Chapter 1

# Bipolar disorders in DSM-5: changes and implications for clinical research

Michael J. Ostacher, Mark A. Frye, and Trisha Suppes

## Introduction

The focus of this chapter is the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) conceptualization of bipolar disorder and the associated implications for DSM-5 diagnostic and clinical research. In comparison to earlier DSM iterations, there are several fundamental revisions in DSM-5 criteria and nomenclature. *First*, the diagnosis has moved from the inclusive categories of "Mood Disorders" in DSM-IV/IV TR and "Affective Disorders" in DSM-III (each of which included all depressive and bipolar disorders) to its own stand-alone category, Bipolar and related disorders – distinct from depressive disorders. *Second*, the fundamental Criterion A for the diagnosis of a manic or hypomanic episode now requires increased energy or activity to be present with elevated, expansive, or irritable mood. *Third*, mixed episodes – the presence of a concurrent manic and major depressive episode – has been removed and replaced with a "mixed specifier" feature, allowing "mixed" to be used when subsyndromal depressive or manic/hypomanic symptoms are present in the alternate syndromal episodes. *Fourth,* antidepressant or other treatment-induced full-syndromal mania or hypomania is no longer diagnosed if symptoms persist and meet episode criteria beyond the physiological effects of the drug, essentially allowing all people whose manic symptoms appear during antidepressant treatment and continue despite stopping the antidepressant to be formally diagnosed with bipolar I or II disorder. Finally, an "anxious distress" modifier has been added as anxious symptoms are commonly present in bipolar disorder but are not accounted for in its diagnostic criteria. Short-duration hypomania with depressive episodes was considered as a diagnostic entity and ultimately included in Section III as a condition for further study; it should also be noted that the Not Otherwise Specified (NOS) category is now replaced throughout DSM-5 by Other Specified and an Unspecified category. The Other Specified is intended to identify four distinct bipolar spectrum conditions, including short-duration hypomania with depression.

DSM-5 is intended to bridge the gap between the evidence collected in the Research Domain Criteria (RDoC) context – "new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures" – and practice. The National Institute of Mental Health (NIMH)'s RDoC sets up a framework for the understanding of domains of brain functioning and impairment independent of the current diagnostic structure. It is hoped and anticipated that such work will allow for a better understanding of psychopathology across clinical entities (Insel et al., 2010). While RDoC is not intended to provide clinical insights and direction, it is anticipated that findings from studies focused on brain function and not diagnostic categories will be useful to further our understanding of the underlying causes of mental illness and eventually in a clinical and treatment context. These changes will be reviewed in their historical context and implications for future research discussed.

## DSM-5: process and development: bipolar and related disorders as a distinct chapter

The workgroup responsible for the development of the bipolar and related disorders chapter initiated with the

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Mood Disorders Workgroup that arose out of DSM-IV. As with all workgroups, the group was internationally represented to prevent the regionalism that might occur if it were left to US or North American representation alone and to include multinational perspectives in DSM-5. This is of particular importance for bipolar disorders, as much of the longitudinal study of the disorder has been undertaken outside the USA. DSM-5 as a whole was developed in parallel and with full knowledge of the NIMH's RDoC initiative and was intended to complement it (as RDoC's work has only recently begun) and to use its finding in further iterations, and was written with the knowledge that the World Health Organization's International Classification of Diseases, 11th revision (ICD-11) classification system was to be completed in 2015 or so. Particularly the early phases of development of the DSM-5 highlighted our overall lack of progress in understanding the underlying neuroscience of mental disorders, as the original charge for DSM-5 was to base the diagnostic changes on neuroscience, but it quickly became clear that the state of the science did not allow this.

