Clinical Description

2

2.1 Normal Emotions, Neurobiology and Ethological Considerations

Modern approach distinguishes between 'mood' which is the long-lasting internal emotional tone and largely characteristic of the individual; 'affect' which is the general emotional status during the last few days or weeks, and it is observable through the individual's behaviour; and 'emotion' which corresponds to the transient emotional state which also manifests itself through motor behaviours (face mimics, body movements, complex behaviours, etc.). Mood has an enduring nature, tends to be unfocused and diffused, involves expectation of the future and is manifested in subtle ways, while, in contrast, emotions tend to be short lived and to have a clear focus.

In terms of etymology, the word 'mood' comes from Proto-Germanic 'modaz' and is related to the old high German 'muot' (in German: Mut) and the old Saxon mod (in Dutch: moed). Similar words exist in Scandinavian languages, and they mean 'anger' and 'emotion'. The ancient Greek word μῶθαι (mothai) and the Latin *mos* (=mores) come from the same Indo-European root. The word 'affect' comes from the middle French word 'affecter' which in turn derived from the Latin *afficere* (*ad*+ *facere* which means 'to act upon', 'influence', 'attack with disease'). It seems that it had entered the English language in the fourteenth century and it is first recorded in Geoffrey Chaucer's 'Troilus and Cressida'. 'Emotion' comes from the French word 'émouvoir' which is based on the Latin *emovere* (e-movere means 'without move'). Thus, the original meanings of these terms relate to anger and to the tendency to act or remain still. It is interesting that one of the etymological approaches to the word 'mania' suggests it comes from the Greek word μένω which means 'remain still' (also see Chap. 1).

Aristotle's concept of affect is 'that which leads one's condition to become so transformed that his judgment is affected, and which is accompanied by pleasure and pain' (Aristotle, 'Rhetoric' 6). While he was the first to elaborate on human affective states and various terms can be found in his works, in Greek the word for

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mood is διάθεση (diathesi=disposition, tendency, availability), for affect is συναίσθημα (synaesthima= complex or combined feelings, sentiment) and for emotion is αίσθημα (aesthima=feeling)

Affects and emotions serve two main aims. The first concerns the internal functioning of the individual and provides the individual with fast decisions which serve the survival of the individual but also of the species. Some of these decisions are easy to understand (e.g. fear of animals), but others are incomprehensible in principal (aesthetics and attraction to the opposite sex). In the same frame, emotions provide feedback concerning the behaviour of the individual, and in this way they enhance the expression of the specific behaviour or preclude its future manifestations. For example, sadness constitutes the emotional response to loss, defeat, disappointment or other adversities. Its adaptive function includes permitting withdrawal to conserve resources, asking for support from significant others and the autonomic arousal which might be present facilitates the search for the lost object or an appropriate substitute.

The second aim is to communicate the internal emotional state of the individual to others, and this is achieved with facial expressions, gestures, bodily moves and posture and voice verbal and nonverbal elements. These ways of communicating emotions vary between cultures, but most of the repertoire is universal for human beings. They constitute a main source for the interaction with others, since the emotions of an individual influence the emotions, thoughts and behaviours of others, produce positive or negative feedback and give birth to circles of future interactions and reciprocal influence.

The feelings of one individual evoke feelings in the others by 'emotion contagion' (i.e. others tend to automatically and unconsciously mimic behaviours) and 'emotion interpretation' (i.e. others perceive the individual's emotions and react with complementary or any kind of appropriate emotions). It is interesting that positive affect promotes social interaction and activity and is related to high functional support. How and why this happens is unknown, but it is likely to be mediated through the induction of positive feelings and pleasant emotional states to others.

In the early 1970s, Paul Ekman (Ekman and Friesen 1971) classified emotions into the basic: anger, disgust, fear, happiness, sadness and surprise, and the in the early 1980s Robert Plutchik (1927–2006) (Plutchik 2002) developed the 'wheel (or cone) of emotions' (Fig. 2.1), by proposing the existence of four bipols with eight emotions (joy vs. sadness, anger vs. fear, trust vs. distrust and surprise vs. anticipation) corresponding to situations of promoting or rejecting behaviour, fight or flight, social interaction and expectation. Combinations of these basic emotions might produce other feelings human beings experience. Plutchik suggested that basic emotions relate in specific ways and the existence of one modifies the possibility for the coexistence of another. However, it has not been proven that the existence of one pole precludes the existence of another (e.g. that anger and fear cannot coexist). It still remains controversial whether affective (or emotional) states should include emotional experiences related to bodily functions (e.g. hunger, sex, etc.).

The first modern neurobiological theory of emotions was independently developed in the 1880s by William James (1842–1910) and Carl Lange (1834–1900).

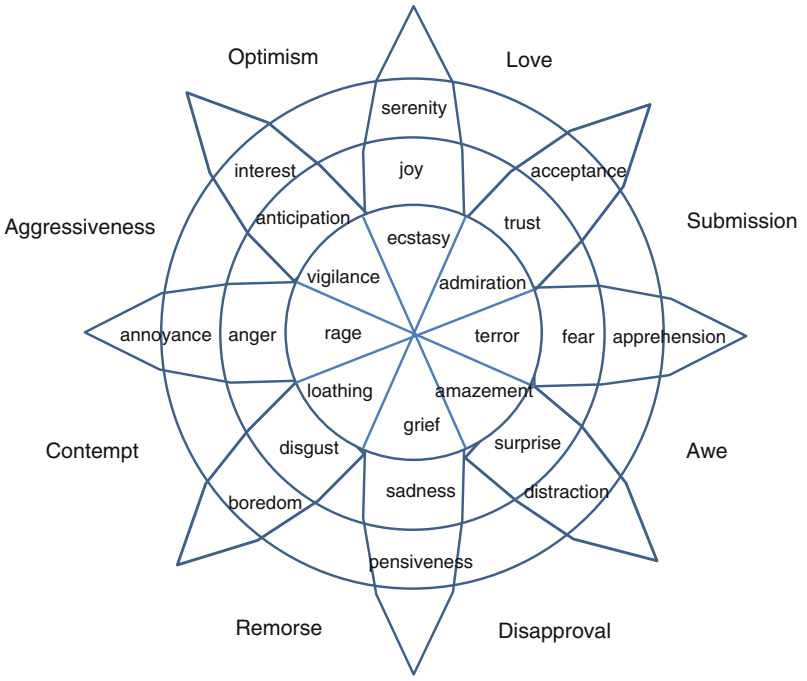

Fig. 2.1 The 'wheel (cone) of emotions' according to Robert Plutchik

That theory proposed that emotions are the result of changes in the physiology of the body caused by a stimulus and not the result of the stimulus directly.

A modern approach to the issue goes through a basic approach to brain function which could suggest that there are two distinct mental processes: logical thinking and emotions. While emotions are present also in animals, logical thinking is present primarily in humans, while some elements are also evident in the behaviour of primates.

Traditionally, the left hemisphere is considered to be the site of logical thinking, while the right hemisphere serves the creation of emotions. Although this assumption is supported by some neuropsychological data, especially in neurosurgical patients and head injury, it is almost certain that complete and opposite lateralization of logic and emotions does not exist. A consequence of the above assumption is that the dysfunctions leading to schizophrenia are supposed to be localized in the left hemisphere, while those leading to depression are localized in the right.

A very simplified neurobiological model may propose that 'mood' derives probably from processes largely taking part in the amygdala and the insula, while 'emotion' is generated mainly in the anterior cingulate cortex (ACC) and more specifically in area 25. However, its effortful regulation is likely to implicate area 24 and the dorsolateral prefrontal cortex (DLPFC). In the middle between 'mood' and 'emotion' lies the 'affect' which is at least partially generated in the ACC and partially in other brain areas including the prefrontal cortex (PFC) (Phillips et al. 2003).

Emotional processes are evolutionary older and are characterized by speed and dominance. They lead to fast decision-making, on the basis of predetermined strong assumptions concerning the gross characteristics of the situation. For example, fear is triggered immediately and almost before conscious recognition of the stimuli, and it leads to the fast manifestation of adaptive behaviour (fight or flight). A snake will always trigger fear, no matter whether it is poisonous or not. On the contrary, logical thinking is slow, requires the conscious elaboration on the stimuli, demands concentration and effort and is not as strong as emotion concerning the effect on behaviour. Emotion is biased towards the triggering of those behaviours that serve the survival of the individual and the species, while logical thinking aims towards an 'objective' assessment of the situation. In the language of artificial intelligence, the closest description which can be made today is that of a 'fuzzy' vs. 'digital' systems.

The database of assumptions emotions use is of unknown origin, probably partially inherited and partially acquired through experience, and possibly it is characteristic of the species. Logical thinking is based mainly on training. Decisions based on emotions are stronger than those based on logical thinking, and when they collide, the person faces a difficult dilemma, since it is very difficult for logical thinking to override emotional pressure.

The two processes, although independent in principle, interact and influence each other. The emotional status causes bias in logical thinking, and logical analysis triggers emotions depending on the positive or negative outcome. This interaction is likely to happen at multiple levels (e.g. selective memory recall, reinforcement through new analysis, biased selection of possible solutions, etc.).

Normal mental functioning includes low emotional condition, called 'grief' in response to significant separations and losses (e.g. death, divorce, romantic disappointment, bereavement, various catastrophes), and high emotional condition called 'elation' in response to significant positive events (e.g. success and achievement). Sometimes it is neither uncommon nor abnormal for the individual to manifest a paradoxical reaction, which is low emotion as response to positive events or high emotion as response to negative events. These paradoxical emotional experiences are usually the result of hidden threats in the positive events or stem out of complex dynamic intrapsychic processes aiming to protect the person from experiencing grief.

As previously mentioned, according to current ethological theories, the expression of emotions through physical behaviour communicates to others information concerning the individual's emotional state, and this is considered to be one of the most important elements in social behaviour and interaction with others.

Interest in emotions from an evolutionary perspective was triggered by the publication of the book *The Expression of the Emotions in Man and Animals* by Charles Darwin (1809–1882) in 1872. In that book, Darwin stresses the universal nature of emotions and the connection of mental states to the neurological organization of movement. Central to his understanding was a shared human and animal ancestry in sharp contrast to the contemporary claims that there were divinely created human muscles to express uniquely human feelings. Darwin's original suggestion was that

emotions evolved via natural selection and therefore have cross-culturally universal counterparts, a proposal confirmed almost a century later by the works of Paul Ekman. Furthermore, animals undergo emotions comparable to those of humans.

2.2 The Conceptualization of Bipolar Disorder

Normal affects and emotions are characterized by their correspondence in terms of intensity and duration to the respected stimuli which had triggered them. Intensity depends on the significance of the stimuli and the threat they constitute for the person, while duration is related to the duration of exposure plus some time the individual needs to regain internal homeostasis. However, eventually, affects and emotions disappear (after the stimulus disappears first), and the individual returns to its normal steady affective state. However, in contrast, pathological affects are characterized by intensity which is disproportional (higher or lower) to the triggering stimuli, inappropriate duration (too short or prolonged) and possibly problematic nature (emotions are inappropriate, alternate or coexist). The 'quality' is often similar between 'normal' and 'pathological' affects and emotions, and only in the more severe cases pathological affect obtains a 'difference in quality' which is often difficult to describe accurately and possibly reflects a collapse in the ways affects and emotions are behaviourally expressed. It is also possible that this difference in 'quality' merely reflects the impact of more severe pathological affect on other mental processes including insight, judgment and overall functioning. Another abnormal element which suggests a 'qualitative' difference is that pathological affects and emotions, especially when very severe, might be independent of environmental events, either positive or negative, congruent or incongruent to the affective state of the person. Although the term 'endogenous' is often used to denote that the mood episode is occurring in the absence of precipitants, many authors prefer the term 'endoreactive' which denotes that once the episode is triggered, it tends to persist in an autonomous way. The homeostatic dyscontrol of mood, which is part of a more pervasive mood dysregulation, resists reversal to the habitual baseline affective tone.

Normal mood permits the normal function of affective and emotional processes in response to environmental cues. Grief or elation rarely leads to depression or mania, with maybe the exception of major catastrophes and very traumatic events. However, bereaved persons exhibit many depressive-like symptoms during the first 1–2 years after their loss, but only 5 % of them progress to clinical depression. Severity of grief might be predictive of future depression especially if features like marked psychomotor retardation and thoughts of guilt of commission are present. Grief might constitute a severe medical condition, and it is not uncommon for elderly people to die within a few months of the death of their spouse.

However, pathological mood disrupts these functions and has a pervasive impact on the individual. The result of pathological mood is pathological affect and emotions which characterize a group of mental disorders under the collective label of 'mood disorders'. It is indeed problematic that until today there are no

pathophysiological methods identified and no biochemical laboratory tests developed to assist the diagnosis and to distinguish 'normal' from 'abnormal' mood and affect. Because of this failure, the diagnostic decision is based on intensity, severity and maybe the presence of some 'qualitative' differences. Of course the words 'intensity', 'severity' and 'quality' have intrinsically problematic definitions when it comes to behaviour and internal experience. This is a major drawback concerning the adoption of the biomedical model vs. the psychosocial model. The former has always been dominant in Europe, while the second was dominant in the USA for most of the twentieth century. Another problematic area was the adoption of a categorical diagnostic model vs. a dimensional model. It is interesting that while Emil Kraepelin strongly endorsed the categorical distinction between schizophrenia and manic–depressive illness, Eugen Bleuler, on the contrary, suggested that both illnesses lie on a continuum with no sharp line of demarcation. According to Bleuler, a patient could be conceptualized as being predominantly schizophrenic or predominantly manic–depressive, and additionally, his position on the continuum between the two illnesses was not considered to be stable but ever changing during the course of the illness. Currently, the categorical model, which is closer to the mentality of the biomedical model and more 'user-friendly' for the average clinician, is utilized in most clinical and research approaches. In the past the term 'affective' disorders was used, but today the term 'mood' disorders is preferred, and this is because it refers to more enduring and deeply rooted emotional states.

The World Health Organization's tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) includes such a chapter; however, the American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes a separate chapter for bipolar disorders and a separate for unipolar depressions. In details the classification systems (American Psychiatric Association 2013; WHO 1992) are described in Chap. 12 of the current book. Both systems include a number of personality disorder diagnostic categories with strong emotional components. Also they both include 'not-otherwise-specified' categories.

