000; Singh et al. 2007; Hirshfeld-Becker et al. 2006; Henin et al. 2005; Birmaher et al. 2009, 2010; Faraone et al. 1997, 2001).

As mentioned before, the nature of BD/ADHD comorbidity is complex and of unclear nature; however, a familial aggregation seems probably, and this points towards a developmental neurobiological association between ADHD and BD, going beyond symptomatic similarities (Skirrow et al. 2012). On the other hand, the careful review of all available data across different domains of research suggests that most findings are equivocal concerning the true nature of this comorbidity (Wingo and Ghaemi 2007).

The reported rates concerning the presence of ADHD in BD patients are shown in detail in Table 10.9. The pooled rate suggests that 6 % of BD patients suffer from ADHD. There is no separation in cross-sectional and lifetime rates.

10.1.4 Comorbid Complicated Grief (CG)

The vast majority of BD patients also report a lifetime history of a significant loss. This issue has not been adequately studied, and there is only one publication on 120 patients, 103 of whom (86 %) reported such a significant loss, and one-quarter met diagnostic criteria for CG. These patients were also more likely to manifest comorbid panic disorder, alcohol abuse and increased rate of lifetime suicide attempts, greater functional impairment and poorer social support (Simon et al. 2005).

10.1.5 Comorbid Eating Disorders

Any eating disorder (ED) is seen in 0–21 % of BD patients (Cassano et al. 1998; Dittmann et al. 2002; Edmonds et al. 1998; MacQueen et al. 2003; Mantere et al. 2006, 2010; McElroy et al. 1995, 2001, 2011; Wildes et al. 2008; Seixas et al. 2012; Pashinian et al. 2006) and especially in females (Seixas et al. 2012). Reversely two-thirds of patients with ED also suffer from BD (Simpson et al. 1992). Furthermore, close to half of BD patients report significant loss of control concerning food consumption (Wildes et al. 2008). It seems that when the ED spectrum is studied along with the BD spectrum, comorbidity and clinical correlates become stronger and more meaningful (McElroy et al. 2005).

Table 10.9 Cross-sectional and lifetime rates of ADHD comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Sentissi et al. (2008)	73			22 (30.1 %)		Euthymic pts
Tamam et al. (2006)	44			7 (15.9 %)		Euthymic BD-I pts
Tamam et al. (2008)	159			26 (16.4 %)		Pts remission
Weber et al. (2011)	27,054			854 (3.2 %)		National Hospital Discharge Survey (NHDS)
McIntyre et al. (2010b)	176	MDD	213	31 (17.6 %)	11 (5.2 %)	
Nierenberg et al. (2005)	1,000			95 (9.5 %)		STEP-BD
Merikangas et al. (2011)	721			199 (27.6 %)		World mental health survey
Perugi et al. (2013)	96			19 (19.8 %)		
Sachs et al. (2000)	56			8 (14.3 %)		Childhood-onset ADHD
Kessler et al. (2006)	3,199			678 (21.2 %)		Epidemiological study
Pooled	*32,578*			*1,939 (6.0 %)*		

MDD major depressive disorder

Concerning specific ED, around 8.8–12.9 % of BD patients are also suffering from binge eating disorder (BED) (Bellani et al. 2012; Kruger et al. 1996; McElroy et al. 2011, 2013; Schoofs et al. 2011; Krishnan 2005; Fornaro et al. 2010; Angst 1998). Around two times, these rates manifest subthreshold BED, and 42.3 % of patients with comorbid BED and BD are obese (McElroy et al. 2013; Kruger et al. 1996). Reversely in 9.3 % of BED patients, BD is also present (Javaras et al. 2008). Menstrual cycle significantly influences BED by worsening it prior to menses. It is reported that 80 % of BD-BED patients noticed regular weight gain prior to menses (Schoofs et al. 2011). Anorexia nervosa (AN) is seen in 0–3.1 % of BD patients, and more frequent in younger ones (Dell'Osso et al. 2011; Fogarty et al. 1994; McElroy et al. 2001, 2011; Pini et al. 1999; Seixas et al. 2012; Fornaro et al. 2010). It might be absent during periods of mania (Fogarty et al. 1994). Bulimia nervosa (BN) is seen in 1.4–7.5 % of BD patients (Baldassano et al. 2005; McElroy et al. 2001, 2011; Pini et al. 1999; Strakowski et al. 1992, 1993; Vieta et al. 2001; Seixas et al. 2012; Fornaro et al. 2010) and up to 7–12 % in bipolar females (Baldassano et al. 2005; Strakowski et al. 1992; Schuckit et al. 1996). Reversely, BN patients are at a 4.5 times higher risk to also suffer from BD (Lunde et al. 2009). Most if not all BN-BD patients are female (Ramacciotti et al. 2005; Seixas et al. 2012).

Several studies report that BD-ED patients have specific clinical features. Female patients with ED have an earlier onset of BD and an increased number of mood episodes, predominantly depressive (Mantere et al. 2010; Brietzke et al. 2011). Rapid cycling and comorbid drug abuse might be more common in BED-BD patients (Brietzke et al. 2011; Fornaro et al. 2010) After controlling for obesity, BED was found to correlate with suicidality, psychosis, mood instability, anxiety disorder comorbidity and substance abuse comorbidity (Brietzke et al. 2011; McElroy et al. 2013). Reversely, after controlling for BED status, obesity was found to correlate with greater general medical comorbidity, but lower substance abuse comorbidity (McElroy et al. 2013). The correlation of ED with BD subtype and especially with BD-II is controversial, and data are inconclusive (McElroy et al. 2011; Simpson et al. 1992).

There are some but rather limited data suggesting the familial coaggregation of eating disorders with BD (Mangweth et al. 2003; Ramacciotti et al. 2005).

The reported rates concerning the presence of eating disorders in BD patients are shown in detail in Table 10.10. The pooled rates suggest that any eating disorder is present in 9.6 % of BD patients, anorexia in 2.4 %, bulimia in 4.4 % and binge eating disorder in 9.6 %. All these rates are significantly higher than those seen in the general population.

10.1.6 Various Other Comorbid Conditions

A number of other psychiatric conditions can be found as comorbid in BD patients. For these conditions, the literature is poor, and data are scarce.

One study reported that one-third of BD patients manifest a comorbid behavioural addiction (three times higher rate in comparison to controls), with

Table 10.10 Cross-sectional and lifetime rates of eating disorders comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any eating disorder						
Cassano et al. (1998)	47			3 (6.4 %)		BD-I pts with psychotic features
Dittmann et al. (2002)	108			10 (9.4 %)		BD-I pts, lifetime rates
Dittmann et al. (2002)	38			0 (0.0 %)		BD-II pts, lifetime rates
Edmonds et al. (1998)	64			4 (6.3 %)		
MacQueen et al. (2003)	139			21 (15.1 %)		
Mantere et al. (2006)	191	MDD	269	15 (7.9 %)	2 (0.7 %)	Acute BD pts, cross-sectional rates
Mantere et al. (2010)	191			12 (8.3 %)		Half depressed, cross-sectional rates
McElroy et al. (1995)	71			6 (8.5 %)		BD-I pts, acute mania
McElroy et al. (2001)	288			4 (1.4 %)		STANLEY foundation data, cross-sectional rates
McElroy et al. (2001)	288			17 (5.9 %)		STANLEY foundation data, lifetime rates
Wildes et al. (2008)	81			17 (21.0 %)		
Seixas et al. (2012)	356			19 (5.3 %)		
Pashinian et al. (2006)	56			8 (14.3 %)		
McElroy et al. (2011)	875			125 (14.3 %)		Lifetime rate
Pooled	*2,793*			*269 (9.6 %)*		
Anorexia nervosa						
Dell'Osso et al. (2011)	508			9 (1.6 %)		Cross-sectional rates
Seixas et al. (2012)	356			11 (3.1 %)		
Fogarty et al. (1994)	22			0 (0.0 %)		Epidemiological study on 3,258 general population subjects, identified 22 manic pts
McElroy et al. (2001)	288			0 (0.0 %)		STANLEY foundation data, cross-sectional rates
McElroy et al. (2001)	288			6 (2.1 %)		STANLEY foundation data, lifetime rates

McElroy et al. (2011)	875			27 (3.1 %)		Lifetime rate
Pini et al. (1999)	125			3 (2.4 %)		BD-I
Pooled	2,337			56 (2.4 %)		
Bulimia nervosa						
Baldassano et al. (2005)	482			36 (7.5 %)		STEP-BD pts, 12 % rate in females
Seixas et al. (2012)	356			8 (2.2 %)		
McElroy et al. (2001)	288			4 (1.4 %)		STANLEY foundation data
McElroy et al. (2001)	288			11 (3.8 %)		STANLEY foundation data
Pini et al. (1999)	125			5 (4.0 %)		BD-I
Strakowski et al. (1992)	41			3 (7.3 %)		12 % rate in females
Strakowski et al. (1993)	60			4 (6.6 %)		BD-I, first episode of mania
McElroy et al. (2011)	875			42 (4.8 %)		Lifetime rate
Vieta et al. (2001)	129			3 (2.3 %)		BD-I pts in remission
Pooled	*2,644*			*116 (4.4 %)*		
Binge eating						
Bellani et al. (2012)	205	MDD	105	25 (12.2 %)	5 (4.8 %)	Cross-sectional rates
McElroy et al. (2011)	875			77 (8.8 %)		Lifetime rate
Kruger et al. (1996)	62			8 (12.9 %)		
McElroy et al. (2013)	717			68 (9.5 %)		
Pooled	*1,859*			*178 (9.6 %)*		

MDD major depressive disorder

pathological gambling, compulsive buying and sexual and work addictions being the most important (Di Nicola et al. 2010).

Tourette's disorder seems to be more frequent among BD patients in comparison to the general population, with a four times higher risk; however, this comorbidity is not adequately studied (Robertson 2006; Kerbeshian et al. 1995). Similarly, impulse control disorders seem to correlate with BD with the overlapping of symptoms being a significant problem for the differential diagnosis (McElroy et al. 1996). The risk of firesetting could be five times higher in BD in comparison to the general population (Blanco et al. 2010). Shoplifting is also prevalent (Blanco et al. 2008).

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are frequent in BD and especially in BD-II patients. The reverse is also true with PMS and PMDD patients being at an increased risk to develop BD-I (Cirillo et al. 2012).

One study suggested that mania was observed in 4.2 % of somatization patients (Brown et al. 1990).

10.1.7 Comorbid Psychiatric Disorders and BD-II

There are some studies suggesting that there is no differences in comorbidity between patients with BD-I vs. BD-II (Koyuncu et al. 2010; Vieta et al. 2000; McElroy et al. 2001, 2011); however, other studies strongly support the higher comorbidity rate in BD-II (especially anxiety and eating disorders) along with a higher familial load especially in first-degree relatives and in relationship with substance abuse (Mantere et al. 2006; Baek et al. 2011; Mula et al. 2008a; Judd et al. 2003; Rihmer et al. 2001).

10.2 Medical Comorbidity

10.2.1 General Medical Comorbidity

General medical comorbidity has been recognized as an important problem especially for BD patients. They are reported to have up to four times higher health care costs in comparison to patients without mental disorders, and a significant determinant of this is medical comorbidity (Bryant-Comstock et al. 2002; Stender et al. 2002; Gardner et al. 2006; Centorrino et al. 2009). It is disappointing that despite the above well-known issues, it is usual that medical conditions remain underrecognized and under-treated in the real world, and as a consequence, the life expectancy for patients with BD is approximately 30 % lower than that of the general population, and it is lower also in comparison to other mental disorders (Fagiolini and Goracci 2009; Alstrom 1942; Babigian and Odoroff 1969). This is not only because medical comorbidity increases the already great burden of the bipolar illness but also because BD patients are less likely to receive proper care and diagnosis, like the rest of the population. The presence of stigma and their own lack of

cooperation are largely responsible for this (Morriss and Mohammed 2005). Even when properly diagnosed and appropriately treated, their adherence is problematic, and the overall outcome is generally less favourable. Additionally, their care is more complex and expensive, with more frequent use of health services and more hospitalizations because of their somatic problems (Sullivan et al. 2006). These have a significant impact on the patients' quality of life, but the increased mortality is even more important. The decrease in life expectancy is primarily due to premature cardiovascular mortality (Colton and Manderscheid 2006). In this frame, it is embarrassing that some pharmacological interventions put the patient at a higher risk for the manifestation of specific somatic disorders, especially cardiovascular.