The process and development of DSM-5 as a whole and of the bipolar and related disorders chapter have been described elsewhere (Kupfer et al., 2011; Regier et al., 2013), but a general review of it is merited here. Because of the determination that DSM-IV's classification system was outdated due to its descriptive and phenomenological approach, it was felt that an organizational framework in which disorders would be grouped instead based on known pathophysiology, genetics, and risk would be combined with findings from neuroscience (e.g., imaging and neuropsychology) and from clinical experience. With regard to bipolar disorder, it became evident that the genetic liability for psychotic disorders and mood disorders was somewhat continuous and overlapping, suggesting a continuum of risk. For this reason, a more nuanced classification system was developed in which bipolar and related disorders would be a classification grouping between schizophrenia spectrum and other psychotic disorders, and depressive disorders (Phillips and Kupfer, 2013). This did away with the mood disorder classification, *per se*, and is consonant with the developmental and dimensional approach to classification central to DSM-5. Ultimately this new structure, rather than seeing bipolar disorder as a distinct entity (as having its own chapter would suggest), instead posits it as a waypoint along a continuum of shared etiology, neuroscientific evidence, and symptomatology. While our understanding of the biologic basis of these illnesses is still limited, the genetic evidence based on large samples clearly indicates a continuum across these broad categories.

The question of why bipolar disorder was not included in psychotic disorders needed to be addressed. It is estimated that half to two-thirds of patients with bipolar I disorder have psychotic symptoms in their lifetime, and there is strong family genetic overlap between schizophrenia, schizoaffective disorder, and bipolar disorder (Cosgrove and Suppes, 2013). Genetic polymorphisms such as the an intron of the L-type voltage-dependent calcium channel alpha 1C subunit (*CACNA1 C*) confer risk in both schizophrenia and bipolar disorder, but no evidence exists that the risk for the most obvious symptom overlap between existing diagnoses – psychosis – is accounted for by that variant. Pharmacological treatments for psychotic disorders and bipolar disorder also overlap, at least in terms of the efficacy of antipsychotics, yet the most specific treatment for bipolar disorder, lithium (and, to some extent, lamotrigine), has little evidence for its use in psychotic disorders. While the biological evidence was tantalizing, ultimately a decision was made to keep bipolar disorder separate from psychotic disorders and in its intermediate place. If RDoC is successful in finding processes common across disorders – for example, a neurodevelopmentally continuous model of psychosis – this could certainly change future iterations of DSM (Insel et al., 2010; Cosgrove and Suppes, 2013).

## Criterion A: energy and activity

There is no dispute that in clinical practice the diagnosis of bipolar disorder has expanded, especially since the inclusion of bipolar II disorder, a new diagnosis in DSM-IV – and perhaps in part because of the marketing of drugs for the treatment of bipolar disorder, notably second-generation antipsychotics and anticonvulsants. There was concern that this would be perpetuated in DSM-5 through the inclusion of broader criteria for diagnosis, and the committee in its overall review of potential changes did consider changes that could have broadened the criteria for bipolar II disorder but ultimately did not do so (Frances, 2014; Suppes et al., 2014a). In spite of the generally open nature of the DSM-5 committee process, there remained misunderstandings about how the criteria would be settled upon. One way in which the broadening or narrowing of the bipolar disorder diagnosis was addressed was considering whether

adding the requirement that patients exhibit increased energy and activity along with elevated, expansive, or irritable mood in order to be diagnosed with a manic or hypomanic episode should be an AND or an OR requirement. This was not without controversy. Jules Angst, for example, has pointed out that this might result in making the diagnosis more specific and limiting, in that people who in the past would meet criteria for mania – meeting mood criteria with accompanying symptoms but without increases in energy or activity (Angst, 2013) – would no longer be diagnosed as manic. Overall this change has been seen as making the threshold for diagnosis of bipolar I as more specific but no less sensitive. This represents an opportunity in the face of this to potentially differentiate between mood states using the structure that RDoC provides to further our understanding of this illness.

## Mixed features specifier

See Table 1.1.