The core concept for the diagnosis of these disorders is the polarity, intensity, duration and frequency of change of affects and their correspondence and appropriateness, relation and autonomicity with respect to stimuli. In terms of polarity, (hypo)manic and dysthymic/depressive states denote the presence of high or low affect, respectively. Both classification systems consider that BD consists of at least one manic or mixed episode and a depressive episode. DSM distinguishes two types of the presence of manic (BD-I) or hypomanic (BD-II) episodes. However, apart from these hallmarks of clinical picture, BD is a highly complex disorder with many facets, aspects and special issues in its clinical picture (Table 2.1).

It is both interesting and important to look at the literature which predates the psychopharmacology era, that is, the nineteenth century and the first half of the twentieth century. This literature is important not only because patients were experiencing the 'natural' course of the illness without the 'contamination' of psychopharmacotherapy but also because at that time, nosological categories had not been identified and distinguished yet and authors were describing the clinical picture with less

Table 2.1 List of the multiple clinical aspects of manic–depressive illness

1. Manic episodes
2. Depressive episodes
3. Mixed episodes
4. Subthreshold manic symptoms
5. Subthreshold depressive symptoms
6. 'Mixed' states and 'roughening'
7. Mood lability/cyclothymia/'personality-like' behaviour
8. Predominant polarity
9. Frequency of episodes/rapid cycling
10. Psychotic features
11. Neurocognitive disorder
12. Functional deficit and disability
13. Drug/alcohol abuse
14. Comorbid anxiety and other mental disorders
15. Self-destructive behaviour and suicidality

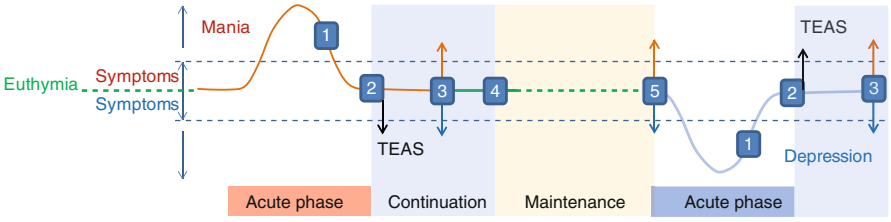

Fig. 2.2 Graphic representation of the alteration of types of mood episodes and the course of bipolar disorder. *1* Response, *2* remission, *3* relapse, *4* recovery, *5* recurrence. *TEAS* treatment emergent affective switch

channelling and top-down bias. On the other hand, one should bear in mind that in these times, physicians were confronting with the most severe group of patients, and their observations were based mainly on chronic institutionalized patients, often distorted by personal issues and philosophical and often religious and political influences.

Unfortunately, more than a century after the first modern nosology was formulated, the boundaries between personality, temperament, grief and mood disorder, mood-congruent and mood-incongruent psychotic features and, even worse, the schizophrenic group of disorders and mood disorders remain unresolved.

The definition of bipolar disorder (BD, previously called manic–depressive psychosis) as conceptualized by Emil Kraepelin a century ago suggests that this disorder is characterized by the presence and alteration of manic and depressive episodes (mixed episodes are usually considered to be a variation of manic) with a return to premorbid level of functioning between the episodes and a favourable outcome in comparison to schizophrenia (Kraepelin 1921). A graphic chart of this prototypical concept is shown in Fig. 2.2. Today we know that this is not always the case (Tohen

et al. 1990). The Kraepelinian concept largely corresponds to BD type I (BD-I) according to DSM-5 (American Psychiatric Association 2013). Another type, BD-II, is officially recognized as a bipolar illness subtype, and it is characterized by the presence of hypomanic instead of manic episodes. It was first proposed as a subtype by the group of Fred Goodwin at the NIMH (Dunner et al. 1976). However, it is important to note that according to DSM-5 hypomania is defined mainly in terms of a shorter duration and lower severity of the episode. BD-II is more prevalent than BD-I. Today we also know that the categorical distinction between manic and depressive episodes in the frame of BD is not as clear as previously thought, since 94 % of acutely manic or hypomanic patients and 70 % of depressed patients also manifest symptoms of the opposite pole at a clinically significant level. Even more important is the observation that these symptoms correlate positively and not inversely to each other (Bauer et al. 2005). In this frame, it seems more important to focus on the coexistence of the two poles, the transitional phases between them as well as their fluctuating nature rather than to insist on the description and treatment of the rigid 'classical' and pure clinical pictures of either pole.

The first mood episode typically begins in late adolescence, the 20s or the 30s and could be manic, depressive or mixed. Its onset could be acute or insidious and arise from a low-grade, intermittent and protracted mood substrate which could resemble a dysthymic or cyclothymic state or even personality features (Fogel et al. 2006). These mood states could also prevail during the inter-episode period and might give rise to low quality of life, interpersonal conflicts and significant global disability. Also, these subthreshold disorders are quite frequent in the families of patients (Shankman et al. 2008). On the other hand, the first episodes with severe psychotic symptoms in the frame of mania are not rare and many times resemble schizophreniform episodes. Frequently the correct diagnosis is put after several years because the first episode is psychotic like or depressive, and the diagnosis is put only after a manic or mixed episode emerges. It has been estimated that more than half of patients originally manifesting a depressive episode will turn out to be bipolars in the next 20 years (Angst et al. 2005). Also, it seems that patients spend more time during depressive episodes than manic ones (Mitchell and Malhi 2004). More, subsyndromal depressive symptoms are usually present during the interepisode period (Judd et al. 2002). An additional problem for the diagnosis is that patients usually experience hypomania as a recovery from depression and almost always as a pleasant ego-syntonic mood state, and they, as well as their families, often fail to report these hypomanic episodes and tend to consider them as normothymic recovery periods. This has profound implications concerning the treatment and its overall efficacy. On average, manic episodes predominate in youth, and depressive episodes predominate in later years. Although the overall sex ratio is approximately 1:1, men, on average, undergo more manic episodes, and women experience more mixed and depressive episodes.

The term 'rapid cycling' refers to patients suffering from at least four mood episodes in a year. It seems that females are more often rapid cyclers as well as higher social class subjects. In essence, these patients tend to be symptomatic most of their life and are considered to be refractory to lithium. The diagnosis might elude for

prolonged periods of time and the patients can receive the diagnosis of a personality disorder or cyclothymia. Their treatment is based on a complex, delicate and difficult to design multiple pharmacotherapy which includes atypical antipsychotics, anticonvulsants and even antidepressants, although the latter are believed to induce rapid cycling (Bauer et al. 1994a).

It is of outmost importance for both clinicians and researchers to create a biographical chart with the patient's course over time. This was first introduced by Kraepelin who used colours to mark the polarity of episodes and was further developed by Robert Post at the NIMH. This biographical chart should include any important event in the developmental history of the patient, the main events and hallmarks of his/her life and his full psychiatric and medical history. The use of such charts is of great importance not only for mood patients but for all psychiatric patients, since it clarifies both the diagnosis and the course of the disease and response to therapeutic interventions.

2.3 Bipolar Depression

Depressive episodes are considered to be a diagnostic pillar of BD. However, in contrast to manic episodes which lead to the diagnosis of BD immediately, depressive episodes pose a dilemma to the clinician whether he faces a unipolar depression of a BD. This is an important dilemma to solve since the treatment is different between these disorders.

The data suggest that more often the first episode of BD is depressive, especially in females (Angst et al. 2005; Perlis et al. 2005). In 15 % of patients, depressive episodes appear abruptly (Winokur et al. 1969) and are characterized by a constellation of symptoms and signs, with depressed mood and anhedonia being the most characteristic. As mentioned above, depressed mood is the pathological equivalent of grief and mourning and is characterized by a painful negative emotion, which is typically experienced as worse than severe physical pain. This experience is out of proportion and out of frame of existing stimuli and is characterized by groundless apprehensions with severe inner turmoil and torment. The suffering is persistent although in milder cases spontaneous fluctuation even during the same day can occur (typically in the morning or in the afternoon). It is paradoxical that although depressed patients experience a hypervigilant state with heightened perception of pain, many also experience an inability to experience emotions, and they are even unable to cry. Previous opinions that anxiety and hypervigilance and anhedonia are more or less mutually exclusive were not confirmed by empirical research which showed higher levels of anxiety in those patients with more severe form of depression and melancholia (Regier et al. 1998). Anhedonia does not simply mean the patient has lost the sense of pleasure. It also means that has abandoned previously enjoyed pastimes. In milder cases, anhedonia manifests itself by decreased interest in hobbies and life, but in most severe cases it leads the patient to lose feelings for loved significant ones (kids, spouse) and to be cut off from other people and the world in general. Patients typically describe their environment as without any

colours, as if everything is black and with shades of grey. This is a quite odd experience which alienates patients from others and from the environment. Depersonalization and derealization might follow and often the experience has a psychotic-like quality, with impairment of the patient's judgment. This lack of feeling emotions in severely depressed patients is itself painful, and in this way it differs from flat affect experienced by patients with schizophrenia and constricted affect experienced by obsessive–convulsive patients. It is important to note that often the interviewer cannot assess the depth and the severity of depression on the basis of its outward expression. Often tears are present on a motionless face, and the patient seems calm and indifferent, where in other instances a smile, expression of sardonic humour or even elements of joy might accompany the verbal expression of self-accusation or self-derogatory thoughts. In the majority of patients (64–72 %), there is significant diurnal variation of mood (Casper et al. 1985; Winokur et al. 1969).

Two-thirds of bipolar depressed patients present with multiple physical pains and complains (e.g. headache, epigastric pain, precordial distress, etc.) in the absence of any physical illness (Winokur et al. 1969) especially in primary care. These patients also might deny the experience of depressed mood. These conditions have been described as masked depression, but current classification systems do not recognize such a syndrome, mostly because lack of depressive mood is not complete and there is significant overlap with undiagnosed or difficult to diagnose medical conditions.

Irritability is pervasive in BD patients and is manifested by almost 75 % of them (Winokur et al. 1969). The picture includes also psychomotor disorder with the form of either agitation or retardation. These terms correspond to changes in the motor expression of mental and emotional activity. Agitation is easily observed since it includes commission of behaviours (increased speech, restlessness, increased gesturing, hand wringing, nail biting, hair pulling, etc.). On the contrary psychomotor retardation is characterized by the lowing of psychomotor activity and lack of spontaneous behaviours which are usually included in the usual 'every minute' activity of the individual (e.g. lack of the usual body posture, visual exploration of the environment or usual gestures during speech, etc.). Thus, patients with psychomotor retardation manifest a slumped posture, downcast gaze, fatigue, poor concentration and effortful thinking and indecisiveness. Additionally, they don't speak much and often discussion and interview is difficult. Sometimes psychomotor slowing is so extreme that in elderly patients gives the impression of organic confusion or dementia-like syndrome, while in younger patients it might evolve into a stupor with patients being unable to participate even in basic everyday functions, such as feeding themselves or going to the toilet.

Activity and behaviour become slower during periods of depression. Patients move and walk slowly and react sluggishly, their movements are restricted to the absolutely necessary ones, the whole body and especially the face lack muscle tone and vitality, and the eyes are dull and reflect the inner retardation, often with a far-away unnatural stare. Fatigue and psychomotor retardation dominate the clinical picture in 75 % of patients (Carlson and Strober 1978; Winokur et al. 1969). It is important to note that in most patients features of both agitation and retardation seem to coexist. In gross clinical observation, retardation rather than agitation is

more characteristic for depression, and the presence of overt agitation poses a question of diagnosis, whether the episode is in fact mixed. Some authors suggest that retardation constitutes the core problem in depression since mental slowness leads to inertia and makes the patients unable to act physically and mentally. They also suggest psychomotor retardation is the main cause for the high disability related to depression.

Although depression is characterized by depressed mood, an important feature in its psychopathology is depressive thought content. Thought disorder is also called 'cognitive disorder', and this term should be distinguished from 'neurocognitive disorder' which refers to disorders of concentration, memory, executive function, etc. (this distinction is not mandatory, however, and many authors use both terms in a confusing way). The fundamental depressive thoughts are negative evaluations of the self, the world and the future (the negative triad) which according to cognitive theory are central to the aetiopathogenesis of depression. However, it is equally likely that the depressed mood biases thought process towards a negativistic way of thinking. To the author's opinion, our neurobiological and ethological understanding of emotion and logical thinking does not support the possibility that negative thoughts induce depressed affect in such a pervasive and enduring way. It is more reasonable to consider the cognitive disorder as being part of the psychopathological manifestations of depression.

The essential characteristic of depressive thinking is that the patient views everything in an extremely negative light. In line with Kurt Schneider's theory on humankind's four basic insecurities (health, financial status, moral worth and relationship to others), thought disorder includes, among others, ideas of deprivation and loss; low self-esteem and self-confidence; ideas of poverty and disaster; self-reproach and pathological guilt; helplessness, hopelessness and pessimism; hypochondriacal thoughts; and recurrent thoughts of death and suicide. It is as if the patients are actively looking for the negative and unpleasant aspect in everything. These negative thoughts are typically unjustified or are blown out of proportion and sometimes could be truly delusional. Sometimes extreme impairment because of psychomotor retardation might trigger thoughts of low self-esteem which although seem exaggerated and almost delusional, in fact they accurately reflect the perception the patient has concerning his disability.

When depressive thoughts acquire delusional proportions, then delusions of worthlessness and sinfulness, reference, infidelity and persecution appear (often in the form of prosecutor). Delusions are present in 12–66 % of bipolar depressed patients (Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969). Other delusions include delusions of poverty, disaster and ill health (suffering from an occult illness, like cancer or AIDS). A special form is nihilistic delusions, which include thoughts that parts of the body are missing, also known as Cotard's syndrome after Jules Cotard (1840–1889) who described it for the first time in 1880. Under the influence of delusional depression, not only suicide but also homicide can occur, usually with an 'altruistic' motive. For example, under delusions of poverty, disaster or moral decay, a father might kill his children in order to 'save' and 'protect' them and afterwards commits suicide. Another

not unusual scenario is infanticide by mothers with psychotic depression during the postpartum period.

The above-mentioned delusions are mood-congruent, that is, they are in line with the depressed mood. However, mood-incongruent delusions can be also present (e.g. persecutory delusions which cannot be considered in the frame of the depressed mood); however, if bizarre delusions are present, then the diagnosis of schizoaffective disorder should be considered.

Psychotic symptoms during bipolar depressive episodes include also hallucinations, most often auditory. They are less frequent (8–50 %) in comparison to acute mania (Baethge et al. 2005; Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969). Typically they are extremely unpleasant, and their content is in accord with depressed mood and delusional ideation. They can be mood-congruent (e.g. accusatory or derogatory) or mood-incongruent (e.g. two voices discussing without any reference to the patient). It has been reported that depressed patients with psychotic symptoms are more often turned to be bipolars than those without (Akiskal et al. 1983). Also, it is believed that psychotic features constitute a stable trait which tends to repeat itself across episodes, although the studies suggesting this use a mixture of bipolar and unipolar patients and generalizability is problematic (Helms and Smith 1983; Nelson et al. 1984; Aronson et al. 1988a, b).