Depending on the study sample, 11.5–75.7 % of BD patients are reported to manifest some somatic comorbidity with cardiovascular, endocrinological, gastrointestinal disorders and pain being the most prevalent (Beyer et al. 2005; Carney and Jones 2006; Douzenis et al. 2012; Feldman et al. 2012; Kilbourne et al. 2004; Magalhaes et al. 2012; McIntyre et al. 2006a; Oreski et al. 2012; Subramaniam et al. 2013; Weber et al. 2011; Strakowski et al. 1992, 1994; Perron et al. 2009; Krishnan 2005; Castelo et al. 2012; Kemp et al. 2013; McIntyre et al. 2007b). At least some specific medical conditions like thyroid disease, migraine, and obesity appear to be more frequent in females (Carney and Jones 2006). This high medical comorbidity seems to lead to an overall worse long-term course and outcome (Thompson et al. 2006; McIntyre et al. 2006a) and greater disability (Perron et al. 2009). There is one study disputing the effect of medical comorbidity on the overall outcome (Strakowski et al. 1992), but other studies further confirm it and suggest that this effect is not generic, but on the contrary it is a specific effect of each specific somatic comorbidity on outcome and disability (Pirraglia et al. 2009) as well as of age and duration of illness (Soreca et al. 2008, 2009). Inpatient data suggest that hypothyroidism, viral hepatitis, obesity and various diseases of the skin and subcutaneous tissue and of the nervous, respiratory and musculoskeletal systems are found significantly more often in BD patients. The relative risk for these somatic disorders varies from 1.5 to 4 depending on the specific illness and the population under study (Weber et al. 2011; Chou et al. 2013; Laursen et al. 2011), and there is some stronger relationship to depressive symptoms (Thompson et al. 2006; Kemp et al. 2013). Multiple somatic comorbidity seems to be the rule rather than the exception with BD patients suffering from an average of 2.7 or more medical conditions (Soreca et al. 2009; Kilbourne et al. 2009b; McIntyre et al. 2006a). Unfortunately, up to 70 % of them might be unaware of their somatic problems (Feldman et al. 2012). Psychiatric comorbidity further increases the risk for the presence of somatic disorders (Daratha et al. 2012; Kemp et al. 2013; Magalhaes et al. 2012), and probably this is partially mediated by the high stress load BD patients experience (McIntyre et al. 2007b). A gender effect could be present in at least some of these comorbidities especially thyroid disease (Arnold 2003).

The link between BD and medical conditions is not known; however, probably medical comorbidity is not solely the secondary result of the overall burden of BD, but it is highly likely that at least some conditions like diabetes mellitus and autoimmune disorders to share aetiopathogenetic mechanisms, probably of an

immunoinflammatory nature in the frame of 'stress-sensitive' medical disorders (Altamura et al. 2011; Soreca et al. 2009).

As expected, the treatment of these multiple comorbidities is even more difficult, and several principles exist to manage the increasingly complex problems. Central are the establishment of the diagnosis, the risk assessment, determining the appropriate setting for the treatment, planning for the long-term management, determining the sequence of treatments since simultaneous treatments might be problematic and detailed assessment of the different faces of the outcome with the use of psychometric and neuropsychological tools and laboratory testing (McIntyre et al. 2012; Ramasubbu et al. 2012; Soreca et al. 2008). More specifically, cardiovascular disorder appears to be the most consistent cause of premature mortality in BD (Roshanaei-Moghaddam and Katon 2009). Since cardiovascular disease has known and modifiable risk factors, the improvement of the general health of BD patients and the increase of their life expectancy appear to be achievable goals though very difficult ones.

The reported rates concerning the presence of any medical comorbidity in BD patients are shown in detail in Table 10.11. The pooled rates suggest that any medical comorbidity is present in half of BD patients. This rate is similar to the rate reported for patients with schizophrenia and double of what is reported concerning the general population.

10.2.2 Metabolic Syndrome and Related Medical Conditions

10.2.2.1 Obesity

Obesity is a condition defined as body mass index (BMI) above 30 or waist circumference over 102 cm (40 in.) in men and 88 cm (35 in.) in women and waist-to-hip ratio >0.9 for men and >0.85 for women. Waist circumference might be a better index concerning central (abdominal) obesity which is considered to be more medically problematic. A problem is that other cut-off points are also used in various studies to define obesity (e.g. BMI >25 or waist circumference >105 cm).

Although the epidemiological data are inconclusive, obesity is a frequent problem in mental patients, and this is especially true concerning BD. Whether obesity constitutes a problem specific for BD or mental disorders in general is a matter of debate, because obesity is also highly frequent in the general population (McElroy et al. 2002) and weight loss is reported in a minority of BD-I patients (Carney and Jones 2006). Obesity has been reported as a significant health issue concerning the whole bipolar spectrum population with 90 % of severely obese patients belonging to that spectrum and BD-II being the most usual diagnosis (Alciati et al. 2007, 2011).

The reported prevalence of obesity in BD varies from 1.4 to 55.4 % (Kim et al. 2009; Sicras et al. 2008; McIntyre et al. 2010c; Kemp et al. 2010, 2013; Guo et al. 2006; Carney and Jones 2006; Krishnan 2005; Salvi et al. 2008; Weber et al. 2011; Petry et al. 2008; McIntyre et al. 2007a; McElroy et al. 2002, 2004, 2013; Elmslie et al. 2000, 2001; Mather et al. 2009; Maina et al. 2008; Fagiolini et al. 2002; Calkin

Table 10.11 Cross-sectional and lifetime rates of any medical comorbidity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Beyer et al. (2005)	1,379			607 (44.0 %)		Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed cross-sectional data
Carney and Jones (2006)	3,557	In- and outpatients	726,262	2,694 (75.7 %)	328,886 (45.3 %)	BD-I pts from the Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Douzenis et al. (2012)	228			120 (52.6 %)		Inpatients, cross-sectional data
Feldman et al. (2012)	61			7 (11.5 %)		Acute bipolar depression, from the NCT00276965 trial
Feldman et al. (2012)	17			3 (17.6 %)		Anxious BD pts from the NCT01172652 trial
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	980 (22.7 %)	678,512 (19.9 %)	VA national patient population, cross-sectional data
Magalhaes et al. (2012)	3,399			1,998 (58.8 %)		STEP-BD data
McIntyre et al. (2006a)	938	Gen pop	35,848	603 (64.3 %)	17,386 (48.5 %)	Canadian Community Health Survey, lifetime rates
Oreski et al. (2012)	97	Schiz	192	65 (67.0 %)	97 (50.5 %)	Inpatient records
Subramaniam et al. (2013)	88			46 (52.3 %)		BD-I pts
Strakowski et al. (1992)	41			9 (21.9 %)		
Perron et al. (2009)	1,548			502 (32.4 %)		BD-I pts
Pooled	*15,663*			*7,634 (48.7 %)*		
		Gen pop	*4,171,062*		*1,024,881 (24.6 %)*	

Schiz schizophrenia

et al. 2009; Chwastiak et al. 2011; Muller-Oerlinghausen et al. 1979; Fiedorowicz et al. 2008, 2011; Birkenaes et al. 2007), and this high variability of results makes conclusions difficult. Reversely, in morbidly obese patients, BD is diagnosed at a rate of 2.8–11 % (Black et al. 1992; Britz et al. 2000; Simon et al. 2006).

Medication seems to have a significant impact (McIntyre 2002; Keck and McElroy 2003). Lithium (Vendsborg et al. 1976; Sachs et al. 2006) and valproate (Dinesen et al. 1984; Pylvanen et al. 2002; Swann 2001) can cause weight gain. It has been reported that patients on lithium gain weight in contrast to patients under lamotrigine (Bowden et al. 2006; Muller-Oerlinghausen et al. 1979; Atmaca et al. 2002; Vendsborg et al. 1976) and weight gain during lithium treatment has shown to lead to poor adherence (Gitlin et al. 1989). Treatment with antipsychotics and especially with those belonging to the second generation has also been related to weight gain (Henderson et al. 2000; Simpson 2005; Volavka et al. 2002; Zipursky et al. 2005; Nasrallah 2003). It seems that most of weight gain happens during the acute phase and not during the maintenance (Fagiolini et al. 2002).

Beyond iatrogenic effects, individuals with bipolar disorder often adopt unhealthy lifestyles, may have poor diets and receive inadequate exercise (Kilbourne et al. 2007).

Patients with a more chronic course and longer duration manifest higher rates of overweight and obesity (Calkin et al. 2009; Maina et al. 2008) with depressive episodes being responsible for most of this effect (Maina et al. 2008; Keck and McElroy 2003; Fagiolini et al. 2002). There does not seem to be a significant effect of gender (Maina et al. 2008; Elmslie et al. 2000, 2001) although women with obesity and extreme obesity seem to be more likely to have atypical major depressive episodes in their bipolar illness (Pickering et al. 2007). Substance abuse is inversely related with obesity in BD patients (McIntyre et al. 2007a). The comorbidity of eating disorders can partially but not completely explain the prevalence of overweight and obesity in BD patients (Maina et al. 2008) since in these patients, preference for carbohydrate consumption and low levels of physical activity and exercise are seen very often (Keck and McElroy 2003).

The reported rates concerning the presence of obesity in BD patients are shown in detail in Table 10.12. The pooled rates suggest that obesity is present in 15 % of BD patients, and this rate is 30 % higher than the reported in unipolar depressed patients and four to five times higher than the respected rate in the general population.

10.2.2.2 Dyslipidaemia

Dyslipidaemia could concern the presence of hypertriglyceridaemia (above 150 mg/dL) or low HDL-C (<40 mg/dL in men and <50 mg/dL in women). The first report on the presence of higher lipid levels in the blood of BD patients was published in the late 1960s (Brandrup and Randrup 1967). The rates vary greatly probably because of different definitions and methods utilized. For example, one method of assessing the rates is to monitor antilipidaemic prescriptions. One such study reported that around 16 % of BD and patients with schizophrenia were receiving such medication but only 10 % of controls (Bai et al. 2013).

Table 10.12 Rates of obesity in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Birkenaes et al. (2007)	110	Gen pop	18,770	27 (24.5)	2,647 (14.1 %)	
Calkin et al. (2009)	276			108 (39.1 %)		Tertiary care patients, 2/3 BD-I
Carney and Jones (2006)	3,557	In- and outpatients	726,262	163 (4.6 %)	7,828 (1.1 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Carney and Jones (2006)	3,557	Gen pop	726,262	163 (4.6 %)	7,828 (1.1 %)	BD-I medical registry
Chwastiak et al. (2011)	9,522			3,733 (39.2 %)		Epidemiological
Elmslie et al. (2000)	89	Controls	445	17 (19.1 %)	52 (11.7 %)	BD-I euthymic
Fagiolini et al. (2002)	50			16 (32.0 %)		BD-I
Fagiolini et al. (2003)	175			62 (35.4 %)		BD-I
Fagiolini et al. (2005)	171			84 (49.1 %)		BD-I
Fiedorowicz et al. (2008)	161			77 (47.8 %)		2/3 BD-I
Fiedorowicz et al. (2011)	135	MDD	524	40 (29.6 %)	57 (10.9 %)	Epidemiological
Guo et al. (2006)	6,178			533 (8,6 %)		Health-care database
Kemp et al. (2010)	125			63 (50.4 %)		RCT patients
Kemp et al. (2013)	260			96 (36.9 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kemp et al. (2013)	260			96 (36.9 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kim et al. (2009)	184			56 (30.4 %)		BD-I inpatients, 2/3 manic
Maina et al. (2008)	76	OCD	65	1 (1.4 %)	0 (0.0 %)	Half BD-I
Mather et al. (2009)	885			192 (21.7 %)		Epidemiological
McElroy et al. (2002)	644			135 (21.0 %)		

(continued)

Table 10.12 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
McElroy et al. (2013)	717			307 (42.8 %)		
McIntyre et al. (2007a)	938	Gen pop	36,046	520 (55.4 %)	17,158 (47.6 %)	BD-I Canadian Community Health Survey
McIntyre et al. (2010c)	99			37 (41.1 %)		Euthymic patients, diabetic excluded
Salvi et al. (2008)	99			50 (50.0 %)		
Sicras et al. (2008)	178	Gen pop	85,850	41 (23.0 %)	9,701 (11.3 %)	Health-care database
Thompson et al. (2006)	174			58 (33.3 %)		BD-I
Wang et al. (2006)	267			29 (10.9 %)		BD-I STEP-BD
Wang et al. (2006)	97			24 (24.7 %)		BD-II STEP-BD
Weber et al. (2011)	27,054	Gen pop	2,325,247	1,668 (6.2 %)	96,949 (4.2 %)	US hospital discharges between 1979 and 2006
Pooled	*56,038*			*8,396 (15.0 %)*		
		Gen pop	*3,918,882*		*142,163 (3.6 %)*	

MDD major depressive disorder, *OCD* obsessive–compulsive disorder, *Gen pop* general population

Overall the literature reports that any kind of dyslipidaemia is present in 0.9–57.5 % of BD patients (Salvi et al. 2008, 2011; Kim et al. 2009; Chang et al. 2009; Sicras et al. 2008; McIntyre et al. 2010c; Kemp et al. 2010; Guo et al. 2006; Garcia-Portilla et al. 2008; Fiedorowicz et al. 2008; Centorrino et al. 2009; Oreski et al. 2012; Fenn et al. 2005; Weber et al. 2011; Kilbourne et al. 2004; Carney and Jones 2006; Lin et al. 2007; Fagiolini et al. 2005; Kemp et al. 2013). Second-generation antipsychotics constitute a major factor for the development of hyperlipidaemia in BD patients (Huang and Chen 2005; Henderson 2001; Henderson et al. 2000; Osser et al. 1999).

The reported rates concerning the presence of dyslipidaemia in BD patients are shown in detail in Table 10.13. The pooled rates suggest that dyslipidaemia is present in 17.2 % of BD patients, and this rate is probably similar to the rate reported concerning patients with schizophrenia and tenfold higher than the respected rate in the general population.