**Table 1.1** Mixed features specifier

| |
|---|
| **With mixed features:** The mixed features specifier can apply to the current manic, hypomanic, or depressive episode in bipolar I or bipolar II disorder: |
| **Manic or hypomanic episode, with mixed features:** |
| A Full criteria are met for a manic episode or hypomanic episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania: |
| 1 Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful) |
| 2 Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others) |
| 3 Psychomotor retardation nearly every day (observable by others; not merely subjective feelings of being slowed down) |
| 4 Fatigue or loss of energy |
| 5 Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick) |
| 6 Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide |
| B Mixed symptoms are observable by others and represent a change from the person's usual behavior |
| C For individuals whose symptoms meet full-episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, due to the marked impairment and clinical severity of full mania |
| D The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) |
| **Depressive episode, with mixed features:** |
| A Full criteria are met for a major depressive episode, and at least three of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression: |
| 1 Elevated, expansive mood |
| 2 Inflated self-esteem or grandiosity |
| 3 More talkative than usual or pressure to keep talking |
| 4 Flight of ideas or subjective experience that thoughts are racing |
| 5 Increase in energy or goal-directed activity (whether socially, at work or school, or sexually) |
| 6 Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) |
| 7 Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia) |
| B Mixed symptoms are observable by others and represent a change from the person's usual behavior |
| C For individuals whose symptoms meet full-episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features |
| D The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) |

*Note:* Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.

*Source:* American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th edn). Arlington, VA: American Psychiatric Publishing.

Mixed episodes in DSM-IV were defined as meeting full criteria for concurrent manic and major depressive episodes for a week. As such, these episodes by definition were limited to bipolar I disorder, were in practice rarely seen when accurately diagnosed, and did not allow the clinical observation that depressive and manic *and* hypomanic symptoms were frequently seen together but not necessarily present in a full syndromal picture. Mixed episodes as diagnosed in DSM-IV did not account for subthreshold symptoms of mania (or hypomania) when present during a depressive episode, nor for subsyndromal symptoms of depression to be accounted for during manic or hypomanic episodes.

Much of the epidemiological evidence suggested that mixed symptoms of depression and mania/hypomania were present in many patients who did not meet full mixed-episode criteria, and that the presence of such subsyndromal symptoms was predictive of illness severity and future course (Suppes et al, 2005; Frye et al., 2007; Goldberg et al., 2009; Perlis et al., 2010). While there is not direct biological evidence responsible for this yet identified, it is clear that broadening the acknowledgment that "mixed" symptoms occur both in mania and depression (including unipolar depression, though not discussed in this chapter) reduced the strictly bounded concept of the mixed episode to one that clinicians face in clinical practice. One may consider that it might not have been possible to recognize this unless the limitations of DSM-IV were apparent in practice. Aside from biology, perhaps the most important implication of this change will be in the epidemiology of bipolar disorder and depression, as it is unknown whether changing the criteria in this way will have an impact on the prevalence of either bipolar disorder or depression, as patients with major depression who meet the mixed features specifier during episodes of depression may no longer be diagnosed with a bipolar spectrum disorder.

As mixed states tend to occur in the context of clinical features – early onset of illness, prolonged periods of instability, frequent episodes, suicidal behavior – and comorbid substance use and stress-related disorder, the presence or absence of mixed symptoms may represent a rich area for understanding underlying and interacting psychopathology (Swann et al., 2013). Patients tend to come to treatment complaining of symptoms, not problems in behavioral or neurophysiological domains, so this parsing of mixed symptomatology provides an opportunity for studying selected groups of patients.