Overall, psychotic symptoms are more frequent in bipolar in comparison to unipolar depression (Goes et al. 2007).

Suicide is the worst outcome of depression. Often suicidal thoughts are present during the whole course of the disease. Attempts may happen, but the majority of patients do not commit suicide in spite of the continuous presence of suicidal ideation. It seems that the risk of suicide is less pronounced during acute severe depression, and traditionally, the suggestion made by Emil Kraepelin that when psychomotor activity starts improving, but still mood and thinking are still severely depressive, at that particular period the patient has the combination of ideation and energy to commit the suicide. This often happens in an unpredictable impulsive way. According to Aaron Beck hopelessness is the specific symptom that should alert the clinician concerning high suicidal risk. Empirical research rejected the hypothesis that inquiring about suicide provokes it. On the contrary, patients are often relieved that the physician appreciates the magnitude of their suffering. Suicidal ideation is commonly expressed indirectly (e.g. in a wish not to wake up or to die from a malignant disease), while it is not unusual the patients to conceal their suicidal ideation behind a joyful behaviour. Some depressed persons are tormented with suicidal obsessions and are constantly resisting unwanted urges or impulses to destroy themselves. Others might yield to such urges passively (e.g. by careless driving or by walking into high-speed traffic). A third group harbours elaborate plans, carefully preparing a will and taking out insurance. Deliberate planning indicates a high suicidal risk.

Since antiquity, depression was linked to the disturbance of a number of somatic functions including appetite, circadian rhythms, sleep and sex. Typically depression is related to a reduction in the quantity of these functions (insomnia, loss of appetite

and weight, loss of libido); however, there is a subgroup of patients experiencing an increase (overeating, oversleeping and maybe increase of sexual activity). This latter group is also characterized by higher anxiety, personality psychopathology, mood reactivity, fatigue and long-term sensitivity to rejection. It is interesting that this latter symptom is then only one in DSM-5 Axis I which resembles more the personality disorder criteria of Axis II rather than the criteria of mood disorders.

Depending on the study sample composition, changes in appetite for food are seen in almost all patients (Winokur et al. 1969), with one-fourth manifesting overeating and one-fourth losing significant weight (Casper et al. 1985). Women are especially vulnerable to manifest these symptoms and signs (Kawa et al. 2005). Anorexia and weight loss could be a core independent symptom of depression, but it can also be secondary to blunted olfactory or taste sensations or a decreased enjoyment of food. Anorexia should be distinguished from avoidance of food, for example, because of a delusional belief that it is poisoned. Especially in elderly persons, it can lead to malnutrition and electrolyte disturbances which both represent medical emergencies. On the contrary, overeating especially in combination might result in weight gain which in turn increases the burden of overall morbidity and mortality especially in middle-aged patients, especially if diabetes mellitus, hypertension or coronary artery disease coexists.

Sleep disturbance constitutes a cardinal (although non-specific) sign of depression. Almost all bipolar depressed patients experience some kind of sleep problem (Winokur et al. 1969; Casper et al. 1985). It has been described as abnormally deep or abnormally light. It includes difficulty to fall asleep, multiple awakenings during the night and especially in the early hours of the morning and often early morning awakening. Not only quantity but also quality of sleep seems to be disordered with deep stages of sleep (III and IV) being decreased or deficient. In this frame, some patients try to self-medicate them with alcohol or sedative–hypnotic medication, which may initially succeed but ultimately aggravates the sleep patterns and insomnia because in the long term they further diminish stage III and stage IV sleep. Dreams are typically vivid, restless and anxious. On the contrary, a subgroup of bipolar depressed patients (up to 25 %) often exhibit excessive sleep and have difficulty getting up in the morning (Winokur et al. 1969). Often these patients are failed to be diagnosed properly, and it is supposed to be ‘laziness’ or ‘character disorder’.

Decreased sexual desire is seen in more than 75 % of patients (Casper et al. 1985; Winokur et al. 1969) and concerns both sexes. Some women experience temporary interruption of their menses while male experience erectile dysfunction. Both conditions might lead the patient to seek expert opinion from endocrinologists, urologists or gynaecologists. Disruption of sexual life might cause marital problems especially when the patient is female. In turn, marital problems fuel depression, and many therapists focus on the problems within the couple’s relationship rather than the causal element which is depression. Especially sexual dysfunction and the resulting marital problems might delay the correct assessment of the problem and the appropriate therapy. Especially problematic is that most of antidepressant agents might worsen the problem, while the use of agents like sildenafil is not always

successful. It is not common for depressed patients to manifest hypersexuality. In these cases the presence of a mixed episode should be considered.

Until now there were a lot of efforts to describe and classify depressive symptomatology in detail. Essentially these efforts do not distinguish between unipolar and bipolar depression. The core concept in almost all classifications was the psychological vs. biological aetiopathogenesis and concern depression as a syndrome without distinguishing between unipolar and bipolar. Kraepelin believed that the two types (psychological and biological) were naturally divided (Kraepelin and Johnstone 2010), and in 1896, he accepted the aetiological classification of 'exogenous' and 'endogenous' diseases by Paul Julius Möbius (1853–1907). This was in part the source of the nature/nurture split in the conceptualization of psychiatric disorders and led to an unfortunate link between phenomenology and aetiology bypassing the syndrome notion of Thomas Sydenham (1624–1689). Gillespie (Gillespie 1926) further contributed to the confusion between phenomenology and aetiology since the main difference of the depressive types he proposed was reactivity of mood. On the contrary, Aubrey Julian Lewis (1900–1975) suggested in 1934 that reactive and endogenous depressions could not be separated. A more pragmatic approach is reflected in the thoughts of Raymond Bernard Cattell (1905–1998) (Cattell 1943) who strongly supported the separation of nosology from aetiology.

Kraepelin described 'melancholia gravis' as a more severe form of depression with psychotic features. He also proposed the term 'fantastic melancholia' for even more severe forms with more pronounced psychotic symptoms, alternation of agitation with stupor and clouding of consciousness. According to Kraepelin the most severe form of depression is 'delirious melancholia' with very severe and almost 'schizophrenic-like' delusions and hallucinations. In these cases, clouding of consciousness dominates the clinical picture (Kraepelin 1921).

Most classification systems include a subtype who is melancholic like under several different names, like 'endogenous depression' (Roth 1959), 'vital depression' (Van Praag et al. 1965), 'retarded depression' (Overall et al. 1966), etc. Diagnostic operationalizations of the melancholic (endogenous) concept are found in all DSM editions after the third one, in the ICD-10, the Research Diagnostic Criteria (Spitzer et al. 1978), the World Health Organization Depression Scale (Bech et al. 1980) and the Newcastle Scales (Carney et al. 1965; Roth et al. 1983). The most usual profile all these systems describe for melancholic patients is a constellation of symptoms which includes psychomotor retardation, late insomnia, early morning worsening, weight loss, psychomotor agitation and guilt. The most frequently specified non-symptom clinical feature is normal personality. Several reviews of the literature have been published on this matter (Davidson et al. 1984; Mendels and Cochrane 1968; Nelson and Charney 1981; Parker et al. 1989; Rush and Weissenburger 1994).

Most classification efforts also include a pole opposite to the 'endogenous/melancholic'. This pole has received various names like 'reactive' or 'neurotic'; however, the most recent label given was that of 'atypical depression' and has been the focus of research during the last few decades, but it was not recognized by official classification systems until DSM-IV (American Psychiatric Association 2000).

Originally, this category has been proposed to describe depressed patients who respond poorly to tricyclics (TCAs) and well to monoamine oxidase inhibitors (MAOIs) (West and Dally 1959; Dally and Rohde 1961; Liebowitz et al. 1988); however, subsequent research suggested that these patients are refractory to all classes of antidepressants. It is not yet clear how best to define the subtype (Davidson et al. 1982; Thase 2007; Fountoulakis et al. 1999), and very little are known concerning its reliability, prevalence, relationship to other subtypes of depression and the performance characteristics of various possible defining items (Rabkin et al. 1996). The Columbia definition (Liebowitz et al. 1984) has been the most advanced and the predecessor of the DSM definition. These patients generally have laboratory testing similar to control subjects.

The terms 'endogenous depression', 'neurotic depression', 'anxious depression', 'involutional melancholia' and 'psychotic depressive reaction' are not included in modern classification systems for a variety of reasons. The term 'neurasthenia' is maintained in ICD-10, but its meaning is vague.

A term used in the past to denote this particular group of patients was 'hysteroid dysphoria' which combined reverse vegetative signs (overeating and oversleeping) with giddy behaviour in romantic affairs and intensive dysphoria with anxiety, anger and suicidality as a response to romantic disappointment. Craving for chocolate and sweets as well as impaired anticipatory pleasure but preserved consummatory reward have been also described in these patients. Anticipatory pleasure is more closely linked to motivation and goal-directed behaviour, leading one to have the experience of wanting more, and that consummatory pleasure is more closely linked to satiation or a resolution of desire (Klein 1984; Depue and Collins 1999; Morrone-Strupinsky and Depue 2004). The term 'hysteroid' denotes the presence of a biologically based character-like pathology. Clinically it seems that hysteroid dysphoria is probably a variant of BD-II with cyclothymic and irritable temperament traits.

The question whether melancholic features are merely a severity dimension cannot yet be answered. Studies on the stability of depressive subtypes across episodes of depression revealed that 'non-endogenous' depressions may develop endogenous features during subsequent episodes, but endogenous depressions are likely to remain that way (Kendell 1974; Paykel et al. 1976; Coryell et al. 1994). Reports on ways of defining melancholia without the confounding effect of severity (Parker et al. 1990) are not convincing. The question on the true nature of melancholic features is complicated by methodological problems concerning all the spectrum of the research methodology used (Zimmerman et al. 1990; Everitt 1981) and particularly by the poor definition of depression severity. The lack of data specifically for bipolar depression confuses the picture even more.

To date, there is no satisfactory definition for severity. If one relies on the number of symptoms, then a circular reasoning leads to the conclusion that melancholia is a more severe form of depression and no difference in quality exists between melancholic and non-melancholic depressives. A different approach would be to take into consideration the degree of disability as an index of severity. But again, often the definition of disability, e.g. in the General Assessment of Functioning Scale (American Psychiatric Association 1994), is related to specific symptoms like

suicidal ideation, anhedonia or fatigue, so reasoning may again be circular. Biochemical evidence provided no way out from this problem.

Unfortunately, the recognition of the disorder might delay by as much as 8–10 years, mainly because manic or hypomanic episodes appear late in the course of the illness (Angst 2007). As mentioned before, maybe more than half of hospitalized patients originally manifesting a depressive episode will turn out to be bipolars in the next 20 years (Angst et al. 2005). We can divide these patients into two groups: the 'false unipolars' that is those patients who turn eventually to be bipolars but do not manifest any manic or bipolar characteristic during depressive episodes and before the manifestation of a full manic or hypomanic episode, and the 'pseudounipolars', that is, those patients with subthreshold or subtle symptoms and signs belonging to the manic pole. It seems that the belief that the chances of a patient being bipolar instead of unipolar decreases by successive depressive episode is not true and the chances remain relatively stable thought the course of depressive disorder (Goodwin and Jamison 2007). According to DSM-5 both groups of patients are considered to be unipolar.

There is a large literature on the possibility to distinguish unipolar from false unipolar and pseudounipolar depressives. Karl Leonhard had already since 1957 noted that bipolar depressives manifest greater variability in their symptomatology across episodes (Leonhard 1957). Later this was confirmed mainly concerning BD-II depressives (Hantouche and Akiskal 2005). Overall it is believed that bipolar depressives manifest less anxiety, somatic complaints, psychomotor agitation, appetite and weight loss and early insomnia and more tension, fearfulness, psychomotor retardation, atypical features, variability across episodes, mood lability within an episode, late insomnia and hypersomnia, postpartum appearance, psychotic features and substance abuse (Goodwin and Jamison 2007).

Pseudounipolar patients often manifest agitation during a depressive episode. This 'agitated depression' has also named 'depressive mixed state' (Koukopoulos 1999). These patients, when assessed carefully, are reported to manifest additional manic-like features (Maj et al. 2003) and more frequently family history of BD (Maj et al. 2006). Up to 70 % of depressed were reported to have had significant manic symptoms but without fulfilling the definition of a mixed episode (Bauer et al. 2005). Since agitation and irritability are frequent symptoms during the course of a depressive episode (Serretti and Olgiati 2005), there are concerns whether 'agitated depressions' and 'depressive mixed states' should be included in the bipolar spectrum or whether such an inclusion will cause important problems in the conceptualization of BD. In accord with this concern, DSM-5 kept this condition in the chapter of (unipolar) depressive disorders.

Unipolar depressed patients who later 'convert' to BD over time, as well as bipolar depressives, manifest more frequently 'atypical' depressive features (hypersomnia, hyperphagia, leaden paralysis, long-term interpersonal rejection sensitivity) (Perugi et al. 1998), psychomotor retardation, psychotic features, pathological guilt and mood lability. Especially those who convert to BD-I (by manifesting mania) are characterized by early age at onset and pleomorphic psychopathology beyond the usual affective realm, high rates of substance abuse;

Table 2.2 Signs and symptoms which could assist in the differentiation between unipolar and bipolar depression

In comparison to unipolar, bipolar depression is characterized by:
Younger age at onset
Presence of either agitation or retardation
Less
Anxiety
Somatic complaints
Appetite and weight loss
Early insomnia
More
Irritability
Tension
Fearfulness
Atypical features
Late insomnia
Hypersomnia
Frequent postpartum appearance
Frequent psychotic features
Substance abuse
Variability in symptomatology across episodes
Mood lability within an episode
Family history

educational, marital and occupational disruption; and minor antisocial behaviour (Akiskal et al. 1995). BD patients also tend to have younger age of onset, more prior episodes of depression, shorter depressive episodes and family history of BD (Mitchell et al. 2008; Akiskal and Benazzi 2008; Rao et al. 1995; Geller et al. 1994, 2001). The latter is a strong predictor of bipolarity even in children and adolescents (Geller et al. 1994).

The clinical features more common in bipolar depression are summarized in Table 2.2. The characteristics could be useful in the prediction of a future manic or hypomanic episode in false unipolar or pseudounipolar depression.