10.2.2.3 Diabetes Mellitus (DM)

DM is defined as fasting blood glucose ≥100 mg/dL. The first reports concerning a possible increased prevalence of DM in BD patients were published in the early twentieth century (Raphael and Parsons 1921; Kasanin 1926). Again one method to calculate the rates of DM is to count antidiabetic prescriptions. One such study reported that around 10 % of BD and patients with schizophrenia were receiving such medication but only 6 % of controls (Bai et al. 2013). The literature suggests that 1.1–43.5 % of BD patients suffer from DM (Ramsey et al. 2010; Beyer et al. 2005; Carney and Jones 2006; Cassidy et al. 1999; Centorrino et al. 2009; Chang et al. 2009; Chien et al. 2010; Fagiolini et al. 2005; Fenn et al. 2005; Fiedorowicz et al. 2008, 2011; Garcia-Portilla et al. 2008; Guo et al. 2006; Hirschfeld et al. 2003; Kemp et al. 2010, 2013; Kilbourne et al. 2004; Kim et al. 2009; Laursen et al. 2011; Lin et al. 2007; McIntyre et al. 2006a; Oreski et al. 2012; Regenold et al. 2002; Ruzickova et al. 2003; Salvi et al. 2008, 2011; Subramaniam et al. 2013; Thompson et al. 2006; van Winkel et al. 2008a; Weber et al. 2011). In BD-II, the mean rate is around 10 % (Krishnan 2005). The range of reported rates is significant, and although the results are suggestive of the presence of increased rate in BD patients in comparison to the general population, the conclusions are problematic.

It has been reported that the age at first hospitalization and duration of illness are not related to the development of DM in BD patients (Cassidy et al. 1999). Impaired glucose metabolism, insulin resistance and diabetes mellitus are related to treatment with lithium (Hermida et al. 1994), valproic acid (Dinesen et al. 1984; Pylvanen et al. 2002) and second-generation antipsychotics (Henderson 2001; Henderson et al. 2000; Guo et al. 2006; Lambert et al. 2005; Ollendorf et al. 2004; Sernyak et al. 2005; Gianfrancesco et al. 2003).

The reported rates concerning the presence of DM in BD patients are shown in detail in Table 10.14. The pooled rates suggest that DM is present in 9.8 % of BD patients, and this rate is probably similar to the rate reported concerning patients with schizophrenia, unipolar depression and the general population.

Table 10.13 Rates of dyslipidemia in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Carney and Jones (2006)	3,557	Other patients	726,262	438 (12.3 %)	55,495 (7.6 %)	Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, BD-I pts
Centorrino et al. (2009)	28,531	Gen pop	85,593	5,861 (20.5 %)	14,170 (16.6 %)	Health-care data
Chang et al. (2009)	117			43 (36.8 %)		
Fagiolini et al. (2005)	171			70 (40.9 %)		
Fenn et al. (2005)	290			65 (22.4 %)		Inpatients, mostly BD-I
Fenn et al. (2005)	290			81 (27.9 %)		Inpatients, mostly BD-I
Fiedorowicz et al. (2008)	73			42 (57.5 %)		2/3 BD-I pts
Garcia-Portilla et al. (2008)	194			66 (30.0 %)		
Guo et al. (2006)	6,178			86 (1.4 %)		Health-care database
Kemp et al. (2010)	125			39 (31.2 %)		RCT pts
Kemp et al. (2013)	264			81 (30.7 %)		Lithium Treatment—Moderate Dose Use Study (LiTMUS) study
Kemp et al. (2013)	263			50 (19.0 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS) study
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	973 (22.6 %)	0 (0.0 %)	VA national patient population
Kim et al. (2009)	184			38 (20.7 %)		BD-I inpatients, 2/3 manic
Lin et al. (2007)	2,289	Gen pop	16,413	20 (0.9 %)	48 (0.3 %)	All sample underwent appendectomy
McIntyre et al. (2010c)	99			33 (38.8 %)		Euthymic pts, diabetic excluded
Oreski et al. (2012)	97	Schiz	192	49 (50.5 %)	86 (44.8 %)	Inpatient records
Salvi et al. (2008)	99			35 (37.4 %)		Inpatients

Salvi et al. (2011)	200			68 (34.0 %)		2/3 BD-II pts
Sicras et al. (2008)	178	Gen pop	85,850	41 (23.0 %)	9,701 (11.3 %)	Health-care database
Weber et al. (2011)	27,054	Gen pop	2,325,247	999 (3.7 %)	132,389 (5.7 %)	US hospital discharges between 1979 and 2006
Pooled	*47,509*			*8,179 (17.2 %)*		
		Gen pop	*4,322,878*		*79,414 (1.8 %)*	

Schiz schizophrenia, *Gen pop* general population

Table 10.14 Rates of diabetes mellitus in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Beyer et al. (2005)	1,379			59 (4.3 %)		BD-I, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed
Carney and Jones (2006)	3,557	In- and outpatients	726,262	63 (1.8)	4,401 (0.6)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, diabetes, complicated
Carney and Jones (2006)	3,557	In- and outpatients	726,262	146 (4.1)	17,205 (2.4)	Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, diabetes, uncomplicated
Cassidy et al. (1999)	345			34 (9.9 %)		BD-I inpatients representative of US general population
Centorrino et al. (2009)	28,531	Gen pop	85,593	3,663 (12.8 %)	5,955 (7.0 %)	Health-care data
Chang et al. (2009)	117			16 (13.7 %)		
Chien et al. (2010)	1,848	Gen pop	764,579	199 (10.8 %)	42,591 (5.6 %)	National medical claims database
(Fagiolini et al. (2005)	171			14 (8.2 %)		
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, DM-I
Fenn et al. (2005)	290			24 (8.3 %)		Inpatients mostly BD-I, DM-II
Fiedorowicz et al. (2008)	142			43 (30.3 %)		2/3 BD-I
Fiedorowicz et al. (2011)	135	MDD	524	8 (5,9 %)	47 (9,0 %)	Epidemiological data
Garcia-Portilla et al. (2008)	194			23 (11.9 %)		
Guo et al. (2006)	6,178			920 (14.9 %)		Health-care database
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	156 (7.3 %)	5,826 (7.0 %)	Epidemiological data
Kemp et al. (2010)	125			11 (8.8 %)		RCT patients
Kemp et al. (2013)	259			50 (19.3 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS) study

Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	743 (17.2 %)	532,926 (15.6 %)	VA national patient population
Kim et al. (2009)	184			80 (43.5 %)		BD-I inpatients, 2/3 manic
Laursen et al. (2011)	6,215	Gen pop	2,428,518	74 (1.2 %)	12,950 (0.5 %)	Population-based cohort study
Lin et al. (2007)	2,289	Gen pop	16,413	101 (4.4 %)	363 (2.2 %)	All sample underwent appendectomy
McIntyre et al. (2006a)	938	Gen pop	35,848	40 (4.3 %)	1,721 (4.8 %)	Canadian Community Health Survey
Oreski et al. (2012)	97	Schiz	192	9 (9.3 %)	8 (4.2 %)	Inpatient records
Regenold et al. (2002)	136			35 (25.73 %)		Inpatients, BD-I, DM-II
Ruzickova et al. (2003)	222			26 (11.7 %)		¾ BD-I pts
Salvi et al. (2008)	99			11 (11.1 %)		Inpatients
Salvi et al. (2011)	200			21 (10.5 %)		2/3 BD-II pts
Subramaniam et al. (2013)	88			3 (3.4 %)		BD-I pts
Thompson et al. (2006)	174			2 (1.1 %)		BD-I pts
van Winkel et al. (2008a)	60			4 (6.7 %)		
Weber et al. (2011)	27,054	Gen pop	2,325,247	1,962 (7.3 %)	262,382 (10.0 %)	US hospital discharges between 1979 and 2006
Ramsey et al. (2010)	58	Gen pop	1,339	2 (3.4 %)	64 (4.8 %)	Epidemiological Catchment Area
Pooled	*87,529*			*8,547 (9.8 %)*		
		Gen pop	*9,875,783*		*886,384 (9.0 %)*	

Schiz schizophrenia, *Gen pop* general population

10.2.2.4 Hypertension

Hypertension is defined as the presence of a systolic blood pressure ≥130 mmHg and a diastolic blood pressure ≥85 mmHg. The literature suggests a rate of 2.4–67.5 % in BD patients, and conclusions are difficult (Ramsey et al. 2010; Huang et al. 2009; Carney and Jones 2006; Centorrino et al. 2009; Chang et al. 2009; Fagiolini et al. 2005; Fenn et al. 2005; Fiedorowicz et al. 2008, 2011; Garcia-Portilla et al. 2008; Guo et al. 2006; Hirschfeld et al. 2003; Johannessen et al. 2006; Kemp et al. 2010, 2013; Kilbourne et al. 2004; Lin et al. 2007; McIntyre et al. 2006a, 2010c; Perron et al. 2009; Salvi et al. 2008, 2011; Subramaniam et al. 2013; Weber et al. 2011; Beyer et al. 2005; Douzenis et al. 2012).

The reported rates concerning the presence of hypertension in BD patients are shown in detail in table 10.15. The pooled rates suggest that hypertension is present in 14.7 % of BD patients, and this rate is probably similar to the rate reported concerning patients with unipolar depression and the general population.

10.2.2.5 Comorbid Metabolic Syndrome

The term metabolic syndrome refers to a cluster of risk factors for cardiovascular disease, diabetes mellitus and premature mortality (Gans 2006) and is best defined according to the Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) which considers abdominal adiposity, hypertension, impaired fasting glucose or diabetes mellitus and atherogenic dyslipidaemia as its principal components (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2002). The prevalence of the metabolic syndrome in the western world is approximately 15–25 % in the general population, it increases with age, and it is more frequent among women (Ford et al. 2002; Hu et al. 2004; Laaksonen et al. 2002).

The literature suggests that the rate of metabolic syndrome in BD patients ranges from 0.37 % to 66.6 % (Taylor et al. 2010; Cardenas et al. 2008; Centorrino et al. 2009; Chang et al. 2009; Correll et al. 2008; Fagiolini et al. 2005; Fiedorowicz et al. 2008; Garcia-Portilla et al. 2008; John et al. 2009; Kemp et al. 2010, 2013; McIntyre et al. 2010c; Salvi et al. 2008, 2011; Sicras et al. 2008; van Winkel et al. 2008a, b; Vuksan-Cusa et al. 2009; Yumru et al. 2007; Jakovljevic et al. 2007). One study reported the respected rate for schizoaffective disorder bipolar type to be 42.4 % (Basu et al. 2004).

The prevailing conclusion is that it is increased in BD patients. Disparate estimates are reported ranging from comparability to approximately two- to threefold greater than the general population, and this seems to be a worldwide fact (McIntyre et al. 2005, 2010a). It is important to note that as patients spend more time in BD, the rates of the metabolic syndrome increase dramatically and this happens at a rate which implies it is rather an effect of the disease (and its correlating features including treatment) rather than of increasing age (Salvi et al. 2012; Taylor and MacQueen 2006).

Comorbid medical conditions such as diabetes, hypertension, dyslipidaemia and obesity are under-diagnosed and under-treated in hospitalized psychiatric patients compared with the non-psychiatric population. The attitude of psychiatrists is rather

Table 10.15 Rates of hypertension in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Carney and Jones (2006)	3,557	In- and outpatients	726,262	645 (18.1 %)	66,575 (9.2 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Centorrino et al. (2009)	28,531	Gen pop	85,593	6,418 (22.5 %)	14,787 (17.3 %)	Health-care data
Chang et al. (2009)	117			11 (9.4 %)		
Douzenis et al. (2012)	228			34 (14.9 %)		Inpatients
Fagiolini et al. (2005)	171			67 (39.2 %)		
Fenn et al. (2005)	290			94 (32.4 %)		Inpatients mostly BD-I
Fiedorowicz et al. (2008)	166			112 (67.5 %)		2/3 BD-I
Fiedorowicz et al. (2011)	135	MDD	524	38 (28,1 %)	144 (27,5 %)	Epidemiological
Garcia-Portilla et al. (2008)	194			39 (20.1 %)		
Guo et al. (2006)	6,178			1,460 (23,6 %)		Health-care database
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	327 (15.3 %)	10,237 (12,3 %)	Epidemiological
Johannessen et al. (2006)	25,339	Gen pop	113,698	602 (2.4 %)	2,375 (2.1 %)	Nationwide register study; BD diagnosis should had preceded that of hypertension
Kemp et al. (2010)	125			8 (6.4 %)		RCT patients
Kemp et al. (2013)	264			114 (44.0 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	1,500 (34.8 %)	1,256,034 (36.8 %)	VA national patient population
Lin et al. (2007)	2,289	Gen pop	16,413	105 (4.6 %)	359 (2.2 %)	All sample underwent appendectomy
McIntyre et al. (2006a)	938	Gen pop	35,848	98 (10.4 %)	5,341 (14.9 %)	Canadian Community Health Survey
McIntyre et al. (2010c)	99			28 (29.7 %)		Euthymic patients, diabetic excluded

(continued)

Table 10.15 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Perron et al. (2009)	1,548	Gen pop	41,545	377 (24,3 %)	7,889 (19 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Salvi et al. (2008)	99			42 (40.0 %)		Inpatients
Salvi et al. (2011)	200			106 (53.0 %)		2/3 BD-II
Subramaniam et al. (2013)	88			12 (13.6 %)		BD-I
Weber et al. (2011)	27,054	Gen pop	2,325,247	3,692 (13.6 %)	389,633 (16.8 %)	US hospital discharges
Huang et al. (2009)	41,557	MDD	76 430	5,436 (13.1 %)	7,719 (10.1 %)	Health registry
Ramsey et al. (2010)	58	Gen pop	1,339	15 (25.9 %)	316 (23.6 %)	ECA
Pooled	*145,669*			*21,454 (14.7 %)*		
		Gen pop	*6,837,929*		*1,753,546 (25.6 %)*	
		MDD	*76,954*		*7,863 (10.2 %)*	

MDD major depressive disorder, *Gen pop* general population

problematic with only half of them ever having diagnosed metabolic syndrome in their patients and less than three-quarters believing that it poses their patients at a significant health risk (Bauer et al. 2008). Subsequently it is well documented that patients with mental illness in general have significantly less preventive intervention during hospitalization (Briskman et al. 2012). In this frame, it is extremely important to mention that at least some metabolic syndrome cases are due to medication (Sicras-Mainar et al. 2008; Cardenas et al. 2008).