## Short-duration hypomania with depressive episodes

As described above, some have proposed that inclusion of bipolar II disorder in the DSM, beginning with DSM-IV, is responsible for the more liberal use of the bipolar disorder diagnosis in practice (Frances and Jones, 2012). Nevertheless, the clinical relevance of shorter-duration hypomanic episodes (2 days rather than the 4 days required by DSM-IV) was discussed and considered as a change in the criteria for a hypomanic episode. Some data suggest that, during the course of major depressive disorder, a high proportion of patients will ultimately develop a bipolar spectrum picture if shorter duration of hypomania is included. It may be that such an entity does represent a continuum between major depressive disorder and bipolar II disorder, or even that bipolar II disorder should be redefined in such a way. The significance of short-duration hypomania remains to be determined, however, and the biological and longitudinal coordinates associated with it yet to be explored fully. For instance, it is unclear whether short-duration hypomania is a pathological entity itself or whether its prevalence in the general population (i.e., those who have never had a depressive episode) is such that it is expected within the range of average experience. While detailed consideration was made for changing the duration criterion for a hypomanic episode to less than 4 days, the overall data were not adequately strong and implications for prevalence changes significant, so that it was decided more focused studies were needed on this potential subtype of bipolar disorder before such changes were made. Potentially if significant strides are made in our understanding of the biological basis of these illnesses, the distinction between syndromes and spectrum may become moot. Regardless, the placement of this potentially separate diagnostic entity into Section III is intended to encourage prospective studies of patients meeting the criteria for short-duration hypomania with a history of major depression episodes.

## Antidepressant or other treatment-induced mania

Patients exposed to antidepressants have long been known to develop mania or hypomania, but it is not known whether this is an entirely causal relationship. Patients with bipolar disorder develop mania while on antidepressants. Patients without any prior history may

also develop mania or hypomania during a period after the initiation of antidepressant treatment. This has left may patients who have developed mania or hypomania after antidepressant treatment without a formal bipolar I or II disorder diagnosis, but left, in DSM-IV, in the category of bipolar disorder NOS. While the diagnosis of substance-induced mania or hypomania remains in DSM-5 (generally reserved for symptoms in the context of use of drugs such as stimulants and cocaine), there is now specific language that states that, if full syndromal symptoms of mania persist that meet duration criteria after the physiological effects of a drug are no longer present, a diagnosis of mania (bipolar I disorder) or hypomania (bipolar II disorder) should be made:

> Manic symptoms or syndromes that are attributable to the physiological effects of a drug of abuse (e.g., in the context of cocaine or amphetamine intoxication), the side effects of medications or treatments (e.g., steroids, L-dopa, antidepressants, stimulants), or another medical condition do not count toward the diagnosis of bipolar I disorder. However, a fully syndromal manic episode that arises during treatment (e.g., with medications, electroconvulsive therapy, light therapy) or drug use and persists beyond the physiological effect of the inducing agent (i.e., after a medication is fully out of the individual's system or the effects of electroconvulsive therapy would be expected to have dissipated completely) is sufficient evidence for a manic episode diagnosis (Criterion D).
>
> (American Psychiatric Association, 2013)

This change in language significantly reduces the likelihood that a bipolar diagnosis will be missed, although for hypomania clinicians are cautioned that if there are only limited subsyndromal symptoms consistent with hypomania (e.g., irritability, edginess, agitation), these are not to be taken as adequate to make a bipolar diagnosis. The biological factors associated with susceptibility to mood elevation symptoms while under treatment with an antidepressant remain unknown, although several putative targets have been identified (Frye et al., 2015). Understanding how different circumstances can cause symptom change versus 'unmask' an underlying bipolar diathesis is an active area of current and appropriate future research targets.

## Anxious distress modifier

Co-occurring anxiety disorders are common in bipolar disorder, including posttraumatic stress disorder, panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder. There is clearly overlap between the diagnoses made in the current psychiatric nomenclature in DSM-5, however, and the presence of anxiety symptoms is quite common. This "comorbidity" may in fact be an extension of the underlying disorder, even if it is not precisely captured by the current diagnosis. Comorbidity, a term coined by Alvin Feinstein in 1970, referred to "a distinct clinical entity" (Feinstein, 1970) present along with another disease, and was intended to mean a fully independent illness. It is unlikely that anxiety present during depression, as an example, represents a distinct clinical entity, but rather an associated symptom. Not meeting criteria for a full anxiety disorder left anxiety symptoms outside the diagnosis. To address this, an "anxious distress" modifier was added to both depressive disorder and bipolar disorder diagnoses (Table 1.2). Longitudinal