The above clearly point to the fact that 'melancholic' features as defined by DSM are not useful in this differentiation. Atypical features, on the other hand, seem to be a better predictor and might even constitute the 'bridge' between unipolar and BD-II cases (Akiskal and Benazzi 2005, 2006), although some data dispute this relationship (Parker et al. 2005). Atypical depression puts forward also the question concerning the relationship between bipolar illness and personality disorders. Clinically they are often inseparable, but it is generally preferable in most cases to diagnose mood disorders at the expense of a diagnosis of personality disorders.

There seems to be some differences between BD-I and BD-II patients in terms of their depressions. BD-II patients tend to be female, with less but more chronic episodes of lower severity, less frequently psychotic features and with more atypical features and anxiety (Goodwin and Jamison 2007).

2.4 Mania

Acute manic episodes constitute the second diagnostic pillar of BD and they put the diagnosis of bipolarity in a definite way. Typically, acute mania develops over a period of 1–2 weeks although both more protracted and more sudden onsets have also been described. Its major feature is a distinct period characterized by elevated or irritable mood or both, which clearly represents an observable and significant change from the normal behaviour, mood and functioning of the individual.

In general, the clinical features of classic mania are the opposite of those of depression. Thus, classic mania is characterized by elevated mood, rush of ideas, greater energy, psychomotor acceleration, impulsivity and ideas of grandiosity. However, there are features that can be seen both in depression and in mania, like irritability, anger, insomnia and agitation, even hypersexuality, although the exaggerated presence of them suggests the diagnosis of a mixed episode rather than that of a depressive or manic. Classic acute mania (i.e. without mixed features) is relatively easy to recognize, in spite of the fact that more severe cases with psychotic features might be misdiagnosed as schizophrenia, while milder cases might be misdiagnosed as personality disorders (especially borderline, narcissistic and antisocial personality disorders).

The patient's mood during acute mania is characteristically elated with euphoria, jubilation, laughing, punning and gesturing. Euphoria is observed in 30–97 % of patients during acute mania (Abrams and Taylor 1976; Beigel and Murphy 1971; Carlson and Goodwin 1973; Clayton and Pitts 1965; Taylor and Abrams 1973, 1977; Winokur et al. 1969; Winokur and Tsuang 1975; Leff et al. 1976; Loudon et al. 1977; Cassidy et al. 1998b). Mood is unrestrained and expansive in the majority of patients (44–66 %) (Loudon et al. 1977; Taylor and Abrams 1973, 1977) and typically lifts that of the observer, especially in cases of classic euphoric mania. Elevated mood, jokes, gestures and overall behaviour cheer up the others and often the patient is at the centre of fun. A deep feeling of general well-being is present. However, in cases of dysphoric mania or anger, or even in cases of very 'silly' or dramatic behaviour, the result could be irritating for the others. This is in contrast to the indifferent or cold emotional feeling induced by patients with schizophrenia to those observing or examining them. The prevailing positive mood in mania is often not stable and brief intrusions of crying and tears are common. Additionally, acceleration and expansion are so excessive that many patients experience high levels of anxiety, tension and nervousness. Patients are dissatisfied and intolerant and the vast majority manifests mood lability and instability (42–95 %) (Abrams and Taylor 1976; Carlson and Goodwin 1973; Cassidy et al. 1998b; Loudon et al. 1977; Taylor and Abrams 1977; Winokur et al. 1969). Lability seems to be a dominant feature with only a few patients being free of it and often resembles a 'personality-like' feature, being capricious and intense. Irritability is also very frequent (51–100 %) (Carlson and Goodwin 1973; Cassidy et al. 1998b; Serretti and Olgiati 2005; Winokur et al. 1969; Taylor and Abrams 1973, 1977; Winokur and Tsuang 1975; Abrams and Taylor 1976; Loudon et al. 1977). Thus, irritability seems to be an inherent component of manic mood. Since also omnipotent thoughts are often

present, when crossed, these patients might become irritable, hostile (with verbal as well as physical aggressiveness) and even dangerous. However, even significant depressive symptoms are experienced by as many as 29–100 % of acutely manic patients (Beigel and Murphy 1971; Carlson and Goodwin 1973; Cassidy et al. 1998b; Kotin and Goodwin 1972; Loudon et al. 1977; Murphy and Beigel 1974; Prien et al. 1988; Winokur et al. 1969). This intrusion of depressed features during an acute manic episode seems to be more frequent and significant in females (Winokur et al. 1969). When excessive they give rise to dysphoric or mixed mania. This is not identical to a mixed episode. In at least a significant proportion of patients, the ratings of depressive symptoms are higher during their acute mania periods in comparison to their acute depressive periods (Kotin and Goodwin 1972). During periods of dysphoric mania, irritability, anger, panic attacks, agitation, suicidal ideation, severe insomnia and persecutory delusions often coexist with more classic manic symptoms.

It has been proposed that acute mania starts with increased activity accompanied by euphoria or mild irritability, while thinking remains coherent (stage I), then progresses to the experience of dysphoria and the manifestation of open hostility and anger and disorganization (stage II) and finally to an undifferentiated psychotic state with dysphoria, severe disorganization and psychotic features (stage III). The episode disappears in the reverse order, from stage III to stage I and normality (Carlson and Goodwin 1973).

However, 'pure' affective states are rare. It has been reported that 94 % of DSM-IV manic patients had significant depressive but without fulfilling the definition of a mixed episode (Bauer et al. 2005). That study suggested that mixed pictures are more frequent than pure ones, and interestingly, they reported (in accord to an earlier study) a positive correlation between manic and depressed symptoms in contrast to what common sense would have predicted (Bauer et al. 2005; Kotin and Goodwin 1972).

Accelerated psychomotor activity, which constitutes the hallmark of mania, is characterized by overabundant energy, activity and rapid, pressured speech, which is fast and often witty. It is observed in the vast majority of patients (56–100 %) (Abrams and Taylor 1976; Carlson and Goodwin 1973; Carlson and Strober 1978; Cassidy et al. 1998a, b; Leff et al. 1976; Loudon et al. 1977; Serretti and Olgiati 2005; Taylor and Abrams 1973; Winokur et al. 1969). Pressured speech is observed in almost all patients (Abrams and Taylor 1976; Carlson and Goodwin 1973; Cassidy et al. 1998a; Clayton and Pitts 1965; Loudon et al. 1977; Serretti and Olgiati 2005; Taylor and Abrams 1973; Winokur et al. 1969; Carlson and Strober 1978; Leff et al. 1976). Subjectively, the patient experiences an unusual sense of well-being and physical and mental strength. Increase in goal-directed activity is characteristic of the situation, with patients starting multiple unrelated tasks simultaneously and often continue with new tasks before completing the previous ones, and in spite of the fact that it is obvious, they will be unable to cope with them. These tasks vary from simple everyday works (cleaning, cooking, painting the house, etc.) to complex ambitious enterprise (opening multiple new businesses, etc.). Pressured writing leads to the production of a large number of declarations, poems and various texts

or a combination of text and some kind of drawing. Handwriting becomes irregular and often peculiar. Often the risk associated with these multiple goals is significant both in financial and in physical terms. It is to be noted that although an appetite disorder is not present in manic patients, often they lose weight due to excess physical activity and neglect of nutrition.

Thought disorder in manic patients includes problems with abstract thinking, conceptualization and coherence. Thought disorder should be separated from speech disorder, although the two concepts as well as clinical pictures relate to each other and overlap. Most studies reported that there is no 'quantitative' difference (Harrow et al. 1982, 1986; Breakey and Goodell 1972), although others find a slightly better thought functioning in manic patients in comparison to patients with schizophrenia (Resnick and Oltmanns 1984). However, there seems to be a qualitative difference with manic patients having more disordered structure, with a dominance of extravagance, playfulness and humour, over inclusion, tangentiality, circumstantiality and incoherence, while patients with schizophrenia have more disordered thought content with underinclusiveness, poverty of content, idiosyncratic and autistic thinking, conceptual deficit, tangentiality, peculiar and fluid ideas and unstable structure and disorganization (Simpson and Davis 1985; Daniels et al. 1988; Solovay et al. 1987; Andreasen and Powers 1975; Jampala et al. 1989). It is interesting also that this thought disorder is reversible in a significant proportion of BD patients, and this improvement is greater in comparison to schizophrenia, although a surprisingly high number of them (up to one-third) show severe thought disturbance which cannot be attributed to the presence of psychotic features alone (Harrow et al. 1986; Grossman et al. 1986).

A number of studies reported that manic patients have more complex speech and more overall quantity in comparison to patients with schizophrenia (Morice and Igram 1983; Morice and McNicol 1986; Docherty et al. 1996; Thomas et al. 1996; Lott et al. 2002). It is reported that the speech in manic patients is mainly because of shifting from one discourse to another. In comparison, patients with schizophrenia have significant difficulty in elaborating any discourse (Hoffman et al. 1986). Furthermore, the speech of manic patients is more complex in terms of syntax and with fewer errors (Lott et al. 2002; Thomas et al. 1996), less predictable in comparison to controls but more in comparison to that in schizophrenia (Ragin and Oltmanns 1983). Speech analysis alone seems to be able to identify up to 80 % of BD patients and normal controls (Fraser et al. 1986).

Pressured writing is characteristic of acute mania and leads to the production of an astonishing number of various texts, from poems to political manifesto. In milder cases these writings could be impressive; however, with increasing severity they become incoherent and the style becomes bizarre.

The content of thoughts is dominated by inflated self-esteem, ideas of grandiose, high confidence and a sense of very important achievements. Thinking is excessively positive, optimistic and expansive. Insight and judgment are impaired and transient. The line between nonpsychotic manic thought content and psychotic is very thin, and for many authors it does not exist at all. These mean that clinicians should routinely obtain clinically relevant information concerning the previous

psychiatric history of the patient from significant others, and often the hospitalization is arranged on an involuntary basis. The thinking process is accelerated, and it is subjectively experienced as flight of ideas. Thinking and perception are unusually sharp; however, creativity is facilitated only in very mild cases. Sharpening is usually accompanied by instability thus leading to easy distraction by irrelevant stimuli and inability to differentiate between unimportant and important stimuli. It is not unusual that the examiner has difficulty to interrupt and ask a question. The patient may speak with such pressure that associations are difficult to follow. Often hoarseness develops, but this usually does not have a significant effect on the pressure to speak. In more severe cases the patient might 'jump' from one topic to another with loose associations or even his speech becomes completely incomprehensive. 'Clang' associations often based on rhyming or chance perceptions might appear. This puts the possibility of schizophrenia or gives the impression of organic confusion and even of some type of aphasia. To make things more complex, the patients might experience periods of amnesia (hours or days) when their mental activity is extremely accelerated because of inability to register any memories at that particular time period. This often covers much of the manic episode itself, and as a result the patients cannot recall and report it to the examiner.

'Delirious' mania constitutes an extremely severe expression of mania. It is also known as Bell's mania after Luther Bell (1806–1862) who first described it in 1849, and today it is very rare. It has an abrupt onset, ranging from hours to days, and it involves extreme physical activity with loss of appetite, insomnia, confusion, paranoia, confabulations and extremely bizarre hallucinations and delusions. Patients often run nude in the street, or on the contrary they isolate themselves inside their house, lock doors and shut windows. It constitutes a life-threatening medical emergency since fever, tachycardia, hypertension and rapid breathing often exist. During episodes of delirious mania, mood shifts rapidly between extreme mania and severe depression, suggesting a possible link to mixed states. Speech follows this shifting and logorrhoea alternates with mutism. A number of symptoms and signs which are unusual during mood episodes, like negativism, stereotypical movements, posturing, echolalia and echopraxia, are prominent. Typically, the presence of these symptoms and signs should be used in the differential diagnosis between schizophrenia and mood disorders, but Bell's mania constitutes an exception. Bell's mania responds to standard antimanic treatment although the use of typical antipsychotics might led to clinical worsening especially when given in combination with anticholinergic drugs (Fink 1999; Bipeta and Khan 2012; Bond 1980; Friedman et al. 2003; Jacobowski et al. 2013; Jarvie and Hood 1952; Karmacharya et al. 2008; Lee et al. 2012; Swartz et al. 1982).

The overall behaviour in mania is characterized by impulsivity and disinhibition. Patients act impulsively and show interest in every new activity that strikes their fancy. Judgment is thus impaired, and they engage in various activities which are often embarrassing, problematic or even dangerous in many ways and can lead to long-term problems (physical, personal, financial) that persist in the life of the patient long after the remission of the episode. Typical examples include dancing in the street; flirting indiscretionally; paying the bills of total strangers in bars; abusing

phone calls; buying cars, jewellery or other unnecessary expensive items; giving away property; gambling; engaging in risky business venture, etc. Also, manic patients are meddlesome; they show abnormal familiarity with total strangers and are intrusive and with increased involvement with others. This embarrasses family, friends and colleagues. On the other hand, manic patients are often violent and interpersonally aggressive because of low tolerance to confrontation, paranoid tendencies and impulsivity.

One of the most problematic behaviours is hypersexuality which usually leads to sexual indiscretion and marital problems. It is present in 25–80 % of patients (Allison and Wilson 1960; Carlson and Goodwin 1973; Carlson and Strober 1978; Clayton and Pitts 1965; Leff et al. 1976; Loudon et al. 1977; Winokur et al. 1969). Typically women have provocative and embarrassing sexual affairs, while males spend large amounts of money on prostitutes and other sex-related activities. The risks because of hypersexuality in combination with poor judgment and impulsivity include disasters in personal life, financial problems and sexually transmitted diseases (e.g. AIDS).

During periods of acute mania, patients show a characteristic decreased need for sleep (hyposomnia). This is present in 63–100 % of patients (Carlson and Strober 1978; Cassidy et al. 1998a; Clayton and Pitts 1965; Leff et al. 1976; Loudon et al. 1977; Serretti and Olgiati 2005; Winokur et al. 1969), and in spite of the fact that they sleep only for a few hours (or even not at all of several nights in the row), they feel fresh, full of strength and energy on awakening. Some patients may actually go sleepless for several days. Severe hyposomnia worsens manic symptomatology and especially excitation, while the same time precludes resting, thus leading to physical exhaustion.

As mentioned above, the line between manic thought content (e.g. inflated self-esteem and grandiose ideas accompanied with impaired judgment and insight) and delusional beliefs is very thin, and some authors suggest that manic thought content is ‘psychotic’ by definition. However, formally, milder cases of increased self-esteem and ideas of superiority can be considered as stemming out of the heightened mood and being extreme manifestations of normal human thoughts. However, the rule rather than the exception is that during an acute manic episode, patients experience ideas of delusional quality and intensity (exceptional mental and physical fitness and talent, wealth, power, influence or affiliation, aristocratic ancestry). Delusions of reference and persecution are common, usually embedded on the on the belief that others envy them because of their special abilities or talents. Often delusional thinking is bizarre, e.g. patients might adopt a different grandiose identity, or they think they possess supernatural powers. Auditory and visual hallucinations are also very often experienced and typically are congruent with the elevated mood (e.g. voice of the God or the angels). Non-congruent delusions or hallucinations are less often experienced, and in these cases the diagnosis of schizoaffective disorder should be considered.