The reported rates concerning the presence of metabolic syndrome in BD patients are shown in detail in Table 10.16. The pooled rates suggest that the metabolic syndrome is present in 29.5 % of BD patients, and this rate is probably similar to the rate reported concerning patients with schizophrenia and double for that in the general population.

10.2.3 Comorbid Vascular Disease

Whether there is a true temporal association between BD and cardiovascular comorbidity is unknown, as is the nature of any such association (Weiner et al. 2011). According to early studies, cardiovascular disease was very common, was appearing at a younger age in BD patients (Slater 1938; Bumke 1928) and was the leading cause of mortality among BD patients (Derby 1933; Alstrom 1942; Tsuang et al. 1980; Weeke et al. 1987; Weeke and Vaeth 1986; Sharma and Markar 1994; Laursen et al. 2007; Osby et al. 2001).

The possible excess cardiovascular mortality associated with schizophrenia and BD in comparison to the general population is attributed in part to an increased risk of the modifiable coronary heart disease risk factors: obesity, smoking, diabetes, hypertension and dyslipidaemia. Antipsychotic medication and possibly other psychotropic medication like antiepileptics and antidepressants can induce weight gain or worsen other metabolic cardiovascular risk factors. Smoking is more common in those with BD, even when compared to other serious mental illnesses (Lasser et al. 2000). BD patients may have limited access to general health care with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population (De Hert et al. 2009). The observations concerning a higher cardiovascular morbidity and mortality in BD patients precede the era of modern pharmacotherapeutics, and thus the twofold risk in these patients should be considered as primary (Weiner et al. 2011). Maybe BD-I patients manifest higher mortality rates due to cardiovascular disease in comparison to BD-II and unipolar depressives (Angst et al. 2002).

10.2.3.1 Heart Disease

The literature suggests that circulatory disease in general has a prevalence of 13–22.7 % in BD patients (Ramsey et al. 2010; Oreski et al. 2012; Beyer et al. 2005) and in the same patients a variety of heart disorders including congestive heart failure, valvular disease and arrhythmias are reported to be more frequent in comparison to the general population (Carney and Jones 2006). More specifically, any

Table 10.16 Rates of the metabolic syndrome in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Cardenas et al. (2008)	98			48 (49.0 %)		90 % males
Centorrino et al. (2009)	28,531	Gen pop	85,593	105 (0.37 %)	136 (0.2 %)	Health-care data
Chang et al. (2009)	117			20 (17.1 %)		
Correll et al. (2008)	74	Schizophrenia	111	32 (43.2 %)	51 (45.9 %)	
Fagiolini et al. (2005)	171			51 (29.8 %)		
Fiedorowicz et al. (2008)	125			45 (36.0 %)		2/3 BD-I pts
Garcia-Portilla et al. (2008)	194			39 (20.1 %)		
John et al. (2009)	39	Schizophrenia	92	26 (66.6 %)	47 (51.1 %)	
Kemp et al. (2010)	125			45 (36.0 %)		RCT pts
Kemp et al. (2013)	264			79 (29.9 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS) study
McIntyre et al. (2010c)	99			31 (32.6 %)		Euthymic pts, diabetic excluded
Salvi et al. (2008)	99			25 (25.3 %)		Inpatients
Salvi et al. (2011)	200			53 (26.5 %)		2/3 BD-II pts
Sicras et al. (2008)	178	Gen pop	85,850	44 (24.7 %)	12,362 (14.4 %)	Health-care database
van Winkel et al. (2008a)	60			10 (16.7 %)		
van Winkel et al. (2008b)	112	Schizophrenia	503	26 (23.2 %)	145 (28.8 %)	
Vuksan-Cusa et al. (2009)	40			11 (27.5 %)		
Yumru et al. (2007)	125			40 (32 %)		BD-I Health-care database
Pooled	*2,120*			*625 (29.5 %)*		
		Gen pop	*85,850*		*12,362 (14.4 %)*	
		Schiz	*614*		*196 (31.9 %)*	

Schiz schizophrenia, *Gen pop* general population

cardiovascular disease is reported to affect 2.7–48.6 % (Beyer et al. 2005; Fenn et al. 2005; Fiedorowicz et al. 2011; Guo et al. 2006; Kemp et al. 2013; Magalhaes et al. 2012; McIntyre et al. 2006a; Oreski et al. 2012; Perron et al. 2009; Ramsey et al. 2010; Subramaniam et al. 2013; Thompson et al. 2006), arrhythmias 2.8–17.9 % (Carney and Jones 2006; Fenn et al. 2005; Perron et al. 2009), congestive heart failure 0.5–4.9 % (Carney and Jones 2006; Kilbourne et al. 2004; Laursen et al. 2011; Ramsey et al. 2010; Strakowski et al. 1992), ischaemic heart disease 0.4–18 % (Ramsey et al. 2010; Huang et al. 2009; Carney and Jones 2006; Guo et al. 2006; Fiedorowicz et al. 2011; Centorrino et al. 2009; Fenn et al. 2005; Kilbourne et al. 2004; Laursen et al. 2011; Perron et al. 2009) and peripheral vascular disease 0.3–2.9 % of BD patients (Kilbourne et al. 2004; Laursen et al. 2011; Carney and Jones 2006).

Reversely, hospital registries suggest that approximately 2 % of hospitalized patients with acute myocardial infarction also suffer from BD (Abrams et al. 2009). Vascular risks factors were greater and current cholesterol levels higher in the late-onset group (Cassidy and Carroll 2002). Controlling for behavioural factors diminished, but did not eliminate, the impact of heart disease on mortality in BD patients (Kilbourne et al. 2009a). It is interesting that while cardiovascular morbidity might be similar to the general population, mortality is several times higher (Laursen et al. 2009).

The reported rates concerning the presence of cardiovascular disease in BD patients are shown in detail in Table 10.17. The pooled rates suggest that any cardiovascular disease is present in 7.6 % of BD patients, and this rate is probably similar to the rate reported concerning patients with schizophrenia and unipolar depression and double of that in the general population. Arrhythmia is present in 7.5 % of BD patients, and this rate is several times higher than the respective in the general population. On the contrary, congestive heart failure is present at a lower rate in comparison to the general population (1.5 % vs. 2.5 %). The pooled rate for the ischaemic heart disease is 3.3 % of BD patients and is probably several times higher than the reported rate in the general population.

10.2.4 Comorbid Neurological Conditions

Any neurological condition is diagnosed from 10.7 % cross-sectionally to 37.9 % lifetime in BD-I inpatients (Fattal et al. 2007; Beyer et al. 2005; Fenn et al. 2005). There is a variety of neurological syndromes which have been reported to coexist with BD, but the rates depend on the quality and composition of the study sample (Beyer et al. 2005; Kemp et al. 2013; Magalhaes et al. 2012; Oreski et al. 2012; Strakowski et al. 1992; Carney and Jones 2006; Subramaniam et al. 2013; Carta et al. 2012; Shanmugiah et al. 2008; Weber et al. 2011).

The rate of headache is probably similar to that seen in the general population (Kilbourne et al. 2004), but in BD-I the rate is reported to be as high as 20–25 % and four times higher in comparison to other patient groups (Carney and Jones 2006; Thompson et al. 2006). In BD-I inpatients, the rate of head trauma is 1 %

Table 10.17 Rates of cardiovascular disease in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any cardiovascular disease						
Beyer et al. (2005)	1,379			179 (13.0 %)		Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed pts
Fenn et al. (2005)	290			141 (48.6 %)		Inpatients, mostly BD-I, lifetime rate
Fenn et al. (2005)	290			101 (34.8 %)		Inpatients mostly BD-I, cross-sectional rate
Fiedorowicz et al. (2011)	135	MDD	524	12 (8,9 %)	57 (10,9 %)	Epidemiological data
Guo et al. (2006)	6,178			189 (3,1 %)		Health-care database
Kemp et al. (2013)	264			30 (11.4 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS), any heart disease
Kemp et al. (2013)	261			44 (16.9 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS), any cardiovascular disease
Magalhaes et al. (2012)	3,399			398 (11.7 %)		STEP-BD
McIntyre et al. (2006a)	938	Gen pop	35,848	41 (4.4 %)	1,936 (5.4 %)	Canadian Community Health Survey
Oreski et al. (2012)	97	Schiz	192	22 (22.7 %)	14 (7.3 %)	Inpatient records
Perron et al. (2009)	1,548	Gen pop	41,545	41 (2.7 %)	785 (1.9 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Ramsey et al. (2010)	58	Gen pop	1,339	5 (8.6 %)	57 (4.3 %)	ECA
Subramaniam et al. (2013)	88			6 (6.8 %)		BD-I pts
Thompson et al. (2006)	174			32 (18.4 %)		BD-I pts
Pooled	*14,545*			*1,110 (7.6 %)*		
		Gen pop	*78,732*		*2,778 (3.5 %)*	

Arrhythmias						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	116 (3.3 %)	8,740 (1.2 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Fenn et al. (2005)	290			8 (2.8 %)		Inpatients, mostly BD-I pts, cross-sectional
Fenn et al. (2005)	290			11 (3.8 %)		Inpatients, mostly BD-I pts, lifetime
Perron et al. (2009)	1,548	Gen pop	41,545	277 (17.9 %)	2,368 (5.7 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Pooled	*5,395*			*404 (7.5 %)*		
		Gen pop	*767,807*		*12,108 (1.6 %)*	
Congestive heart failure						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	43 (1.2 %)	3,117 (0.4 %)	BD-I Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	136 (3.2 %)	161,171 (4.7 %)	VA national patient population
Laursen et al. (2011)	6,215	Gen pop	2,428,518	28 (0.5 %)	3,065 (0.1 %)	Population-based cohort study
Ramsey et al. (2010)	58	Gen pop	1,339	1 (1.7 %)	9 (6.7 %)	ECA
Strakowski et al. (1992)	41			2 (4.9 %)		First-episode acute mania
Pooled	*14,181*			*210 (1.5 %)*		
		Gen pop	*6,564,879*		*167,362 (2.5 %)*	

(continued)

Table 10.17 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Ischaemic heart disease						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	135 (3.8 %)	13,567 (1.9 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Centorrino et al. (2009)	28,531	Gen pop	85,593	670 (2.3 %)	893 (1.0 %)	Health-care data
Fenn et al. (2005)	290			28 (9.7 %)		Inpatients mostly BD-I pts, coronary artery disease, cross-sectional
Fenn et al. (2005)	290			35 (12.1 %)		Inpatients mostly BD-I pts, coronary artery disease, cross-sectional, lifetime
Fenn et al. (2005)	290			6 (2.1 %)		Inpatients mostly BD-I pts, in process to establish coronary artery disease, cross-sectional
Fenn et al. (2005)	290			11 (3.8 %)		Inpatients mostly BD-I pts, coronary artery disease, lifetime
Guo et al. (2006)	6,178			40 (0,6 %)		Health-care database
Huang et al. (2009)	41,557	MDD	76,430	1,434 (3.5 %)	2,232 (2.9 %)	Health registry
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	455 (10.6 %)	560,626 (16.4 %)	VA national patient population
Laursen et al. (2011)	6,215	Gen pop	2,428,518	23 (0.4 %)	6,156 (0.3 %)	Population-based cohort study
Perron et al. (2009)	1,548	Gen pop	41,545	278 (18 %)	2,381 (5,7 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Perron et al. (2009)	1,548	Gen pop	41,545	18 (1.2 %)	386 (0,9 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Ramsey et al. (2010)	58	Gen pop	1,339	4 (6.9 %)	50 (3.7 %)	ECA
Pooled	*93,792*			*3,092 (3.3 %)*		
		Gen pop	*2,682,969*		*9,866 (0.4 %)*	
Peripheral vascular disease						
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	126 (2.9 %)	132,153 (3.9 %)	VA national patient population
Laursen et al. (2011)	6,215	Gen pop	2,428,518	18 (0.3 %)	7,443 (0.3 %)	Population-based cohort study
Carney and Jones (2006)	3,557	In- and outpatients	726,262	42 (1.2 %)	2,519 (0.4 %)	BD-I
						Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Various cardiovascular disorders						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	2 (0.1 %)	426 (0.1 %)	BD-I
						Pulmonary circulation dis, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Carney and Jones (2006)	3,557	In- and outpatients	726,262	68 (1.9 %)	5,517 (0.8 %)	BD-I
						Valvular disease current
						Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data

Schiz schizophrenia, *MDD* major depressive disorder, *Gen pop* general population

cross-sectionally and 7.6 % lifetime (Fenn et al. 2005). The rate of dementia is similar to that of the general population concerning Alzheimer's disease but double concerning other dementias, probably because of the higher prevalence of cardiovascular risk factors in BD patients (Kilbourne et al. 2004; Laursen et al. 2011). High rates of locomotor disorder and Parkinson's disease have also been reported, but the data are limited (Oreski et al. 2012; Weber et al. 2011; Kilbourne et al. 2004).