Although an early report by Lange, on the basis of study of 700 patients, suggested that psychotic symptoms are rare and present in less than 10 % of manic patients (Lange 1922), the rest of the literature supports the conclusion that

overall, psychotic features are common in bipolar patients, and thus acute mania should be considered primarily a psychotic state (Koukopoulos 2006). Probably 33–96 % of acutely manic patients manifest psychotic features (Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969). Although older studies suggested that a younger age at onset is related to more frequent and florid psychotic symptoms (Rosen et al. 1983), it is possible that this finding was because of confusion of bipolar disorder with schizoaffective especially since more recent studies did not find such a relationship (Perugi et al. 2000; Toni et al. 2001; Baethge et al. 2005). It is almost certain that the presence, quality and intensity of psychotic features correlates with the overall severity of manic symptoms (Abrams and Taylor 1976; Carlson and Goodwin 1973; Young et al. 1983; Baethge et al. 2005)

Delusions are present in 24–96 % of bipolar patients, and it is interesting that persecutory is equally frequent with grandiose (Rennie 1942; Carlson and Goodwin 1973; Carlson and Strober 1978; Clayton and Pitts 1965; Leff et al. 1976; Winokur et al. 1969; Winokur 1984; Black and Nasrallah 1989; Serretti et al. 2002; Keck et al. 2003; Bowman and Raymond 1932; Astrup et al. 1959; Abrams and Taylor 1976; Beigel and Murphy 1971; Loudon et al. 1977; Murphy and Beigel 1974; Taylor and Abrams 1973, 1977; Rosenthal et al. 1980; Goodwin and Jamison 2007). The main difference of delusions in BD patients in comparison to schizophrenia is that in BD they have a changing nature, they usually are appropriate to the patient's mood, and they are not systematized, but they tend to be more wish fulfilling, while in schizophrenia they tend to isolate the patient from the others (Goodwin and Jamison 2007). Delusions of grandiose can be so intense and severe that the term 'manic dementia' was coined by Emil Kraepelin.

Hallucinations are less frequent and present in 13–66 %; they can either be congruent or non-congruent, with auditory, visual and olfactory being almost equally frequent (Goodwin and Jamison 2007; Abrams and Taylor 1976; Astrup et al. 1959; Bowman and Raymond 1932; Carlson and Strober 1978; Lange 1922; Rosenthal et al. 1980; Taylor and Abrams 1973, 1977; Winokur et al. 1969; Black and Nasrallah 1989; Keck et al. 2003; Serretti et al. 2002; Winokur 1984). They are more frequent in females (Baethge et al. 2005), and according to some authors their quality resembles more that of organic psychoses than schizophrenia, including the presence of better insight concerning them (Bowman and Raymond 1932; Lowe 1973; Silberman et al. 1985). Often they are in close relationship with a specific delusion, and thus they are unstable and changing (Winokur et al. 1969). Sixty-one percent of BD patients experience some type of psychotic symptoms at least once in their lifetime with 17 % experiencing first-rank symptoms (Goodwin and Jamison 2007). Almost one-third of acutely manic patients are 'confused', 46–75 % are violent (Abrams and Taylor 1976; Carlson and Goodwin 1973; Cassidy et al. 1998a; Taylor and Abrams 1973, 1977), 23–33 % have significant sexual exposure (Abrams and Taylor 1976; Taylor and Abrams 1973, 1977), and 10–20 % have fetal incontinence (Abrams and Taylor 1976; Taylor and Abrams 1973, 1977). As many as 14–56 % manifest severe regression, catatonia, posturing and negativism often making differential diagnosis from schizophrenia difficult (Carlson and Goodwin 1973;

Carlson and Strober 1978; Kruger et al. 2003; Lange 1922; Taylor and Abrams 1973, 1977; Abrams and Taylor 1981; Braunig et al. 1998). The frequent presence of catatonia is recognized also by the DSM-5.

Unfortunately, the detection of psychotic symptoms is problematic with relatives reporting them accurately in less than 20 % of cases (Orvaschel et al. 1982; Thompson et al. 1982; Price et al. 1984), while very often their detection makes the diagnosis of mood disorder less likely, in favour of schizophrenia (Pope and Lipinski 1978).

The pattern of symptoms seems to be relatively stable from episode to episode at least in the short term in the same patient (Beigel and Murphy 1971; Cassidy et al. 2002) although the progression of the illness changes both its polarity and its dominant clinical manifestations in the long term.

All the studies which analyzed the factorial structure of mania agree that there is a mood component, a psychomotor component (mostly activation) and a component corresponding to irritability and aggression and another one related to psychotic features. It is possible that none of these components is primary and homogenous. Not even the mood component is such, since euphoria and dysphoria does not seem to be mutually exclusive but often coexist (Murphy and Beigel 1974; Double 1991; Cassidy et al. 1998a, 2001; Dilsaver et al. 1999; Swann et al. 2001; Sato et al. 2002; Akiskal et al. 2003; Gonzalez-Pinto et al. 2003). What seems to derive from these factorial studies is that psychomotor activation is the core feature of mania (Bauer et al. 1994b; Akiskal et al. 2001) although this is not in direct accord with the concept of acute mania neither in the way it is defined by contemporary classification systems nor in the way most psychiatrists perceive it.

Two special topics concern chronic and unipolar mania. Around 5 % of BD patients have chronic mania (Akiskal 2000). Technically it is difficult if not impossible to make a distinction between true chronic mania and ultrarapid cycling. It is characterized by lack of adherence to treatment and reduced mental as well as general activity. Mood is often 'silly' rather than euphoric, and there seems as if the finest emotions have disappeared and only the coarser enjoyments still exist (Kraepelin 1921). 'Unipolar mania' is reported in 5–28 % of mood patients in some studies; however, there is much concern on the duration of follow-up and the methods used to identify depressive episodes. A 20-year follow-up study from the NIMH suggested that not more than 4 % of 'bipolar' patients can be considered to suffer from unipolar mania (Solomon et al. 2003). According to an original suggestion by Koukopoulos, mania is primary and depression is a consequence (mania is the fire and depression the ashes) (Koukopoulos 2006). This theory has not been confirmed, and a problem is that under the umbrella of the term 'mania', many states characterized by excitement, agitation and irritability are included. However, it might suit a subgroup of patients, especially those whose illness starts with a manic episode. Of course these patients constitute a minority, manifest also a predominant manic polarity, have a better overall course and outcome and respond very well to lithium, especially the MDI type (mania–depression-free interval).

Secondary mania is another interesting topic. Acute mania in patients without prior bipolar illness and with a characteristically low family history load could be

triggered during postpartum, in the course of various somatic illnesses like thyrotoxicosis, systemic lupus erythematosus, rheumatic chorea, multiple sclerosis, Huntington's disease, cerebrovascular disease, brain tumours, head trauma, complex partial seizures, syphilis and AIDS, or it could be a consequence of their treatment. Although some authors support the concept of 'reactive' mania as a consequence of life events, there are no positive data in support of it.

2.5 Hypomania

Formally, those episodes with manic symptoms but less pronounced in terms of severity and with shorter duration are labelled 'hypomanic'. However, it can also be defined as distinct periods of at least a few days characterized by mild elevation of mood; increase in cheerfulness and jocularity; sharpened and positive thinking; increased self-confidence, optimism, gregariousness, talkativeness and people seeking; greater interest in sex; decreased inhibitions and decreased need for sleep accompanied by increased energy and activity levels. There is no impairment which characterizes full-blown manic episodes, and in this frame it cannot be considered to be merely a milder form of mania. The presence of psychotic symptoms, although in lower frequency in comparison to mania, supports this. Hypomania often heralds the end of a depressive episode (in the form of a rebound relief), and in this case it lasts only 1–2 days.

Hypomania is much more common than mania but its recognition is mostly achieved mainly by interviewing significant others and not the patient. It is distinguished from normal happiness because it tends to recur in an 'endogenous' way and cyclicity and often can be triggered by stimulants, caffeine abuse or antidepressants. If chronic, it can constitute the habitual baseline of a hyperthymic temperament.

Hypomanic episodes cause mild or no impairment at all, and on the contrary, in some cases, they may even contribute to success in business, leadership roles and the arts. Patients often experience the hypomanic episodes as ego-syntonic and pleasant, might not recognize them at all as abnormal or tend to deny them. Often these periods are considered as periods of perfect functioning and recovering from depression. In some cases, hypomanic episodes might be irritable or dysphoric, and in these patients the misdiagnosis of a personality or characterological disorder is usual. Psychotic symptoms are less frequent (around 20 %) in comparison to full-blown manic episodes, but they do occur (Mazzarini et al. 2010). However, in the long term, the recurrence of hypomanic episodes accumulates burden and adverse consequences because of a behaviour which is essentially abnormal and probably dysfunctional in the long term and thus poses the individual at risk at the personal, financial and physical level. The elated mood, although not overtly manic, is related to over optimism, overestimation of abilities, impulsivity and a degree of judgment and insight impairment, while the presence of irritable or dysphoric features causes impairment in occupational and interpersonal functioning over time.

2.6 Mixed States

In spite of the fact that the definition of BD is based on the alteration between two separate and distinct poles, 'pure' affective states are rare. It has been reported that 94 % of DSM-IV manic patients and 70 % of depressed had significant symptoms of the opposite pole, but without fulfilling the definition of a mixed episode (Bauer et al. 2005). That study suggested that mixed pictures are more frequent than pure ones, and interestingly, (in accord with an earlier study) they reported a positive correlation between manic and depressed symptoms in contrast to what common sense would had predicted (Bauer et al. 2005; Kotin and Goodwin 1972).

In this frame, mixed episodes are also considered to be part of the BD picture and clinically are defined as the coexistence of both depressive and manic symptoms. Although as mentioned before, manic and depressive symptoms almost always coexist, the concept of mixed episodes has been proposed to describe cases where this coexistence is profound. Earlier suggestions included also ultrarapid cycling cases. This kind of episodes might appear as a short transitional phase (transitional forms) between the two poles or as independent episodes (autonomic forms) (Kraepelin 1921; Weygandt 1899; Akiskal and Benazzi 2004). The presence of a limited number of depressive symptoms during a full-blown manic episode gives rise to dysphoric mania (Kotin and Goodwin 1972; McElroy et al. 1992; Prien et al. 1988), while similarly, the presence of a limited number of manic symptoms during a full-blown depressive episode leads to mixed agitated depression (Himmelhoch et al. 1976; Koukopoulos and Tundo 1992; Perugi et al. 1997; Cassidy et al. 1998a, b; Dilsaver et al. 1994).

Earlier approaches considered stupor to be a core characteristic of mixed states (Weygandt 1899), but currently psychomotor activation with irritability and mood lability seems to be more important (Winokur et al. 1969; Akiskal and Mallya 1987; Koukopoulos 1999; Sato et al. 2005). In mixed episodes the rate of psychotic symptoms is probably similar to that of manic ones and approximately 40 % (Mantere et al. 2004).

DSM-IV demanded the presence of both full-blown depressive and manic episodes in order to allow the label of a 'mixed' episode, in accord with the approach by Winokur et al. (1969), Evans and Nemeroff (1983) and Strakowski et al. (1992), but DSM-5 included mixed features as a specifier only. Both classification systems classify ultrarapid cases within the mixed pictures domain rather than rapid cycling. Essentially, ultrarapid cycling is the only way full-blown manic/hypomanic and depressive episodes can coexist as DSM-IV required.

The DSM-5 demands the presence of a full-blown episode of either pole together with at least three symptoms of the opposite pole being present in order to allow the label of 'mixed features' specifier. This is largely in accord with the proposals of Susan L. McElroy (McElroy et al. 1992, 1995), while other authors had proposed that the presence of only two (Akiskal et al. 1998) or even only one criterion (Swann et al. 1997) should be sufficient. The proportion of mixed episodes depends both on the study sample and on the definition utilized (McElroy et al. 1992) and varies from 5 % to 70 % (Himmelhoch et al. 1976; Kotin and Goodwin 1972; Winokur

et al. 1969; Murphy and Beigel 1974; Carlson and Goodwin 1973; Keller 1988; Keller et al. 1986; Nunn 1979; Strakowski et al. 1992; Cassidy et al. 1998b, 2001; Dell'Osso et al. 1991; Dilsaver et al. 1999; Gonzalez-Pinto et al. 2003; Kruger et al. 2003; McElroy et al. 1995; Perugi et al. 1997; Post et al. 1989; Prien et al. 1988; Sato et al. 2002; Secunda et al. 1987; Akiskal et al. 1998). When using the definition with the three or more criteria, mixed episodes are more often diagnosed in females, and the disease is more likely to begin with a mixed episode and characterized by fewer episodes of longer duration (McElroy et al. 1995).

Often the criteria for a mixed features specifier are not fulfilled. A special case is the coexistence of hypomanic features or even of a fully blown hypomanic episode in the frame either of type II BD (BD-II) or even unipolar depression. Although full hypomanic episodes are rare (2.8 %), at least three were registered in 28.5 % of unipolar depressed patients. The respective rate was 48.7 % for BD-II patients during a depressed phase (Benazzi 2000; Benazzi and Akiskal 2001).

Sometimes there is an admixture of a number of manic and depressive symptoms in a combination which does not fulfil the specific DSM criteria for a manic or depressive episode; thus, the only possible diagnosis is that of a not-otherwise-specified (NOS) mood episode (Akiskal et al. 1998; Akiskal 1996). There seems to be a constellation of types of affective episodes which are not part of the official classification, and they are so prevalent in real-life clinical practice that many authors consider them to be the rule rather than the exception.

Mixed episodes are also considered to be part of the BD picture and according to DSM-IV-TR are defined as the coexistence of both depressive and manic symptoms to the extent that the criteria for both manic and depressed episodes are fulfilled (Akiskal and Benazzi 2004). In DSM-5 the definition was softened, and instead of 'mixed episodes' a 'mixed features specifier' was included. Alterations in mood characterize several other DSM disorders which have a bipolar character. These include cyclothymic disorder and borderline personality disorder. However, there is a constellation of types of affective episodes which are not part of the official classification, and they are so prevalent in real-life clinical practice that many authors consider them to be the rule rather than the exception.