One of the most frequent findings in brain MRI scan of BD patients is white matter hyperintensities. Their role in the aetiopathogenesis of BD is not well understood. They do not seem to constitute a primary risk factor or endophenotype for BD, and probably they reflect the presence of medical comorbidities (e.g. migraine, cerebrovascular disease, multiple sclerosis, etc.) (Gunde et al. 2011; Ahearn et al. 1998; Iacovides and Andreoulakis 2011).

10.2.4.1 Stroke

Stroke is a vascular disease, and thus it is expected to manifest increased rates in BD patients, since they also manifest higher rates of several risk factors for the development of any vascular disease. The literature concerning stroke in BD patients is limited; however, the reported rates so far are more or less similar to those of the general population. Cross-sectionally, 0.2–1.9 % of BD patients suffer from stroke (Kilbourne et al. 2004; Fenn et al. 2005; Carney and Jones 2006; Laursen et al. 2011), and the lifetime prevalence is reported to be equal to 2.8 % (Fenn et al. 2005). However, it is obvious that these rates significantly depend on the composition of the sample and conclusions are difficult. The list of published studies with stroke rates in BD patients are shown in Table 10.18.

10.2.4.2 Migraine

Migraine is a very common disorder, affecting probably 15 % of the population, with female rates being double than those of males (Vos et al. 2012). It is considered to be a neurovascular disorder (Bartleson and Cutrer 2010), and it is characterized by the recurrence of painful and non-painful episodic phenomena and a variety of neurological manifestations. It is chronic in the sense that acute episodes tend to recur and have a significant global burden on the whole life of the patient. Migraine is considered to be a highly heterogenous disease both in terms of pathophysiology as well as in terms of resulting disability. In most cases, it occurs with a multifactorial inherited character and with a significant association to other neurological diseases (e.g. epilepsy, cerebrovascular disorders and stroke, mitochondrial diseases), cardiovascular disorders and especially mental disorders (anxiety, mood and personality disorders). It is interesting to note that the comorbid presence of hypertension and mental disorders often facilitates changes in the migraine pattern, changing it from an episodic towards a chronic character (Lipton 2009; Radat and Swendsen 2005). Typically, migraine is thought to correlate with certain personality features like perfectionism, neuroticism, repressed aggression and depression; however, the cause and effect of this relationship remains elusive.

The relationship of migraine with mood disorders has been extensively studied, but depression has been the dominant focus. Probably bipolar cases have been

Table 10.18 Rates of stroke in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	73 (1.7 %)	72,793 (2.1 %)	VA national patient population
Fenn et al. (2005)	290			4 (1.4 %)		Inpatients mostly BD-I
Carney and Jones (2006)	3,557	In- and outpatients	726,262	66 (1.9 %)	3,187 (0.4 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data
Laursen et al. (2011)	6,215	Gen pop	2,428,518	15 (0.2 %)	2,054 (0.1 %)	Population-based cohort study
Fenn et al. (2005)	290			8 (2.8 %)		Inpatients mostly BD-I, lifetime rate

Gen pop general population

included in depressive samples, but these studies cannot give information concerning BD. Migraine with aura has been reported to correlate more robustly with psychiatric comorbidity in comparison to migraine without aura, and this seems to concern also comorbidity with BD (Radat and Swendsen 2005; Ortiz et al. 2010). However, the findings to support a link between migraine and BD are inconsistent. The literature suggests the rate of BD in migraine patients ranges from 5 to 10 % (Antonaci et al. 2011; Breslau et al. 1991, 1994; Baskin and Smitherman 2009). The literature is conflicting with some studies reporting no association at all (Swartz et al. 2000), while others report a significant correlation with migraine patients manifesting several times higher rates of BD in comparison to the general population and probably around 17 % (Holland et al. 2011; Chen et al. 2012; Jette et al. 2008; Ratcliffe et al. 2009; Hamelsky and Lipton 2006; Merikangas et al. 1990; Breslau 1998). In patients with migraine, the prevailing type of bipolar illness is BD-II, probably accompanied by high levels of anxiety (Fasmer and Oedegaard 2001; Fasmer 2001; Ortiz et al. 2010).

In patients with BD, the rate of migraine is reported to be 4.7–76.9 % (Blehar et al. 1998; Cassidy et al. 1957; Hirschfeld et al. 2003; Holland et al. 2011; Kemp et al. 2013; Marchesi et al. 1989; McIntyre et al. 2006a, b; Nguyen and Low 2013; Ortiz et al. 2010; Ratcliffe et al. 2009; Weber et al. 2011; Calabrese et al. 2003; Fasmer 2001; Low et al. 2003; Mahmood et al. 1999).

It seems that in the vast majority of patients the onset of migraine precedes that of BD (Ortiz et al. 2010). In BD patients, the type of BD plays a role also, with very low rates for BD-I (<20 %) and around 1/3–3/4 of BD-II patients manifesting migraine sometime in their lives (Low et al. 2003; Fasmer 2001; Ortiz et al. 2010).

It has been reported that the clinical and family history characteristics of unipolar depressed patients with migraine resemble those of BD-II and therefore the presence of migraine should be considered to be a bipolar feature when seen in unipolar patients (Oedegaard and Fasmer 2005).

The list of studies reporting the rates of migraine in BD patients is shown in Table 10.19. The pooled rate is 6.3 % and seems to be fivefold higher from the rate of migraine reported in the general population.

10.2.4.3 Epilepsy

Epilepsy is considered to relate to psychosis, but comorbidity rates are not accurately known. Patients with epilepsy are reported to be at a two- to sixfold higher risk to manifest BD (Ottman et al. 2011; Ettinger et al. 2005; de Oliveira et al. 2010; Clarke et al. 2012; Adelow et al. 2012; Mula et al. 2009) although there are reports suggesting that BD in epileptic patients has a rate similar to that seen in the general population (Harden and Goldstein 2002; Mula et al. 2008b).

In patients with BD, the lifetime rates of epilepsy is 4.9–8.3 % (Hirschfeld et al. 2003; Fenn et al. 2005), and it is higher than cross-sectional rates which are reported to range between 0.5 % and 4.1 % (Kemp et al. 2013; Oreski et al. 2012; Weber et al. 2011; Fenn et al. 2005; Strakowski et al. 1992).

The nature of this comorbidity is elusive. Often, interictal manic symptoms are reportedly in people with epilepsy (Barry 2003), and some of the symptoms

Table 10.19 Rates of migraine in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Blehar et al. (1998)	327			69 (21.1 %)		
Calabrese et al. (2003)	1,167	Gen pop	1,283	280 (24.0 %)	141 (11.0 %)	
Cassidy et al. (1957)	100			49 (49.0 %)		
Fasmer (2001)	14	MDD	35	2 (1.42 %)	16 (45.7 %)	BD-I inpatients
Fasmer (2001)	13	MDD	35	10 (76.9 %)	16 (45.7 %)	BD-II inpatients
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	499 (23.4 %)	8,406 (10.1 %)	Epidemiological data
Holland et al. (2011)	169			8 (4.7 %)		
Kemp et al. (2013)	261			64 (24.5 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Low et al. (2003)	108			43 (39.8 %)		
Mahmood et al. (1999)	81			21 (25.9 %)		
Marchesi et al. (1989)	30			6 (20.0 %)		
McIntyre et al. (2006b)	1,054			79 (7.5 %)		Canadian Community Health Survey
McIntyre et al. (2006a, b)	938	Gen pop	36,046	233 (24.8 %)	3,713 (10.3 %)	Canadian Community Health Survey
Nguyen and Low (2013)	888	Gen pop	32,102	216 (24.3 %)	2,985 (9.3 %)	Canadian Community Health Survey
Ortiz et al. (2010)	323			79 (24.5 %)		2/3 BD-I pts
Ratcliffe et al. (2009)	40			11 (27.5 %)		Epidemiological data
Weber et al. (2011)	27,054	Gen pop	2,325,247	530 (1.9 %)	16,383 (0.7 %)	US hospital discharges between 1979 and 2006
Pooled	*34,701*			*2,199 (6.3 %)*		
		Gen pop	*2,477,902*		*31,628 (1.3 %)*	

Gen pop general population

attributed to a distinct 'epileptic personality' may be attributable to features of a BD. While more than 10 % of epileptic patients might fulfil some type of BD diagnostic criteria, less than 2 % can be considered to suffer from 'real' BD since in most cases, bipolar symptoms are related to phenotype copies of BD (e.g. peri-ictal manifestations or the forced normalization phenomenon) or they represent treatment-emergent adverse effects or even surgery complications (Mula 2010; Mula et al. 2008b).

The list of studies reporting the rates of epilepsy in BD patients is shown in Table 10.20. The pooled rate is 0.9 % and seems to be double in comparison to the rate of epilepsy reported in the general population, but maybe lower to the rate reported in patients with schizophrenia.

10.2.5 Infectious Diseases

10.2.5.1 Hepatitis B and C (HCV)

Hepatitis B is reported to affect 4.5 % of BD patients during lifetime (Fenn et al. 2005).

Patients with HCV are 1.5 times more likely to suffer also from BD in comparison to controls (Butt et al. 2006). Similarly BD patients seems to suffer more frequently from HCV although the rates reported are confusing and range widely from 1.9 to 58.9 % (Kemp et al. 2013; Weber et al. 2011; Fenn et al. 2005; Kilbourne et al. 2004; Beyer et al. 2005; Matthews et al. 2008). The pooled rate for HCV is 10.1 % and is almost tenfold higher in comparison to the general population rate (Table 10.21).

10.2.5.2 Human Immunodeficiency Virus (HIV)

The rate of HIV infection in BD patients is reported to be 0.1–2.8 % (Beyer et al. 2005, 2007; Fenn et al. 2005; Laursen et al. 2011; Carney and Jones 2006; Kilbourne et al. 2004). This is higher than the respected rate of the general population. Reversely, in patients with HIV, BD is diagnosed in 8.1 % and this is up to four-times higher than the rate observed in the general population. Two-thirds of BD patients (4–5 %) were reported to suffer from BD-I (de Sousa Gurgel et al. 2013; Kilbourne et al. 2001; Lyketsos et al. 1993). It is encouraging that maybe patients with AIDS and comorbid psychiatric disorders might receive better care than expected (Goulet et al. 2000); however, often they fail to seek help early in the course of the disease and might manifest more often dementia (Lyketsos et al. 1993). Overall, the comorbidity of BD with HIV is related with poor adherence and worse outcome (Badiee et al. 2012).

The pooled rate for HIV infection in BD patients is 0.7 %, and it is similar to that reported in unipolar depressed patients but several times higher from that reported in the general population (Table 10.21).

The relationship of BD with hepatitis and HIV infection exists probably because of the high prevalence of risk-taking behaviours in BD patients, especially concerning sexual activity and substance abuse. Not only it is reported that the

Table 10.20 Rates of epilepsy in BD patients

Study	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	*N*	Comments
Fenn et al. (2005)			12 (4.1 %)		290	Inpatients mostly BD-I current
Fenn et al. (2005)			24 (8.3 %)		290	Inpatients mostly BD-I, lifetime
Hirschfeld et al. (2003)	Gen pop	83,224	105 (4.9 %)	999 (1.2 %)	2,134	Epidemiological, lifetime
Kemp et al. (2013)			8 (3.1 %)		258	Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Oreski et al. (2012)	Schiz	192	1 (1.0 %)	8 (4.2 %)	97	Inpatient records
Strakowski et al. (1992)			1 (2.4 %)		41	Temp lobe epilepsy, first-episode mania
Weber et al. (2011)	Gen pop	2,325,247	136 (0.5 %)	9,133 (3.9 %)	27,054	US hospital discharges between 1979 and 2006
Pooled			*275 (0.9 %)*		*29,874*	
	Gen pop	*2,408,471*		*10,132 (0.4 %)*		

Gen pop general population

Table 10.21 Rates of hepatitis B and C and HIV infection in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Hepatitis B						
Fenn et al. (2005)	290			9 (3.1 %)		Inpatients mostly BD-I, hepatitis B, cross-sectional rate
Fenn et al. (2005)	290			13 (4.5 %)		Inpatients mostly BD-I, hepatitis B, lifetime rate
Hepatitis C						
Beyer et al. (2005)	1,379			26 (1.9 %)		BD-I pts, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed, hepatitis C, cross-sectional rate
Fenn et al. (2005)	290			39 (13.4 %)		Inpatients mostly BD-I, hepatitis C, cross-sectional rate
Fenn et al. (2005)	290			45 (15.5 %)		Inpatients mostly BD-I, hepatitis C, lifetime rate
Kemp et al. (2013)	262			11 (4.2 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	252 (5.8 %)	38,312 (1.1 %)	VA national patient population, hepatitis C, cross-sectional study
Matthews et al. (2008)	5,026	MDD	4,724	3,006 (59.8 %)	3,860 (81.7 %)	VISN 20 Consumer Health Information and Performance Sets (CHIPS) Data Warehouse
Weber et al. (2011)	27,054	Gen pop	2,325,247	553 (2.0 %)	23,397 (1.0 %)	US hospital discharges between 1979 and 2006
Pooled	*38,321*			*3,893 (10.1 %)*		
			5,734,007		*61,709 (1.1 %)*	

HIV						
Beyer et al. (2005)	1,379			39 (2.8 %)		BD-I pts, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed pts
Beyer et al. (2007)	1,213	MDD	5,621	32 (2.6 %)	79 (1.4 %)	Outpatients
Carney and Jones (2006)	3,557	In- and outpatients	726,262	5 (0.1)	99 (0.0)	Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, BD-I pts
Fenn et al. (2005)	290			4 (1.4 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients, mostly BD-I, lifetime rate
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	35 (0.8 %)	18,364 (0.5 %)	VA national patient population
Laursen et al. (2011)	6,215	Gen pop	2,428,518	3 (0.0 %)	901 (0.0 %)	Population-based cohort study
Pooled	*17,254*			*123 (0.7 %)*		
			6,563,540		*19,364 (0.0 %)*	

Gen pop general population, *MDD* major depressive disorder

coexistence of substance abuse raises the rate dramatically (Beyer et al. 2007), but even more, substance abuse might be the crucial factor without the existence of an independent association between serious mental illness and the risk of HIV infection (Prince et al. 2012).

10.2.6 Cancer

The rates for any cancer in BD patients range from 0.2 to 7.5 % (Kilbourne et al. 2004; Kemp et al. 2013; Magalhaes et al. 2012; McGinty et al. 2012; Oreski et al. 2012; McIntyre et al. 2006a; Beyer et al. 2005; Laursen et al. 2011; Carney and Jones 2006). They seem to concern all organ systems (Carney and Jones 2006), and no racial differences are evident (McGinty et al. 2012). The various rates for specific types vary from negligible concerning leukaemia to 2.5 % for breast cancer (Laursen et al. 2011; McGinty et al. 2012; Kilbourne et al. 2004; Carney and Jones 2006; Fenn et al. 2005).

The list of studies with cancer rates in BD are shown in Table 10.22. The pooled rate for any cancer in BD is 1.8 %, and it is 1.5-fold higher than that observed in the general population and similar to that seen in patients with schizophrenia. Prostate cancer has a pooled rate of 1.4 %, while the rates of other specific cancers are shown in Table 10.22.

Overall the literature suggests that BD patients are roughly in a double risk of developing cancer in comparison to the general population. Probably this is because several risk factors for cancer are disproportionately prevalent in BD patients. The high rates of smoking, low rates of childbearing, increased prolactin levels, the sedentary lifestyle, the diet high in fat and low in fruits and vegetables as well as other risk factors could be the main reason for the increase in cancer rates in BD patients.

10.2.7 Endocrinological Disorders

Any endocrinological disorder is seen in 13.6–28.6 % of BD patients (Fenn et al. 2005; Beyer et al. 2005; Kemp et al. 2013; Oreski et al. 2012). The major problem concerns the thyroid gland, probably not only because of treatment with lithium. Any thyroid disorder is seen in 6.5–15.1 % of BD patients (Kemp et al. 2013; Oreski et al. 2012; Thompson et al. 2006; Magalhaes et al. 2012; McIntyre et al. 2006a; Kilbourne et al. 2004; Krishnan 2005). Hypothyroidism is seen in 0.3–9.2 % (Valle et al. 1999; Fenn et al. 2005), while hypothyroidism in 2.4–13 % of BD patients (Strakowski et al. 1992; Valle et al. 1999; Weber et al. 2011; Carney and Jones 2006; Fenn et al. 2005). Endocrinological disorders and especially hypothyroidism might adversely influence the outcome of BD.

The rates of endocrinological disorders are shown in Table 10.23. The pooled rates suggest that any endocrinological disorder is seen in 17.6 %. Any thyroid disorder is seen in 10.2 % of BD patients, and this rate is very much higher than the respected in the general population and double of that reported in schizophrenia.

Table 10.22 Rates of cancer in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any cancer						
Beyer et al. (2005)	1,379			39 (2.8 %)		BD-I, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	21 (0.6)	2,994 (0.4 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, metastatic cancer, cross-sectional rates
Carney and Jones (2006)	3,557	In- and outpatients	726,262	98 (2.8)	12,341 (1.7 %)	BD-I Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims, nonmetastatic cancer, cross-sectional rates
Kemp et al. (2013)	261			7 (2.7 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Laursen et al. (2011)	6,215	Gen pop	2,428,518	85 (1.4 %)	26,048 (1.1 %)	Population-based cohort study, any cancer, cross-sectional rates
Laursen et al. (2011)	6,215	Gen pop	2,428,518	10 (0.2 %)	4,798 (0.2 %)	Population-based cohort study, metastatic solid tumour, cross-sectional rates
Magalhaes et al. (2012)	3,399			34 (1.0 %)		STEP-BD
McGinty et al. (2012)	1,002			75 (7.5 %)		Maryland Medicaid adult beneficiaries with serious mental illness
McIntyre et al. (2006a)	938	Gen pop	35,848	12 (1.3 %)	717 (2.0 %)	Canadian Community Health Survey, lifetime
Oreski et al. (2012)	97	Schiz	192	5 (5.2 %)	4 (2.1 %)	Inpatient records
Pooled	*20,405*		*3,916,890*	*376 (1.8 %)*		
			3,916,890		*42,100 (1.1 %)*	

(continued)

Table 10.22 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Prostate						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	60 (4.3 %)	6,393 (1.9 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, prostatic benign hyperplasia current
Fenn et al. (2005)	290			2 (0.7 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, lifetime rate
Fenn et al. (2005)	290			14 (4.8 %)		Inpatients mostly BD-I, prostatic benign hyperplasia, cross-sectional
Fenn et al. (2005)	290			22 (7.6 %)		Inpatients mostly BD-I, prostatic benign hypertrophy, lifetime
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	68 (1.6 %)	106,195 (3.1 %)	VA national patient population, cross-sectional
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	43 (1.0 %)	307,160 (9.0 %)	VA national patient population, prostatic benign hyperplasia, cross-sectional
McGinty et al. (2012)	369			1 (0.3 %)		Maryland Medicaid adult beneficiaries with serious mental illness
Pooled	*5,259*			*76 (1.4 %)*		
Other types						
Laursen et al. (2011)	6,215	Gen pop	2,428,518	2 (0.0 %)	885 (0.0 %)	Population-based cohort study, leukaemia current
McGinty et al. (2012)	633	Schiz		16 (2.5 %)		Maryland Medicaid adult beneficiaries with serious mental illness, the breast
McGinty et al. (2012)	1,002	Schiz		11 (1.1 %)		Maryland Medicaid adult beneficiaries with serious mental illness, the colon

McGinty et al. (2012)	1,002	Schiz		13 (1.3 %)		Maryland Medicaid adult beneficiaries with serious mental illness, the lung
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	14 (0.3 %)	29,637 (0.9 %)	VA national patient population, the lung current
Carney and Jones (2006)	3,557	In- and outpatients	726,262	7 (0.2)	1,401 (0.2)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, lymphoma current
Laursen et al. (2011)	6,215	Gen pop	2,428,518	5 (0.1 %)	2,195 (0.1 %)	Population-based cohort study, lymphoma current
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	50 (1.2 %)	0 (0.0 %)	VA national patient population, skin cancer current

Gen pop general population, *Schiz* schizophrenia

Table 10.23 Rates of endocrinological disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any endocrinological dis						
Beyer et al. (2005)	1,379			187 (13.6 %)		Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed pts, cross-sectional
Fenn et al. (2005)	290			66 (22.8 %)		Inpatients mostly BD-I cross-sectional
Fenn et al. (2005)	290			83 (28.6 %)		Inpatients mostly BD-I, lifetime
Kemp et al. (2013)	264			66 (25.0 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Oreski et al. (2012)	97	Schiz	192	22 (22.7 %)	18 (9.4 %)	Inpatient records
Pooled	*2,030*			*358 (17.6 %)*		
Any thyroid dis						
Kemp et al. (2013)	261			17 (6.5 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	303 (7.0 %)	0 (0.0 %)	VA national patient population, cross-sectional
Magalhaes et al. (2012)	3,399			513 (15.1 %)		STEP-BD
McIntyre et al. (2006a)	938	Gen pop	35,848	69 (7.4 %)	2,007 (5.6 %)	Canadian Community Health Survey, lifetime
Oreski et al. (2012)	97	Schiz	192	13 (13.4 %)	13 (6.8 %)	Inpatient records
Thompson et al. (2006)	174			22 (12.6 %)		BD-I pts, cross-sectional
Pooled	*9,179*			*937 (10.2 %)*		
		Gen pop	*3,444,608*		*2,020 (0.1 %)*	

Hyperthyroidism						
Fenn et al. (2005)	290			1 (0.3 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, lifetime
Valle et al. (1999)	54			5 (9.2 %)		Lithium-naïve pts
Hypothyroidism						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	340 (9.6 %)	18,168 (2.5 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional
Fenn et al. (2005)	290			29 (10.0 %)		Inpatients mostly BD-I pts, cross-sectional
Fenn et al. (2005)	290			40 (13.8 %)		Inpatients mostly BD-I pts, lifetime
Strakowski et al. (1992)	41			1 (2.4 %)		First-episode manic pts
Valle et al. (1999)	54			5 (9.2 %)		Lithium-naïve pts
Weber et al. (2011)	27,054			1,936 (7.2 %)		US hospital discharges between 1979 and 2006
Pooled	*30,996*			*2,311 (7.5 %)*		

Gen pop general population, *Schiz* schizophrenia

Hypothyroidism is seen in 7.5 % of BD patients, and it is probably much higher than the rate in the general population.

10.2.8 Gastroenterological Disorders

A variety of gastroenterological problems and conditions are reported in BD patients at higher than expected rates. Cross-sectionally 7.3–33.9 % are reported to suffer from any gastroenterological disorder (Beyer et al. 2005; Thompson et al. 2006; Oreski et al. 2012; Fenn et al. 2005), and the respected rate might be around 33 % for lifetime rates (Fenn et al. 2005). Any liver disease is reported in 0.3–21 % (Kemp et al. 2013; Perron et al. 2009; Fenn et al. 2005; Carney and Jones 2006; Fuller et al. 2011; Laursen et al. 2011), cirrhosis (mostly because of alcohol abuse) in 0.9–2.1 % (Perron et al. 2009; Fuller et al. 2011; Fenn et al. 2005), gastritis in 0.3–15 % (Perron et al. 2009; Fenn et al. 2005; Kilbourne et al. 2004) and peptic ulcer in 0.9–22 % (Goodwin et al. 2009; Perron et al. 2009; Subramaniam et al. 2013; McIntyre et al. 2006a; Fenn et al. 2005; Magalhaes et al. 2012; Carney and Jones 2006; Laursen et al. 2011). Other gastroenterological disorders are reported also like Crohn's disease (McIntyre et al. 2006a) and oesophageal varices (Fenn et al. 2005), incontinence (Fenn et al. 2005) and gastrointestinal fluid and electrolyte disorders (Carney and Jones 2006).

A list with the studies reporting the rates of comorbid gastroenterological disorders is shown in Table 10.24. Pooled rates suggest that liver disease is present in 7.5 % of BD patients and this is much higher than the expected in the general population and similar to that seen in schizophrenia. Peptic ulcer is seen in 3.6 % of BD patients, and this rate is seven times higher than that in the general population.

10.2.9 Disorders of the Blood

Any disorder of the blood is seen in 1.5–3.8 % of BD patients (Beyer et al. 2005; Fenn et al. 2005), anaemia of any kind in 0.5–6.4 % (Kemp et al. 2013; Carney and Jones 2006; Kilbourne et al. 2004) and coagulopathy in 1.1 % of BD patients (Carney and Jones 2006).