Frequently the manic symptoms can go unnoticed by the clinician because instead of being hyperthymic, the mood is irritable, and it is diluted in the presence of depressed thought content and suicidal ideation, leading the clinician to the diagnosis of anxious or agitated depression, or worse, of a personality disorder, instead of a mixed or mixed-NOS mood episode. Frequently, this irritable mood can lead the person to manifest aggressive behaviour especially if confronted or rejected while having grandiose and paranoid delusions, and these patients are maybe the most aggressive seen in the emergency room (Maj et al. 2003; Sato et al. 2005).

Although clinically manic and depressive symptoms appear simply to coexist, there are a number of observations suggesting that there is a deeper and complex interplay of various factors which gives rise to mixed episodes. Originally Kraepelin (1921) and Weygandt (1899) proposed the existence of three separate components which fluctuate independently from each other: mood, cognition and psychomotor activity. The combination of their phases could thus produce six different types of affective episodes: (a)

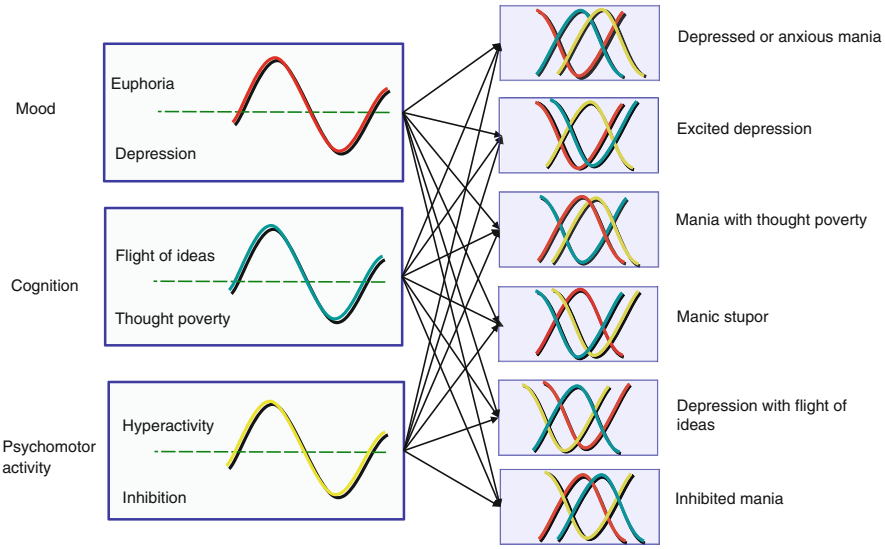

Fig. 2.3 Graphic representation of the three separate components of mood episodes (mood, cognition and psychomotor activity) and their independent fluctuation which gives rise to six different types of mood episodes

depressive or anxious mania (depressed affect with flight of ideas and hyperactivity), (b) excited depression (depressed affect with thought poverty and hyperactivity), (c) mania with thought poverty (manic affect with thought poverty and hyperactivity), (d) manic stupor (manic affect with thought poverty and inhibition), (e) depression with flight of ideas (depressed affect with flight of ideas and inhibition) and (f) inhibited mania (manic affect with flight of ideas and inhibition) (Fig. 2.3).

A more or less similar approach suggests that the superimposition of an affective episode on a temperament of opposite polarity (pointing to a conflict between the components of affect and mood) might explain better the complex psychopathology and quality of patients with mixed episodes (Akiskal 1992). In support of such a distinct quality in psychopathology of mixed patients is the observed mood liability and higher frequency of non-congruent psychotic features (Akiskal and Mallya 1987; Perugi et al. 1997; Akiskal et al. 1998; Winokur et al. 1969; Kotin and Goodwin 1972; Himmelhoch et al. 1976; Post et al. 1989; Strakowski et al. 1992). In accord is also the observation that patients who experience a mixed episode tend to experience only such episodes in the future (Dell'Osso et al. 1991) and that mixed patients tend to have neuropsychiatric abnormalities more often than classic manic patients (Himmelhoch and Garfinkel 1986).

As mentioned before, the admixture of manic and depressive elements may give two 'mirror' clinical pictures, that is, 'dysphoric mania' (Kotin and Goodwin 1972; McElroy et al. 1992; Prien et al. 1988) and 'mixed agitated depression' (Himmelhoch et al. 1976; Koukopoulos and Tundo 1992; Perugi et al. 1997; Cassidy et al. 1998a, b; Dilsaver et al. 1994).

In agitated depression, depressed mood, anxiety, inner tension, unrest and agitation dominate the clinical picture. Anhedonia is also marked, and suicidality is frequently present, although not to the same degree as in unipolar patients (Angst et al. 2002). Typically, there is no speech retardation, and although there is usually an increased overall physical activity, the purposeful activity is significantly reduced. In more severe cases, there is total lack of purposeful activity. It has been reported that mental excitement might be more pronounced in the lack of marked physical agitation. Thoughts are typically fast and overcrowded (Akiskal and Mallya 1987; Koukopoulos 1999; Benazzi and Akiskal 2001). However, in contrast to mania, where mental speed is generally reflected in pressured speech, in agitated depression this is not the case. On the contrary, although these patients experience crowded or racing thoughts, their speech is normal or even retarded and monotonous. 'Racing thoughts' are observed in approximately one-third of hospitalized depressive patients (Braden and Qualls 1979), and they differ from 'flight of ideas' in the sense that the former do not express themselves in the patient's speech directly, and their content torments the patient (in contrast to the flight of ideas whose content is usually joyful). They also differ from 'depressive ruminations' which are clearly depressed thoughts which tend to recur but without high speed and do not completely fill the mind. The content of racing thoughts is not always depressive; it can include also trivial issues. However, this unusual number of thoughts is disturbing and painful, and this experience poses a significant burden on the individual (Koukopoulos et al. 2005).

There is evidence that a development of an excited/irritable state could happen when antidepressants, especially dual action ones, are used. Many patients will not develop a classic manic episode in response; many will either develop a full-blown mixed episode or more likely a DSM-subthreshold mixed-NOS episode with the presence of a small number of manic symptoms in combination with depression, especially agitation, and this state could persist and worsen if more aggressive antidepressant treatment is tried.

At least 50 % of BD patients experience a mixed manic state with two to four depressive symptoms in the frame of a full-blown manic episode. Mixed episodes seem to last longer than manic ones, but it is unclear whether they manifest any difference in the age of onset (Keller et al. 1986; Dell'Osso et al. 1991). While during acute mania suicidality is almost absent, the presence of mixed features induces it in up to 14–55% of patients (Dilsaver et al. 1994; Strakowski et al. 1996; Marneros et al. 2004; Kotin and Goodwin 1972; Winokur et al. 1969). Psychotic and catatonic symptoms are also frequent, and in the case of mixed episodes, they are associated with greater severity and poor prognosis (Kruger et al. 2003). Mixed episodes by themselves do not seem to correlate with severity of illness and rapid cycling (Himmelhoch et al. 1976) although the outcome seems to be poorer.

There is some but not concluding evidence that a development of an excited/irritable state could happen when antidepressants, especially dual action ones, are used. Many patients will not develop a classic manic episode in response; many will either develop a full-blown mixed episode or more likely a DSM-subthreshold mixed-NOS episode with the presence of a small number of manic symptoms in

combination with depression, especially agitation, and this state could persist and worsen if more aggressive antidepressant treatment is tried.

2.7 Psychotic Features

Although psychotic features were described in previous parts of the current chapter in the frame of specific mood episodes, it is important to summarize the knowledge concerning them, since psychosis in BD constitutes an important element with profound consequences for the treatment, prognosis and overall outcome of the patients. However, in spite of the fact that psychosis is very frequent in BD patients, unfortunately the detection of psychotic symptoms is problematic with relatives reporting them accurately in less than 20 % of cases (Orvaschel et al. 1982; Thompson et al. 1982; Price et al. 1984), while very often their detection makes the diagnosis of mood disorder less likely, in favour of schizophrenia (Pope and Lipinski 1978).

Psychotic features may include delusions or hallucinations of any sensory modality, and they can either be congruent or non-congruent, and both could occur in the context of any type of episode, but more often during acute manic and mixed episodes. Sixty-one percent of BD patients experience some type of psychotic symptoms at least once in their lifetime with 17 % experiencing first-rank symptoms (Goodwin and Jamison 2007). Almost one-third of acutely manic patients are 'confused', 46–75 % are violent (Abrams and Taylor 1976; Carlson and Goodwin 1973; Cassidy et al. 1998a; Taylor and Abrams 1973, 1977), and 10–20 % have fetal incontinence (Abrams and Taylor 1976; Taylor and Abrams 1973, 1977). As many as 14–56 % manifest severe regression, catatonia, posturing and negativism often making differential diagnosis from schizophrenia difficult (Carlson and Goodwin 1973; Carlson and Strober 1978; Kruger et al. 2003; Lange 1922; Taylor and Abrams 1973, 1977; Abrams and Taylor 1981; Braunig et al. 1998). It is important to note that catatonia is recognized by the DSM-5 as part of the bipolar clinical picture and not exclusively of schizophrenia.

This often creates a diagnostic dilemma; however, in order to put the diagnosis of schizoaffective disorder according to DSM-5, there must be a psychotic episode of at least 2 weeks duration in the absence of mood symptoms of sufficient intensity to qualify for a major mood episode. In ICD-10 this diagnostic boundary is vague and differential classification is often difficult. In DSM-5 bipolar disorders were included in a separate chapter between the chapters of schizophrenia and depressive disorders so as to stress their position as a bridge between the other two. It has been argued that psychotic features constitute a stable trait which tends to repeat itself across episodes, although the studies which suggest this use a mixture of bipolar and unipolar patients, and therefore, generalizability is problematic (Helms and Smith 1983; Nelson et al. 1984; Aronson et al. 1988a, b).

Psychotic features in BD patients are usually in accord with mood. Thus, not only they differ between acute mania and acute depression but also fluctuate as mood fluctuates, and they are less fixated in comparison to schizophrenia. In BD patients psychotic features have a self-fulfilling quality rather than being part of a fixed system of

beliefs. They present in 9–66 % during periods of acute bipolar depression and probably in 33–96 % of acutely manic patients manifest psychotic features (Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969; Mantere et al. 2004; Goes et al. 2007). In mixed episodes the rate is probably similar to that of manic ones (Mantere et al. 2004). Thus, it seems that psychotic features are somewhat more frequent during acute mania, but this difference is not overwhelming. They are more frequent in bipolar than in unipolar depression (Goes et al. 2007).

During periods of depression, delusions are present in 12–66 % of patients (Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969). They include mood-congruent delusions of worthlessness and sinfulness, reference, infidelity and persecution (often in the form of prosecutor); poverty, disaster or ill health appears (suffering from an occult illness, like cancer or AIDS). A special type is nihilistic delusions (Cotard's syndrome after Jules Cotard; 1840–1889) which include thoughts that parts of the body are missing. Under the influence of depressive delusions, not only suicide but also homicide can occur, usually with an 'altruistic' motive (e.g. under delusions of poverty, disaster or moral decay, a father might kill his children in order to 'save' and 'protect' them and afterwards commits suicide; mothers with psychotic depression during the postpartum period could commit infanticide). Mood-incongruent delusions can be also present (e.g. persecutory delusions which cannot be considered in the frame of the depressed mood); however, if bizarre delusions are present, then the diagnosis of schizoaffective disorder should be considered.

Several authors suggest that manic thought content is 'psychotic' by definition (Koukopoulos 2006). Delusions are present in 24–96 % of acutely manic patients, and it is interesting that persecutory is equally frequent with grandiose (Rennie 1942; Carlson and Goodwin 1973; Carlson and Strober 1978; Clayton and Pitts 1965; Leff et al. 1976; Winokur et al. 1969; Winokur 1984; Black and Nasrallah 1989; Serretti et al. 2002; Keck et al. 2003; Bowman and Raymond 1932; Astrup et al. 1959; Abrams and Taylor 1976; Beigel and Murphy 1971; Loudon et al. 1977; Murphy and Beigel 1974; Taylor and Abrams 1973, 1977; Rosenthal et al. 1980; Goodwin and Jamison 2007). Almost always patients experience ideas of delusional quality and intensity (exceptional mental and physical fitness and talent, wealth, power, influence or affiliation, aristocratic ancestry). Delusions of reference and persecution are common, usually embedded on the belief that others envy them because of their special abilities or talents. Often delusional thinking is bizarre, e.g. patients might adopt a different grandiose identity, or they think they possess supernatural powers and frequently non-mood-congruent. It is almost certain that the presence, quality and intensity of psychotic features correlate with the overall severity of manic symptoms (Abrams and Taylor 1976; Carlson and Goodwin 1973; Young et al. 1983; Baethge et al. 2005).

The main difference of delusions in manic patients in comparison to schizophrenia is that in BD they have a changing nature, they usually are appropriate to the patient's mood, and they are not systematized, but they tend to be more wish fulfilling, while in schizophrenia they tend to isolate the patient from the others (Goodwin and Jamison 2007).

During acute bipolar depression hallucinations are less frequent (8–50 %) in comparison to acute mania (Baethge et al. 2005; Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969) and are most often auditory (Black and Nasrallah 1989; Carlson and Strober 1978; Rosenthal et al. 1980; Winokur et al. 1969; Mantere et al. 2004). Typically they are extremely unpleasant, and their content is in accord with depressed mood and delusional ideation. They can be mood-congruent (e.g. accusatory or derogatory) or mood-incongruent (e.g. two voices discussing without any reference to the patient). Often they are so schizophrenia like that they pose a diagnostic dilemma.

Hallucinations in mania are present in 13–66 %; they can either be congruent or non-congruent, with auditory, visual and olfactory being almost equally frequent (Goodwin and Jamison 2007; Abrams and Taylor 1976; Astrup et al. 1959; Bowman and Raymond 1932; Carlson and Strober 1978; Lange 1922; Rosenthal et al. 1980; Taylor and Abrams 1973, 1977; Winokur et al. 1969; Black and Nasrallah 1989; Keck et al. 2003; Serretti et al. 2002; Winokur 1984). They are more frequent in females (Baethge et al. 2005), and according to some authors their quality resembles more that of organic psychoses than schizophrenia, including the presence of better insight concerning them (Bowman and Raymond 1932; Lowe 1973; Silberman et al. 1985). Often they are in close relationship with a specific delusion, and thus, they are unstable and changing (Winokur et al. 1969).