10.2.10 Respiratory System Disorders

Respiratory disorders are also more prevalent in BD patients in comparison to the general population, and vice versa. In asthma patients, BD has a prevalence of almost 5 % (Goodwin et al. 2003, 2010). In BD patients, a variety of comorbid medical problems of the respiratory system exist. Probably 1–24.1 % of them suffer from any respiratory problem (Laursen et al. 2011; Carney and Jones 2006; Douzenis et al. 2012; Fenn et al. 2005; Beyer et al. 2005; Kemp et al. 2013; Oreski et al. 2012; Thompson et al. 2006; Subramaniam et al. 2013). Asthma is present in

Table 10.24 Rates of gastroenterological disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any gastroenterological dis						
Beyer et al. (2005)	1,379			101 (7.3 %)		Duke University Medical Center outpatient clinical database, BD-I 2/3 manic and 1/3 depressed, cross-sectional rate
Fenn et al. (2005)	290			52 (17.9 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			114 (39.3 %)		Inpatients mostly BD-I pts, lifetime
Oreski et al. (2012)	97	Schiz	192	16 (16.5 %)	21 (10.9 %)	Inpatient records
Thompson et al. (2006)	174			59 (33.9 %)		BD-I, cross-sectional rate
Cirrhosis						
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, alcoholic, cross-sectional rate
Fenn et al. (2005)	290			6 (2.1 %)		Inpatients mostly BD-I, alcoholic, lifetime
Fuller et al. (2011)	5,319	Schiz	6,521	85 (1.6 %)	104 (1.6 %)	VISN 20 Consumer Health Information and Performance Set Data Warehouse, alcohol
Perron et al. (2009)	1,548	Gen pop	41,545	14 (0,9 %)	87 (0,2 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Gastritis						
Fenn et al. (2005)	290			1 (0.3 %)		Inpatients mostly BD-I, gastritis and alcohol, cross-sectional rate

(continued)

Table 10.24 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Fenn et al. (2005)	290			2 (0.7 %)		Inpatients mostly BD-I, alcohol and gastritis, lifetime
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	284 (6.6 %)	169,721 (5.0 %)	VA national patient population, gastritis, cross-sectional rate
Perron et al. (2009)	1,548	Gen pop	41,545	232 (15.0 %)	2,464 (5,9 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Liver disease						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	39 (1.1 %)	1,281 (0.2 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional rate
Fenn et al. (2005)	290			49 (16.9 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			61 (21.0 %)		Inpatients mostly BD-I pts, lifetime
Fuller et al. (2011)	5,319	Schiz	6,521	1,144 (21.5 %)	1,461 (22.4 %)	VISN 20 Consumer Health Information and Performance Set Data Warehouse
Kemp et al. (2013)	263			10 (3.8 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Laursen et al. (2011)	6,215	Gen pop	2,428,518	18 (0.3 %)	1,582 (0.1 %)	Population-based cohort study, cross-sectional rate
Laursen et al. (2011)	6,215	Gen pop	2,428,518	82 (1.3 %)	6,647 (0.3 %)	Population-based cohort study, lifetime rate
Perron et al. (2009)	1,548	Gen pop	41,545	30 (1.9 %)	220 (0.5 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Pooled	*17,192*			*1,290 (7.5 %)*		
		Gen pop	*3,196,325*		*3,083 (0.1 %)*	
Peptic ulcer						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	31 (0.9)	1,515 (0.2)	BD-I pts, Wellmark Blue Cross/ Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional rate
Fenn et al. (2005)	290			13 (4.5 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			36 (12.4 %)		Inpatients mostly BD-I pts, lifetime
Goodwin et al. (2009)	1,411			31 (2.2 %)		National Epidemiologic Survey of Alcohol and Related Conditions
Laursen et al. (2011)	6,215	Gen pop	2,428,518	62 (1.0 %)	13,458 (0.6 %)	Population-based cohort study, cross-sectional rate
Magalhaes et al. (2012)	3,399			217 (6.4 %)		STEP-BD
McIntyre et al. (2006a)	938	Gen pop	35,848	101 (10.8 %)	1,398 (3.9 %)	Canadian Community Health Survey, lifetime
Perron et al. (2009)	1,548	Gen pop	41,545	141 (9.1 %)	1,039 (2.5 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Subramaniam et al. (2013)	88			4 (4.5 %)		BD-I pts
Pooled	*17,736*			*636 (3.6 %)*		
		Gen pop	*3,232,173*		*17,410 (0.5 %)*	

(continued)

Table 10.24 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Other gastroenterological dis						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	216 (6.1)	7,632 (1.1)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, gastrointestinal fluid and electrolyte disorders, cross-sectional rate
Fenn et al. (2005)	290			2 (0.7 %)		Inpatients mostly BD-I, current oesophageal varices
Fenn et al. (2005)	290			3 (1.0 %)		Inpatients mostly BD-I, lifetime, oesophageal varices
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, incontinence current
Fenn et al. (2005)	290			8 (2.8 %)		Inpatients mostly BD-I, incontinence, lifetime
McIntyre et al. (2006a)	938	Gen pop	35,848	38 (4.1 %)	968 (2.7 %)	Canadian Community Health Survey, Crohn's disease, lifetime

Gen pop general population, *Schiz* schizophrenia

2.9–18.3 % (Calabrese et al. 2003; Carney and Jones 2006; Fenn et al. 2005; Hirschfeld et al. 2003; Kemp et al. 2013; Kilbourne et al. 2004; McIntyre et al. 2006a; Weber et al. 2011). Chronic obstructive pulmonary disorder (COPD) is present in 2.2–10.6 % (Hirschfeld et al. 2003; Kilbourne et al. 2004; Fenn et al. 2005; Guo et al. 2006; Lin et al. 2007; Beyer et al. 2005). The rate for sleep apnoea is reported to be 1.7 % cross-sectionally and 3.4 % lifetime (Fenn et al. 2005), and chronic bronchitis is found in 7.9 % of BD patients (McIntyre et al. 2006a), pneumonia in 7.3 % (Strakowski et al. 1992) and history of pulmonary embolism in 0.8 % (Strudsholm et al. 2005). In a bipolar spectrum perspective, subjects at high risk for sleep apnoea were reported to have increased scores on measures of both depression and mania, even when sleep items were not counted in the total scores (Soreca et al. 2012).

The list of published studies reporting rates of comorbid respiratory disorders is shown in Table 10.25. The pooled rate of any respiratory disorder is 7 %, more than triple of that seen in the general population. The respected rate for asthma is 7.4 %, three times higher than that of the general population and that of COPD is 5.4 % and probably similar to that of general population.

10.2.11 Various Comorbid Medical Disorders

10.2.11.1 Dermatological Disorders

Any dermatological disorder is seen in 2–13.2 % cross-sectionally (Fenn et al. 2005; Douzenis et al. 2012; Beyer et al. 2005; Thompson et al. 2006) and in 20.3 % of BD patients lifetime (Fenn et al. 2005). Eczema and psoriasis are seen each in 0.5 % of BD patients which is roughly double of what expected in the general population (Weber et al. 2011). From a reverse angle, patients with psoriasis have double rates of BD (1.1 % vs. 0.5 %), in comparison to controls (Han et al. 2011).

The pooled rate concerning any comorbid dermatological disorder is equal to 4.2 % (Table 10.26).

10.2.11.2 Immunological Disorders

There are reports in the literature suggesting the presence of an immune/inflammatory imbalance in BD. Several laboratory findings of inflammatory factors have been reported (Barbosa et al. 2012), and one of the robust findings concerns the rate of positive TPO-Abs, which is almost double in BD patients in comparison to controls. On the basis of this, a twin study suggested there is a fundamental relationship in the aetiopathogenesis of autoimmune thyroiditis and BD (Vonk et al. 2007).

In accord with the above, it has been proposed that a history of autoimmune disorders including Guillain–Barre syndrome, Crohn's disease and autoimmune hepatitis seems to constitute a 'risk factor' for the latter development of BD (Eaton et al. 2010).

In terms of epidemiology, patients with fibromyalgia have extremely high rates of BD, and maybe up to three-quarters of fibromyalgia patients are also suffering from BD (Alciati et al. 2012; Arnold et al. 2006; Carta et al. 2006). The literature on

Table 10.25 Rates of respiratory disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any respiratory dis						
Beyer et al. (2005)	1,379			101 (7.3 %)		Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	458 (12.9 %)	25,894 (3.6 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data chronic, cross-sectional
Douzenis et al. (2012)	228			16 (7.1 %)		Inpatients, cross-sectional
Fenn et al. (2005)	290			38 (13.1 %)		Inpatients mostly BD-I pts, cross-sectional
Fenn et al. (2005)	290			70 (24.1 %)		Inpatients mostly BD-I pts, lifetime
Kemp et al. (2013)	264			71 (26.9 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Laursen et al. (2011)	6,215	Gen pop	2,428,518	126 (2.0 %)	38,653 (1.6 %)	Population-based cohort study, cross-sectional
Oreski et al. (2012)	97	Schiz	192	1 (1.0 %)	8 (4.2 %)	Inpatient records
Subramaniam et al. (2013)	88			13 (14.8 %)		BD-I pts
Thompson et al. (2006)	174			41 (23.6 %)		BD-I pts, cross-sectional
Pooled	*12,292*			*865 (7.0 %)*		
		Gen pop	*3,154,780*		*64,547 (2.0 %)*	
Asthma						
Calabrese et al. (2003)	1,167	Gen pop	1,283	198 (17.0 %)	128 (10.0 %)	Lifetime
Carney and Jones (2006)	3,557	In- and outpatients	726,262	261 (7.3 %)	12,542 (1.7 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional

Fenn et al. (2005)	290			9 (3.1 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			16 (5.5 %)		Inpatients mostly BD-I, lifetime
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	391 (18.3 %)	7,740 (9.3 %)	Epidemiological, lifetime
Kemp et al. (2013)	263			38 (14.4 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	127 (2.9 %)	85,278 (2.5 %)	VA national patient population, cross-sectional
McIntyre et al. (2006a)	938	Gen pop	35,848	149 (15.9 %)	2,975 (8.3 %)	Canadian Community Health Survey, lifetime
Weber et al. (2011)	27,054			1,751 (6.7 %)		US hospital discharges between 1979 and 2006
Pooled	*39,713*			*2,924 (7.4 %)*		
		Gen pop	*4,255,377*		*108,663 (2.6 %)*	
COPD						
Beyer et al. (2005)	1,379			84 (6.1 %)		BD-I pts
Fenn et al. (2005)	290			23 (7.9 %)		Inpatients mostly BD-I pts, cross-sectional
Fenn et al. (2005)	290			26 (9.0 %)		Inpatients mostly BD-I pts, lifetime
Guo et al. (2006)	6,178			258 (4.2 %)		Health-care database, cross-sectional
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	47 (2.2 %)	1,248 (1.5 %)	Epidemiological, lifetime
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	455 (10.6 %)	318,861 (9.4 %)	VA national patient population, cross-sectional
Lin et al. (2007)	2,289	Gen pop	16,413	23 (1.0 %)	102 (0.6 %)	All sample underwent appendectomy, cross-sectional
Pooled	*16,580*			*890 (5.4 %)*		
		Gen pop	*3,508,397*		*320,211 (9.1 %)*	

(continued)

Table 10.25 (continued)

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Various						
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I pts, sleep apnoea, cross-sectional
Fenn et al. (2005)	290			10 (3.4 %)		Inpatients mostly BD-I pts, sleep apnoea, lifetime
McIntyre et al. (2006a)	938	Gen pop	35,848	74 (7.9 %)	1,111 (3.1 %)	Canadian Community Health Survey, chronic bronchitis, lifetime
Strakowski et al. (1992)	41			3 (7.3 %)		First-episode manic pts, pneumonia
Strudsholm et al. (2005)	25,834	Gen pop	117,815	214 (0.8 %)	699 (0.6 %)	Danish Psychiatric Central Research Register, pulmonary embolism, lifetime

Gen pop general population, *Schiz* schizophrenia

Table 10.26 Rates of dermatological disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any dermatological dis						
Beyer et al. (2005)	1,379			28 (2.0 %)		BD-I pts, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed pts
Douzenis et al. (2012)	228			16 (7.1 %)		Inpatients
Fenn et al. (2005)	290			20 (6.9 %)		Inpatients mostly BD-I, cross-sectional rate
Fenn et al. (2005)	290			59 (20.3 %)		Inpatients mostly BD-I, lifetime rate
Thompson et al. (2006)	174			23 (13.2 %)		BD-I
Pooled	2,071			87 (4.2 %)		
Specific dermatological dis						
Weber et al. (2011)	27,054	Gen pop	2,325,247	144 (0.5 %)	4,427 (0.2 %)	US hospital discharges between 1979 and 2006, eczema
Weber et al. (2011)	27,054	Gen pop	2,325,247	135 (0.5 %)	4,390 (0.2 %)	US hospital discharges between 1979 and 2006, psoriasis

Gen pop general population

comorbidity of BD with various allergies suggest that although the risk of BD in patients with allergies is 1.5–2 in comparison to the normal populations (Patten and Williams 2007), there might be a bias in the methodology of the reported results and the overall comorbidity rate is not different from that seen in the general population, but the presence of BD reduces the chance of correct diagnosis and treatment of allergies (Goodwin et al. 2012). Up to 2.8 % of BD patients also suffer from fibromyalgia and another 3.8 % from chronic fatigue syndrome at some time in their lives, while 2.7 % suffer from rheumatoid arthritis. There rates are two to three times higher to those expected in the general population (McIntyre et al. 2006a; Carney and Jones 2006). A list of studies with rates of comorbid immunological disorders is shown in Table 10.27.

10.2.11.3 Musculoskeletal Disorders

BD could be related to a variety of musculoskeletal disorders since several risk factors leading to them are highly prevalent among BD patients. It is well known that bone metabolism is related to nutritional alterations, polydipsia, smoking and endocrinological disorders including medication-induced hyperprolactinaemia. Lithium, carbamazepine and valproate can also affect bone density (Misra et al. 2004).

Any disorder of the musculoskeletal system is seen in 10.7–49.7 % of BD patients (Thompson et al. 2006; Fenn et al. 2005; Beyer et al. 2005; Kemp et al. 2013). More specifically, it has been reported that 1–30.7 % of BD patients suffer from some type of arthritis cross-sectionally or lifetime (Perron et al. 2009; Weber et al. 2011; Kilbourne et al. 2004; McIntyre et al. 2006a; Carney and Jones 2006; Fenn et al. 2005; Guo et al. 2006). Up to one-quarter of BD patients complain of backache (Carney and Jones 2006; Kilbourne et al. 2004), 13 % report hip problems (Kilbourne et al. 2004), and close to one-third some kind of chronic pain syndrome (Goldstein et al. 2009; Subramaniam et al. 2013). For most of these conditions, the rates are twofold higher than those reported for the general population.

A list of studies with rates of comorbid musculoskeletal disorders is shown in Table 10.28. The pooled rates suggest that any musculoskeletal disorder is present in 16.7 % of BD patients. The pooled rates for arthritis are probably misleading, and the most probable rate is around 14 %, and it is similar to that reported in the general population.