Already since the earlier attempts for the creation of the modern era nosological classification, specific severe psychotic clinical pictures had been identified and described in BD patients. Kraepelin described ‘melancholia gravis’ as a more severe form of depression with psychotic features and ‘fantastic melancholia’ for even more severe forms with more pronounced psychotic symptoms, alternation of agitation with stupor and clouding of consciousness. According to Kraepelin the most severe form of depression is ‘delirious melancholia’ with very severe and almost ‘schizophrenic-like’ delusions and hallucinations. In these cases, clouding of consciousness dominates the clinical picture (Kraepelin 1921). Kraepelin also coined the term ‘manic dementia’ for those cases of acute mania in which the delusions of grandiose were extremely intense and severe.

Even before Kraepelin, in 1849, Luther Bell (1806–1862) had coined the term ‘delirious’ mania for cases of extremely severe expression of mania. It is also known as Bell’s mania and today it is very rare. It has an abrupt onset, ranging from hours to days, and it involves extreme physical activity with loss of appetite, insomnia, confusion, paranoia, confabulations and extremely bizarre hallucinations and delusions. Patients often run nude in the street, or on the contrary they isolate themselves inside their house, lock doors and shut windows. It constitutes a life-threatening medical emergency since fever, tachycardia, hypertension and rapid breathing often exist. During episodes of delirious mania, mood shifts rapidly between extreme mania and severe depression, suggesting a possible link to mixed states. Speech follows this shifting and logorrhoea alternates with mutism. A number of symptoms and signs which are unusual during mood episodes, like negativism, stereotypical movements, posturing, echolalia and echopraxia are prominent. Typically the presence of these symptoms and signs should be used in the differential diagnosis

between schizophrenia and mood disorders, but Bell's mania constitutes an exception. Bell's mania responds to standard antimanic treatment although the use of typical antipsychotics might led to clinical worsening especially when given in combination with anticholinergic drugs (Fink 1999; Bipeta and Khan 2012; Bond 1980; Friedman et al. 2003; Jacobowski et al. 2013; Jarvie and Hood 1952; Karmacharya et al. 2008; Lee et al. 2012; Swartz et al. 1982).

2.8 Other Clinical Issues

Frequently the correct diagnosis is put only after several years have passed since onset because the first episode is often psychotic like or depressive and the diagnosis is put correctly only after a manic or mixed episode emerges. It has been estimated that more than half of hospitalized patients originally manifesting a depressive episode will turn out to be bipolars in the next 20 years (Angst et al. 2005). This has profound implications concerning the treatment and its overall efficacy. An additional problem for the diagnosis is that patients usually experience hypomania as a recovery from depression and almost always as a pleasant ego-syntonic mood state.

The clinical picture of BD includes a number of symptoms and syndromes which according to contemporary classification systems constitute comorbid conditions, but historically one can argue that they constitute core features of BD itself and not separate or semi-separate disorders. In the current textbook they will be discussed in detail in the chapter dedicated to comorbidity and other specifically dedicated chapters. Of special interest are also the neurocognitive impairment which is reported to exist in both BD-I and BD-II patients, although more so in the bipolar I group, and this is true even during the euthymic period (Dixon et al. 2004; Malhi et al. 2004; Sole et al. 2011) and the psychosocial impairment which seems to be significant and present even when patients are euthymic. It is reported that only a minority achieves complete functional recovery (Goldberg et al. 1995a, b; Keck et al. 1998; Strakowski et al. 1998; Martinez-Aran et al. 2007; Mur et al. 2007; Daban et al. 2006). It is reported that in 69.6 % of cases the course resembles that of a recurrent episodic illness, while in 25 % of cases there is a chronic course without clear remissions between episodes. In only 5.4 % there is a single episode of mania. Suicidal ideation is present in 78.6 % of cases at some time in their life. Alcohol and drug abuse/dependence is present in 32.1 %. Around 84.8 % of patients have at least one contact with any health services during the previous year (Morgan et al. 2005). It seems that in the long term at least one-third of patients are symptomatic with depressed episodes manifesting three times more than manic/hypomanic (De Dios et al. 2009).

Clinicians and researchers together often neglect the fact that although mania is the key diagnostic feature of BP, it is depression that is mainly responsible for the burden of the disease (Judd et al. 2002, 2003; Goodwin and Jamison 2007). Bipolar depression is more refractory than unipolar and has poor response to antidepressants, and only limited options for its treatment are available (Fountoulakis et al. 2008, 2011; Fountoulakis and Vieta 2008; Fountoulakis 2009). Subsyndromal

depressive symptoms are usual, they cause significant disability (Judd and Akiskal 2003), and they put the patient at a three-time higher risk to relapse (Judd et al. 2008). On the other hand, potentially insufficient or wrong aggressive monotherapy with antidepressants might worsen the long-term outcome of the illness and put the patient at a higher risk for suicide.

The most frequent comorbid mental disorders are alcohol and drug use and abuse, anxiety disorders, obsessive–compulsive disorder, social phobia, personality disorders, post-traumatic stress disorder, eating disorders and migraine (Altamura et al. 2011; Boylan et al. 2004; Chen and Dilsaver 1995; Fasmer 2001; Kessler et al. 1999; Low et al. 2003; Mahmood et al. 1999; McElroy et al. 2006; Merikangas et al. 2007; Otto et al. 2004; Regier et al. 1990; Simon et al. 2007; Strakowski et al. 1992). Alcohol abuse could be present in more than half of patients and frequently represents self-medication efforts, and it is particularly problematic during adolescence and early adulthood. The drug abuse pattern of BD patients concerns mainly stimulant drugs (Winokur et al. 1998).

Approximately one-third of BP-I patients suffer from one or more general medical conditions, and BP-I constitutes an important risk factor for 7 of 11 general medical conditions (Perron et al. 2009a; b). The most prevalent conditions are cardiovascular (e.g. hypertension, present in 35 %), endocrine (e.g. hyperlipidaemia, 23 %; diabetes, 17 % vs. 15 % for controls), alcohol use disorder (25 %), hepatitis C (5.9 % vs. 1.1 % of controls), lower back pain (15.4 % vs. 10.6 % of controls) and pulmonary conditions (e.g. COPD: 10.6 % vs. 9.4 % of controls) (Goldstein et al. 2008, 2009, 2011; Kilbourne 2005; Kilbourne et al. 2004; Soreca et al. 2008, 2009).

2.9 The Subjective Experience of Manic–Depressive Patients

Hearing what patients can say to describe their experience of living with the illness is important. It is also of value to take into consideration their narrations so as to better understand the nature and the whole spectrum of illness manifestations. Unfortunately, the value of these narrations is problematic because of their subjective nature, the limitations of the language when it comes to the description of unusual inner experiences and the large variability in the experience itself among patients. However, these narrations still constitute the only means to comprehend not only the negative but also the positive aspects of manic depression and its treatment (Jamison 1993; Jamison et al. 1980), the burden and the attitudes towards the illness and treatment with special focus on the subjective experience of adverse effects and the influence of religious, popular and philosophical beliefs. Most narrations share a pattern of tempestuous emotions, religious and/or mystical experience, paranoia, violence, impulsivity and periodicity. In order to understand the inner experience it is important to realize that existential issues are of prime importance. Religious and mystical themes often dominate the patients' existence. In this frame, both the positive and the negative consequences of the illness make sense as they are embedded in the life of the patient.

As mentioned above, depressed mood is the pathological equivalent of grief and mourning and is characterized by a painful negative emotion, which is typically experienced as worse than severe physical pain. This experience is out of proportion and out of frame of existing stimuli and is characterized by groundless apprehensions with severe inner turmoil and torment. The suffering is persistent although in milder cases spontaneous fluctuation even during the same day can occur (typically worse in the morning or in the afternoon). It is paradoxical that although depressed patients experience a hypervigilant state with heightened perception of pain, many also experience an inability to experience emotions, and they are even unable to cry. Anhedonia makes the patient to abandon previously enjoyed pastimes. In milder cases, it is manifested by decreased interest in hobbies and life, but in most severe cases it leads the patient to lose feelings for loved significant ones (kids, spouse). Patients typically describe their environment as without any colours, as if everything is black and with shades of grey. This is a quite odd experience which alienates patients from others and from the environment. Depersonalization and derealization might follow and often the experience has a psychotic-like quality.

Depressed patients usually experience a form of lethargy, mental and physical paralysis and suffocation. Often they experience a tearing of their chest and internal organs as a form of tearing of existence and self. Trivial things and senses could be painful for no reason. Casual and irrelevant memories could be dreadful and horrifying. Even pleasant events and beautiful things trigger despair because of the realization of inability to feel joy. Patients cannot find peace and cannot rest. Sleep is equal to losing consciousness without rest. Cognitive slowing and difficulty in concentration might lead to indecisiveness and feelings of inefficiency. The difficulty in thinking makes patients tied to the actual consciousness of the moment. Depression triggers the dark and negative side of existential dilemmas and fears, including sense of purpose, life and death, values and morality and religious beliefs, thus making internal experience unbearable. Pain, lack of motivation and psychomotor retardation makes even everyday basic casual activities an effort and trigger a vicious cycle of emotional downfall.

During periods of mania, patients experience a pervasive sense of well-being which acts as background for all their experiences and decisions during this period. They often feel that nothing is beyond their abilities. They have a time urgency, their creativity and learning ability are somewhat increased during the mild phase of the episode, and they tend to make notes of everything. Their omnipotent feelings make them feel that money is not important and there are no consequences concerning any risky or compulsive behaviour they take (Goodwin and Jamison 2007).

Often this well-being is accompanied by pleasurable or stimulating somatic sensations, like tingling of the spinal cord or the solar plexus. The experience of somatic sensations changes, and the patients are able to withstand extreme situations like running naked and barefooted on the streets in the cold or on the snow. They often have a ‘heightened sense of reality’ (Henderson and Gillespie 1956) which makes them feel in intimate contact with the universe, all the creatures and God. Sometimes they might feel fused with them, identify with them, and almost they lose identity. Senses become more acute, perception increases, and this leads to a complete

change in the awareness of the environment. Although this is not related to psychotic phenomena per se, the increased awareness of details, the emotional investment of them and on trivial things as well as the simultaneous perception of different objects and situations make the whole experience outside the range of sanity. It is similar in many ways to the experiences induced by psychomimetic substances and in the past might had been considered mystical religious or spiritual trance conditions.

The subjective experience of patients during a mixed episode is reported to be far worse in comparison to a depressive one. Mixed episodes are characterized by the experience of extreme anguish and mental pain as a result of the combination of depression with acceleration, psychoticism and confusion.

2.10 List and Definitions of Symptoms and Signs

It is important to have a list of signs and symptoms along with their description readily available. The following list serves the purpose of a short encyclopaedic lexicon of the most basic and important clinical terms used in the study of manic depression. The list is organized in domains (mood, psychomotor disorder, neurocognitive disorder, thought disorder, psychotic symptoms, somatic and neurovegetative symptoms and behavioural disorder).

A list of comparison of symptoms between depression and mania organized in hypothetical bipols is shown in Table 2.3.

2.10.1 Mood

1. *Euthymia* refers to the normal range of mood and the absence of any disorder.
2. *Mourning* refers to the experience of sadness as a consequence of a loss of a loved one. It includes crying, sadness and preoccupation with the lost person and related memories.
3. *Depressed mood* means that the patient experiences a 'negative' and unpleasant affect, and in Western cultures and languages, the words (or their linguistic equivalents) 'depressed', 'anguished', 'mournful', 'sad', 'anxious' and 'blues' are used. The word 'depressed' is increasingly used because of the higher information (partially because of the Internet) the public has today on depression. The way and the words the patient uses to describe this experience depend on the cultural and educational background and can focus on bodily function or on existential and interpersonal dysphoria and difficulties. Somatic complains are more prominent in milder cases usually seen in the primary care setting in patients with anxious depression. These cases were considered to suffer from 'masked' depression.
4. *Anhedonia* refers to the inability to experience normal emotions. Frequently, patients with anhedonia are incapable of even feeling the depressed affect, and they can't even cry. The patient abandons activities which in the past were a source of joy and gives up interest in life. Patients with more severe depression

Table 2.3 List of manic and depressive bipols of symptoms and signs. Almost any combination is possible in real-life clinical practice and especially in the frame of mixed mood states

Depressive episode	Manic episode
Mood	
Dysphoria	Euphoria
Depressed mood	Mood elevation
Anhedonia	Excessive interest in pleasurable activities
Indifference/irritability	Irritability
Mood lability	Mood lability
Passivity	Anger
Thought disorder	
Crowded thoughts	
Racing thoughts	Racing thoughts
Slow thinking	Flight of ideas
Concentration difficulties	Distractibility
Difficulty in thinking	Sharpened or unusually creative thinking
Low self-esteem	Inflated self-esteem or grandiosity
Depressive thought content	Manic thought content
Hopelessness/helplessness	Omnipotency
Feelings of guilt	Expansive attitude/impulsivity
Somatic symptoms	
Insomnia or hypersomnia	Decreased need for sleep (hyposomnia)
Loss of libido	Increased sexual activity
Tiredness/fatigue/leaden paralysis	High energy level
Weight/appetite changes	Loss of weight due to hyperactivity
Psychomotor change	
Inertia	Full of vitality
Decreased speech	More talkative than usual or pressure to keep talking, articulate and jocular
Decrease in goal-directed activity	Increase in goal-directed activity
Psychomotor slowing/retardation	Psychomotor acceleration
Psychomotor agitation	Psychomotor agitation
Passive behaviour	Verbal/physical aggressiveness
Stupor/catatonia	Stupor/catatonia
Psychotic features	
Delusions	Delusions
Hallucinations	Hallucinations
Sociality	
Psychosocial withdrawal	Increased sociability
	Loss of social inhibitions
	Impulsive behaviour/disinhibition
Others	
Logorrhoea	Mutism

(continued)

Table 2.3 (continued)

Depressive episode	Manic episode
Suicidal thoughts/attempts	Omnipotent thoughts
Anxiety	Anxiety
Indecisiveness	Impulsivity
Relative preservation of insight	Lack of insight

are indifferent even concerning their kids or spouse and isolate themselves. The difference from the flat (blunted) affect seen in schizophrenia is that anhedonia is itself painful. As depression starts remitting, anhedonia is one of the first symptoms to remit.

5. The term *elevated mood* refers to a state of elation, overconfidence and enjoyment, with the person being cheerful, laughing, punning and making happy and expressive gestures. It is not always pathological.
6. *Euphoria* refers to a pathologically too much elevated mood that is inappropriate to real events. It is considered to constitute the opposite pole of 'depressed mood' with 'normality' in the middle. It is interesting and important that experiencing a euphoric mood is pleasant; thus, patients are reluctant to receive treatment.
7. *Euthymia*: Although the original Greek word clearly suggests an elevated mood (in good spirits, a bit lower than during euphoria), the term is used currently in the international literature to denote a normothymic condition.
8. *Expansive mood* is a condition with the patient expressing his feelings without restraint and control, and behaviour is usually coloured by thoughts of grandiose.
9. *Emotional lability* refers to unstable and rapidly changing emotions often because of hyperreactivity to environmental stimuli. It is not always pathological.
10. *Irritable mood* is a state in which the person is easily annoyed by external stimuli and expresses anger and hostility at a low threshold. The presence of an irritable mood is often the cause for misdiagnosis of the patient, especially in combination with lability and mixed states.