10.2.11.4 Genitourinary Disorders

Any genitourinary disorder is reported in 3.7–24.7 % of BD patients (Kemp et al. 2013; Fenn et al. 2005; Beyer et al. 2005; Thompson et al. 2006). Cross-sectionally, there are reported menstruation problems in 12.8 %, endometriosis in 1.7 %, inflammatory disease of the ovary in 8.1 %, cystitis in 1.3 %, mammary dysplasia in 4.8 % (Carney and Jones 2006), complication of gestational pregnancy and childbirth in 0.4 % (Beyer et al. 2005) and various gynaecologic problems in 2.1 % (Oreski et al. 2012). In patients with polycystic ovary syndrome, the rate of BD is 11.1 %, that is, several times higher than that of the general population (Rassi et al. 2010). The list of studies with specific rates is shown in Table 10.29.

Table 10.27 Rates of immunological disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any autoimmune dis						
Fenn et al. (2005)	290			4 (1.4 %)		Inpatients mostly BD-I, current
Fenn et al. (2005)	290			7 (2.4 %)		Inpatients mostly BD-I, lifetime
Allergies						
Calabrese et al. (2003)	1,167	Gen pop	1,283	490 (42 %)	372 (29.0 %)	Lifetime
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	864 (40.5 %)	22,138 (26.6 %)	Epidemiological, lifetime
Hirschfeld et al. (2003)	2,134	Gen pop	83,224	864 (40.5 %)	22,138 (26.6 %)	Epidemiological
Various autoimmune dis						
McIntyre et al. (2006a)	938	Gen pop	35,848	36 (3.8 %)	394 (1.1 %)	Canadian Community Health Survey, chronic fatigue syndrome, lifetime
McIntyre et al. (2006a)	938	Gen pop	35,848	26 (2.8 %)	502 (1.4 %)	Canadian Community Health Survey, fibromyalgia, lifetime
Carney and Jones (2006)	3,557	In- and outpatients	726,262	97 (2.7)	9,407 (1.3)	BD-I Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, rheumatoid arthritis, current

Gen pop general population

Table 10.28 Rates of musculoskeletal disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any musculoskeletal dis						BD-I pts, cross-sectional
Beyer et al. (2005)	1,379			141 (10.7 %)		Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed, cross-sectional
Fenn et al. (2005)	290			68 (23.4 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			144 (49.7 %)		Inpatients mostly BD-I, lifetime
Kemp et al. (2013)	264			87 (33.0 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Thompson et al. (2006)	174			56 (31.2 %)		
Pooled	*2,107*			*352 (16.7 %)*		
Arthritis						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	200 (5.6)	15,939 (2.2)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional
Fenn et al. (2005)	290			33 (11.4 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			46 (15.9 %)		Inpatients mostly BD-I, lifetime
Guo et al. (2006)	6,178			200 (3.2 %)		Health-care database, cross-sectional
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	677 (15.7 %)	549,603 (16.1 %)	VA national patient population, cross-sectional
McIntyre et al. (2006a)	938	Gen pop	35,848	193 (20.6 %)	6,238 (17.4 %)	Canadian Community Health Survey, lifetime

Perron et al. (2009)	1,548	Gen pop	41,545	476 (30.7 %)	8,691 (20.9 %)	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Weber et al. (2011)	27,054	Gen pop	2,325,247	272 (1.0 %)	13,818 (0.6 %)	US hospital discharges between 1979 and 2006
Various musculoskeletal dis						
Carney and Jones (2006)	3,557	In- and outpatients	726,262	919 (25.8)	96,201 (13.3)	Backache, BD-I, Wellmark Blue Cross/ Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional
Goldstein et al. (2009)	883	Gen pop	42,210	219 (24.8 %)	5,023 (11.9 %)	National Epidemiologic Survey on Alcohol and Related Conditions
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	565 (13.1 %)	0 (0.0 %)	VA national patient population, hip problems, cross-sectional
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	10 (0.2 %)	19,855 (0.6 %)	VA national patient population, spinal cord injury, cross-sectional
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	663 (15.4 %)	361,868 (10.6 %)	VA national patient population, lower back pain, cross-sectional
Laursen et al. (2011)	6,215	Gen pop	2,428,518	21 (0.3 %)	18,154 (0.7 %)	Population-based cohort study, connective tissue disease, cross-sectional
Subramaniam et al. (2013)	88			25 (28.4 %)		BD-I pts, pain chronic

Gen pop general population

Table 10.29 Rates of genitourinary disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any genitourinary dis						
Beyer et al. (2005)	1,379			51 (3.7 %)		BD-I pts, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed, current
Fenn et al. (2005)	290			26 (9.0 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			62 (21.4 %)		Inpatients mostly BD-I, lifetime
Kemp et al. (2013)	264			45 (17.0 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Thompson et al. (2006)	174			43 (24.7 %)		BD-I pts, cross-sectional
Specific genitourinary dis						
Beyer et al. (2005)	1,379			5 (0.4 %)		BD-I pts, Duke University Medical Center outpatient clinical database, 2/3 manic and 1/3 depressed and complications of pregnancy, childbirth and the puerperium, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	277 (12.8 %)	19,330 (5.1 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, menstruation disorders, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	37 (1.7 %)	2,359 (0.6 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, endometriosis, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	174 (8.1 %)	9,676 (2.5 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, inflammatory disease of the ovary, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	28 (1.3 %)	1,094 (0.3 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cystitis, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	103 (4.8 %)	11,385 (3.0 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, mammary dysplasia, cross-sectional
Oreski et al. (2012)	97	Schiz	192	2 (2.1 %)	7 (3.6 %)	Inpatient records, gynaecologic disorders

Gen pop general population, *Schiz* schizophrenia

10.2.11.5 Renal Disorders

Renal disorders are important for BD patients since lithium exerts renal toxicity. Any renal disorder is reported to be present in 0.7–6.6 % of BD patients, and probably this is several times higher from what is expected in the general population (Kemp et al. 2013; Fenn et al. 2005; Lin et al. 2007; Laursen et al. 2011). Renal failure is reported cross-sectionally in 0.8–1.3 % of BD patients, and the rate is probably similar to that of the general population (Kilbourne et al. 2004; Carney and Jones 2006). The co-segregation in this family suggests a close proximity between genes for the two disorders. The two known loci of medullary cystic kidney disease are in regions of chromosomes 1 and 16 that have been previously linked to bipolar disorder and schizophrenia. This family may be a useful resource for positional cloning of bipolar candidate genes (Kimmel et al. 2005). The list of studies with specific rates is shown in Table 10.30.

10.2.11.6 Various Other Comorbid Medical Disorders

Various types of accidents and injuries are reported in 11.9–40.9 % of BD patients (Carney and Jones 2006; Kilbourne et al. 2004), otolaryngologic disorders in 9 % cross-sectionally and 23.1 % lifetime (Fenn et al. 2005) and cataract in 1.8 % lifetime (McIntyre et al. 2006a). Any type of pancreatitis is reported in 3.8 % of BD patients cross-sectionally (Kilbourne et al. 2004), infectious aetiology in 0.6 % (Carney and Jones 2006) and alcoholic pancreatitis 0.7 % cross-sectionally and 1.7 % lifetime (Fenn et al. 2005).

Approximately 2.2–3 % of intensive care unit patients suffer also from BD, but this did not seem to increase overall mortality during the next month (Abrams et al. 2010a, b). The rate of BD in systemic lupus erythematosus is reported to be as high as 6 % (Bachen et al. 2009). The list of studies with specific rates is shown in Table 10.31.

10.3 Genetics and Endophenotypes

Comorbidity can be better understood and interpreted by using family studies (Wickramaratne and Weissman 1993), since the pattern of comorbidity seen in families gives important clues on the true relationship between clinical syndromes. In this frame, family studies suggest a genetic relationship between anxiety disorders and BD (Klein and Depue 1985; Dilsaver and White 1986). Some authors suggested that the genetic heterogeneity of BD is the cause of comorbidity with generalized anxiety (MacKinnon et al. 2003a, b) and panic attacks (MacKinnon et al. 1997, 2002; Doughty et al. 2004) and thus they are a core feature of some BD patients rather than comorbid conditions per se. Essentially this means that BD with panic attacks is more or less a separate disorder, since the two clinical pictures tend to appear together in the relatives of BD probands. In previous studies of the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Consortium, familial aggregation was described for panic disorder (MacKinnon et al. 1997, 2002), specific phobia and OCD (Potash et al. 2007), but these analyses did not control for different rates of diagnoses among sites or for additional comorbidity

Table 10.30 Rates of renal disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Any renal dis						
Fenn et al. (2005)	290			7 (2.4 %)		Inpatients mostly BD-I, cross-sectional
Fenn et al. (2005)	290			19 (6.6 %)		Inpatients mostly BD-I, lifetime
Kemp et al. (2013)	264			6 (2.3 %)		Lithium Treatment—Moderate-Dose Use Study (LiTMUS)
Laursen et al. (2011)	6,215	Gen pop	2,428,518	44 (0.7 %)	6,085 (0.3 %)	Population-based cohort study, cross-sectional
Lin et al. (2007)	2,289	Gen pop	16,413	72 (3.1 %)	76 (0.5 %)	All sample underwent appendectomy, cross-sectional
Renal failure						
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	58 (1.3 %)	58,109 (1.7 %)	VA national patient population, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	30 (0.8 %)	1,514 (0.2 %)	BD-I, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, cross-sectional

Gen pop general population

Table 10.31 Rates of various medical disorders in BD patients

Study	*N*	Control population	*N*	Prevalence in BD *N*(%)	Prevalence in control *N*%	Comments
Carney and Jones (2006)	3,557	In- and outpatients	726,262	1,453 (40.9)	145,431 (20.0)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, accidents and injuries, cross-sectional
Carney and Jones (2006)	3,557	In- and outpatients	726,262	21 (0.6 %)	1,058 (0.2 %)	BD-I pts, Wellmark Blue Cross/Blue Shield (BC/BS) of Iowa administrative claims data, pancreatitis viral/infectious, cross-sectional
Fenn et al. (2005)	290			26 (9.0 %)		Inpatients mostly BD-I, otolaryngologic disorders, cross-sectional
Fenn et al. (2005)	290			67 (23.1 %)		Inpatients mostly BD-I, otolaryngologic disorders, lifetime
Fenn et al. (2005)	290			2 (0.7 %)		Inpatients mostly BD-I, alcoholic pancreatitis, cross-sectional
Fenn et al. (2005)	290			5 (1.7 %)		Inpatients mostly BD-I, alcoholic pancreatitis, lifetime
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	514 (11.9 %)	0 (0.0 %)	VA national patient population, accidents/injuries, cross-sectional
Kilbourne et al. (2004)	4,310	VA national cohort	3,408,760	162 (3.8 %)	0 (0.0 %)	VA national patient population, pancreatitis, cross-sectional
McIntyre et al. (2006a)	938	Gen pop	35,848	17 (1.8 %)	1,685 (4.7 %)	Canadian Community Health Survey, cataract, lifetime

Gen pop general population

among the anxiety disorders. The data concerning specific phobia are equivocal (Goes et al. 2012). Familial panic attacks seem to increase the likelihood of rapid cycling (MacKinnon et al. 2003b), and this contributes to the possibility there is a separate cluster of patients. Even a genetic link has been proposed (Logue et al. 2009). A similar proposal has been put forwards for anxiety comorbidity in general (Wozniak et al. 2002).

The distribution of trait anxiety scores in the family members and controls based on their genetic proximity to affected individuals, and diagnostic status suggests that trait anxiety could be an endophenotype in these BD-I families (Contreras et al. 2010). In high-risk offspring of BP parents, anxiety syndromes typically precede the onset of mood syndromes (Duffy et al. 2007; Sala et al. 2010) and often persist throughout adulthood (Mantere et al. 2010). Overall the data are still inconclusive on the true relationship of anxiety and BD (Doughty et al. 2004).

There are studies which suggest that there is a strong connection between ADHD and BD and the comorbid condition runs in families, with over 20 % of offspring or BD parents manifesting ADHD. These particular studies included BD patients with a more severe form of the disorder and high comorbidity, and therefore their conclusions might not be generalizable (Chang et al. 2000; Singh et al. 2007; Hirshfeld-Becker et al. 2006; Henin et al. 2005; Birmaher et al. 2009, 2010; Faraone et al. 1997, 2001). If a familial aggregation is accepted, this points towards a developmental neurobiological association between ADHD and BD, going beyond symptomatic similarities (Skirrow et al. 2012). On the other hand, the careful review of all available data across different domains of research suggests that most findings are equivocal concerning the true nature of this comorbidity and this is also reflected in systematic reviews on this issue (Wingo and Ghaemi 2007; Duffy 2012; Skirrow et al. 2012).

Both patients with unipolar depression and with BD, when they have family history of BD, are reported to be at a three- to fourfold higher risk to suffer also from migraine. This might not be the case concerning a family history of unipolar depression (Dilsaver et al. 2009). Epilepsy seems also to aggregate with psychosis in families (Clarke et al. 2012).

It is of extreme interest that antithyroid antibodies seem to manifest a familial aggregation with BD. One study reported that the TPO-Abs were positive in 27 % of the bipolar index twins, 29 % of the monozygotic bipolar co-twins, 27 % of the monozygotic non-bipolar co-twins, 25 % of the dizygotic bipolar co-twins, 17 % of the dizygotic non-bipolar co-twins and 16 % of the control twins. These findings might suggest that a form of autoimmune thyroiditis might be related to BD but more important to the genetic vulnerability to develop the disorder, thus constituting a potential biomarker and endophenotype (Vonk et al. 2007).

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