2.10.2 Psychomotor Disorder

11. *Flight of ideas* refers to an acceleration of the thinking processes, which almost always manifests itself through rapid speaking. Speech could be coherent and thoughts unusually sharp; however, when speed is excessively high, they both become incoherent and fragmented with content changing abruptly. Associations could be based on rhyme or chance perceptions.
12. *Racing thoughts* refer to the experience of thoughts running fast inside the mind, but this is not evident in speech which is normal or even retarded and monotonous or in behaviour. The content of these thoughts could be manic and depressive but also trivial.

13. *Crowded thoughts*: A large number of thoughts pilling inside the brain, without racing or flying. The patient experiences a large number of them simultaneously occupying his consciousness without moving from the front stage, but instead they tend to accumulate and push each other for space in consciousness. They are seen mainly in depression, and their content could be depressive or trivial.
14. *Psychomotor acceleration* is considered to be the hallmark of mania, characterized by excessive activity which is goal directed, high energy and endurance as well as rapid, pressured speech.
15. In comparison, *psychomotor agitation* also refers to both mental and physical overactivity (pressured speech, restlessness, motor behaviour) usually accompanied by a feeling of an inner turmoil or severe anxiety, with the intensity being so great that in spite of the fact that the patient has normal arousal, most if not all of this activity is purposeless.
16. *Psychomotor slowing* means that the patient is inert and slow, both physically and mentally, but this does not always have an effect on overall performance although everything is done with much effort.
17. When psychomotor slowing is excessive, then *psychomotor retardation* appears, and it includes reduction or disappearance of spontaneous motor activity, slumped posture and gaze, reduced and slow speech and great fatigue.
18. *Stupor* appears in younger patients when the psychomotor retardation is so extreme that they are unable to function even concerning basic everyday needs. In more severe cases, motor immobility appears. It often constitutes an acute medical emergency. Essentially, the patient regresses to a primitive infantile functioning level, with inability to control even basic bodily functions. Physical health is greatly endangered because of immobility, bad nutrition and weight loss, constipation, circulation problems, etc. There is immobility and a strong resistance to all attempts at movements, or on the contrary there is so much muscle relaxation that the body parts can be moulded onto any position and remain there, no matter how inconvenient the position is. Although in most patients there is clouding of consciousness, most of them are able to recall their experience during periods of stupor and the great distress that accompanies it.
19. *Catatonia* is defined as a complex condition which can include diverse symptoms and signs like motor immobility or on the contrary excessive purposeless motor activity not influenced by external stimuli, motiveless negativism, mutism, peculiar or stereotyped movements, mannerisms, grimacing and sometimes echolalia or echopraxia.
20. *Fatigue* is a common problem in all mental disorders but especially in mood disorders and includes feeling tired or weak, sleepy and sometimes irritable.

2.10.3 Neurocognitive Disorder

21. The term *neurocognitive* is often used with reference to higher cognitive function, like attention, concentration, memory, praxis, etc., and in psychiatry

in contrast to the term *cognitive* which often is used with reference to the thought content or style and relates to cognitive therapy. Bipolar patients constitute a clinically heterogenous group; however, they seem to perform poorly on most neuropsychological tests in comparison to healthy controls. They seem to suffer from deficits especially related to attention, inhibitory control, spatial working memory, semantic verbal fluency, verbal learning and memory and maybe executive function, especially when considering the more severe and psychotic end of the bipolar spectrum. Verbal memory and probably executive function impairments may represent a trait rather than a state marker.

22. In extreme cases, neurocognitive disorder is so severe, especially in elderly patients that the picture resembles that of a dementing disease, thus is called *pseudodementia*. However, it seems that at least half of these patients do in fact suffer from a dementing process at its early stages, and later they manifest a formal dementia syndrome. If one looks at the problem from another point of view, depression with mild cognitive disorder may be either the first manifestation or a risk factor for the development of dementia, especially when combined with a family history of dementia.

2.10.4 Thought Disorder

23. *Depressive thought content*: Depressed patients are characterized by a negative evaluation of the self, the world and the future (the negative cognitive triad). In this frame, the depressive thought content includes pessimism, low self-esteem and low self-confidence, ideas of loss, deprivation and guilt, helplessness and hopelessness and ultimately thoughts of death and suicide. The extent to which this negative way of thinking is primary or secondary is a matter of debate.
24. *Clang association*: It refers to the condition when the patient's thought association and subsequently the speech are directed by the sound of a word rather than by its meaning. Thus, words are not connected in a logical way and punning and rhyming serve as the drive.
25. *Thoughts of guilt* concern self-reproach, self-accusing and feeling the need for punishment. Thoughts and feelings of guilt are largely normal, and they could appear during a mood disorder because of the disability the disorder causes and the inability of the patient to fulfil his/her obligations towards significant others. In this frame patients might also feel shame. However, when the intensity and the content are excessive or even inappropriate, then thoughts of guilt should be considered to be part of the symptoms, and in more severe cases these thoughts could obtain a delusional character.
26. *Thoughts of death*: Thoughts of death are particularly important because they might eventually lead to suicidal behaviour. The common belief that inquiring about such thoughts provokes suicidal behaviour has no scientific basis. On the contrary, patients are often relieved this way. These thoughts include thoughts

that the person will die and often the wish to die in some way so as to leave the suffering behind; this way they lead to suicidal ideation.

27. *Suicidal ideation* refers to specific thoughts of killing oneself. It has many different forms, ranging from indirect expression (e.g. in a wish not to wake up or to die from a disease or an accident) to suicidal obsessions (urges or impulses to destroy oneself) and finally to elaborate planning of suicide. Some patients behave in a passive self-destructing way (e.g. careless driving or walking), while others plan their death in detail leaving notes and making sure no help will come on time.
28. *Manic thinking* is excessively positive and optimistic. It is characterized by inflated self-esteem, grandiose sense (concerning importance, power, knowledge or identity), overconfidence and sense of high achievements and abilities. Manic patients are refractory to explanations and confrontation, and to a significant extent they lack self-examination and insight; because of this lack of insight, mania nearly always, sooner or later, acquires a delusional character.

2.10.5 Psychotic Features

29. *Mood-congruent depressive delusions*: Often depressed thoughts could acquire a delusional severity and delusions congruent with depressive mood appear. Their content concerns inappropriate or over-exaggerated thoughts of guilt, sin, worthlessness, poverty and somatic health. Nihilistic delusions constitute a special kind under which the patient believes that parts of his/her body are missing. Delusions concerning persecution and jealousy, although seemingly non-congruent, could be mood-congruent also, if they can be explained by or strongly related to thoughts of sin, guilt, jealousy or worthlessness. This kind of delusional thought makes a parent kill his/her family so as to save them from moral or physical corruption, and then he/she commits suicide.
30. *Nihilistic delusions (Cotard's delusion or Cotard's syndrome, negation delusion)*: This special kind of delusions is related to depressive mood and concerns the delusional belief that all or parts of the patient's body are missing or rotten or decomposing; their internal organs are rotten or solidifying or even are actually dead; the world and everything related to it have ceased to exist.
31. *Mood-congruent manic delusions*: During manic episodes usually the thought content becomes delusional and includes delusions of exceptional mental and physical fitness or special talents. It also may include delusions of wealth, some kind of grandiose identity or importance. Sometimes the delusion can be so excessive that the identity itself changes (e.g. the patient believes that he is incarnation of a messiah or a prophet, etc.). Delusions of reference and persecution are considered to be mood-congruent on the basis of the belief that jealousy of the others at their special abilities is the cause of problems.
32. *Mood-incongruent delusions*: Various delusional ideas seemingly non-congruent (e.g. ideas of persecution or reference) could eventually be understood

as arising from the grandiose sense of self and the belief of the patient that this importance causes the others to envy. However, sometimes there are delusions whose content has no association to current mood (e.g. bizarre delusions without contextual relationship to mood). Sometimes a mixed mood episode can manifest itself with 'mood-incongruent' delusions, e.g. grandiose delusions in the presence of depressed mood.

33. *Depressive mood-congruent hallucinations* are hallucinations whose content is depressed (e.g. voices accusing or humiliating). Depressive mood-congruent hallucinations have an unpleasant content, and they cause significant additional distress to the patient. Sometimes they command the patient to commit suicide and even dictate the method.
34. *Manic mood-congruent hallucinations*: Sometimes it is considered that the intense experience of a mood episode, especially a manic one is characterized, causes such a vivid internal experience that the patients feel they can hear or see their thoughts (e.g. hear hymns or live in the paradise).
35. *Mood-incongruent hallucinations*: These are hallucinations unrelated to the current mood state.
36. *Insight*: Classically, usually the depressive episodes are characterized by a fair degree of insight with the exception of the severer psychotic cases. On the contrary, manic episodes are routinely characterized by a significant lack of insight, and thus clinicians must routinely obtain basic information from significant others. This lack of insight might lead to refusal of any treatment and to the need for an involuntary admission to a hospital.

2.10.6 Somatic and Neurovegetative Symptoms

37. *Anorexia and weight loss*: Anorexia and weight loss are considered to be reliable signs of depression. They can both be considered in the frame of a generalized inability to enjoy things (anhedonia). Weight loss is seen sometimes in paranoid patients who are afraid that food is poisoned, and this should not be confused with anorexia and weight loss in the frame of depression. Weight loss is also frequent in cases of malignant disease so a full medical investigation should accompany any patient with changes in appetite or weight.
38. *Weight gain* has been relatively recently recognized as a depressive feature and could be the result of overeating, decreased activity or both. Apart from its devastating effect on the self-confidence and self-image, it can worsen the general somatic health especially in patients that become obese and suffer from metabolic syndrome.
39. *Insomnia* is one of the hallmarks of depression and one of its most disturbing features. There are many types of insomnia, that is, difficulty falling asleep (initial insomnia), multiple awakenings during the night (middle insomnia) or early morning awakening (terminal insomnia). Insomnia prolongs the depressive agony round the clock. Some patients try to self-medicate and solve the

problem by alcohol or drug abuse (sedatives or hypnotics), but both eventually worsen the problem partially because of tolerance and dependence problems and partially because they both further destroy the architecture of sleep. Unipolar depressed patients tend to exhibit insomnia stereotypically episode after episode, and characteristically in spite of extreme fatigue, they rarely oversleep.

40. *Hyposomnia*: The term suggests a decreased need for sleep. That is, the patient feels energetic on awakening even though he slept for short periods. Some patients feel fresh and energetic even though they haven't slept for days. This condition is usually seen during manic episodes, and sometimes it heralds the beginning of such an episode. It is not synonymous to insomnia.
41. *Hypersomnia*: Some patients, especially younger ones and females, often sleep too much and find it difficult to get up from the bed in the morning. Along with the other atypical features, it is considered to be a marker for an underlying bipolar illness even in case no other bipolar feature is present. This condition should be differentially diagnosed from a number of medical conditions including narcolepsy and the Klein–Levin syndrome. In spite of prolonged sleep, depressed patients are characteristically tired in the morning, meaning that even prolonged sleep is not refreshing for them. The change in the pattern of sleep disruption with insomnia alternating with hypersomnia or hyposomnia suggests the presence of a bipolar illness rather than a unipolar depression.
42. *Circadian dysregulation*: Although many circadian functions could be disrupted in depressed patients, mainly the disturbance of sleep rhythms has been adequately studied. This disturbance includes deficits in delta sleep and more intense rapid eye movement (REM) activity during the first third of the night. A marked shortening of REM latency (i.e. the time from the onset of sleep to the first REM period) is considered to be characteristic for depression of any type and seen even in remitted depressive patients and their healthy relatives.
43. *Seasonality*: Seasonal (especially autumn–winter) emergence or worsening of depression has been recognized since antiquity, and mood has been related to the period of the year. Most patients seem to experience increased energy and activation during spring and the opposite during the fall and winter. Usually patients with strong seasonality also have reverse neurovegetative symptoms (fatigue, crave sugars, overeat and oversleep). In some patients seasonality is so concrete and important that modern classification includes a seasonal pattern for mood disorders.
44. *Sexual dysfunction*: Depressed patients classically report a decreased sexual desire and activity, while additionally some women manifest a temporary interruption of their menses. Sexual dysfunction especially in females could lead to marital conflict and a psychodynamic/psychotherapeutically oriented therapist could mistakenly ascribe depression to the marital conflict with profound negative effects on the therapeutic outcome. Treating the sexual dysfunction or its consequences and leaving depression untreated is not uncommon and includes even surgical or unusual therapeutic interventions. An additional problem is that treatment with antidepressants often has sexual dysfunction as an adverse

effect. The recent emergence of agents that treat impotence (e.g. sildenafil, tadalafil) could add a new method to treat this problematic symptom, but this should never move the focus of treatment away from depression.

45. *Increased sexual desire and activity*: This is typical for manic episodes, but also a subgroup of depressed patients may manifest increased sexual drive or activity, and usually they also manifest other atypical or 'reversed' features. Thus, if seen in the frame of depression, it heralds the presence of a depressive mixed episode. The increased sexual appetite usually leads to sexual indiscretion accompanied by a risky sexual life, often leading to marital problems, multiple separations or divorces, alcohol and drug abuse, gambling and sexually transmitted diseases like AIDS.

2.10.7 Behavioural Disorder

46. *Logorrhoea*: It refers to pressured, excessive and not always coherent speech, which is often uncontrollable. It is observed during manic episodes. Speech could be completely uncomprehending, with destroyed syntax and loose associations, often posing diagnostic dilemmas (e.g. from stroke). Other similar terms used are tachylogia, verbomania and volubility.
47. *Impulsive behaviour*: During mood episodes, either manic, depressive or mixed, patients tend to exhibit impulsive behaviour. Especially during manic episodes they tend to be impulsive, disinhibited and meddlesome. They are intrusive with increased involvement with others, have poor social judgment and engage in a variety of activities without control or restrain (including aggression, sex, gambling, drug and alcohol abuse, spending, making gifts, risk taking, travelling, etc.). Impulsive behaviour is the part of symptomatology that causes most problems and especially financial and interpersonal. In some cases even suicide could be acted on an impulsive basis.

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