**Table 1.2** With anxious distress modifier

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|---|
| **With anxious distress:** The presence of at least two of the following symptoms during the majority of days of the current or most recent episode of mania, hypomania, or depression: |
| 1 Feeling keyed up or tense |
| 2 Feeling unusually restless |
| 3 Difficulty concentrating because of worry |
| 4 Fear that something awful may happen |
| 5 Feeling that the individual might lose control of himself or herself |
| *Specify* current severity: |
| **Mild:** Two symptoms |
| **Moderate:** Three symptoms |
| **Moderate–severe:** Four or five symptoms |
| **Severe:** Four or five symptoms with motor agitation |

*Source:* American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th edn). Arlington, VA: American Psychiatric Publishing.

data suggest that anxiety during depressive episodes is associated with more suicidal behavior, longer illness duration, and lower likelihood of treatment response. Few controlled prospective clinical studies have been completed directly addressing this population of patients with bipolar disorder and anxiety symptoms (Sheehan et al., 2009, 2013; Suppes et al., 2014b). There are no specific biological correlates to anxiety in bipolar disorder, although it is easy to conceptualize its examination in an RDoC structured inquiry: propensity to anxiety and neural correlates of it may help understand disordered emotional processing, and establish potential biomarkers for risk, illness course, and precision treatments. Consideration of how symptoms of bipolar disorder and anxiety occur together may lead to fruitful neuroscientific investigation.

## Discussion

Is there a future for DSM? Always a provocative question and one asked frequently. Since DSM-III in 1980, the DSM has been central to the study of reliable clinical entitites – and its utility as such has been proven in many people's eyes. Arising from the work of Feighner et al. (1972), the DSMs since the third edition (American Psychiatric Association, 1980) have been the basis of nearly all *clinical* investigation in psychiatry. Successive iterations have become larger and more inclusive, but also have attempted – from clinical investigation and the beginnings of scientific inquiry – to refine the diagnoses with use to codify the suffering of patients with mental illness. Clearly it is not enough. Whether RDoC is the correct roadmap to understanding psychiatric illness remains to be seen, but it is clear that the road that DSM has taken will only advance our field so far: for nearly every psychiatric diagnosis for which there are validated treatments, perhaps the majority of patients who receive those treatments do not respond to them and remain ill. It remains uncertain, in bipolar disorder, whether the changes in DSM-5 will lead to more precise treatments for patients, although that ultimately is the goal. RDoC is not intended to lead to treatment, *per se*; it is intended to lead to a comprehensive understanding of the biological and behavioral underpinnings of mental illness (Insel et al., 2010) which in turn is seen as the path to future treatments. The gap remains.

If DSM is to remain relevant, it will have to be structured to be flexible enough to respond to changes in our understanding of the brain. Psychiatric genomics has had perhaps the largest impact on how DSM is structured – putting bipolar disorder on a continuum, perhaps, with psychotic and depressive disorders – but it has not fundamentally changed how we understand mental illness, or how we treat it. If that knowledge does come to light (or as it emerges), DSM will need to adapt to it. Until then it will remain what it is: a nosology of clinical observations that allow us, however imprecisely, to help our patients – and the best current guide we have for treatment research for mental illness (Ostacher, 2014).

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Chapter 2

# Prospects for the development of animal models of bipolar disorder

Trevor R. Norman

## Introduction

Although it is prevalent in a relatively small fraction of the population (between 1 and 2%), bipolar disorder (BD) is a severe and chronic mental illness (Belmaker, 2004). Phenotypical expression of the disorder is complex and alternates between depressed phases, mania, hypomania, and so-called "mixed states." Longitudinal studies of patients of with bipolar I (BPI) disorder show that they had symptoms of the disorder for about half of their time (Judd et al., 2002). Further, depressive symptoms predominated over manic/hypomanic symptoms or cycling/mixed symptoms (Judd et al., 2002). Pharmacological agents are the mainstay of treatment approaches but psychological therapies are utilized particularly for relapse prevention (Belmaker, 2004). Lithium, which was introduced for pharmacotherapy more than half a century ago (Cade, 1949), remains a most valuable mood stabilizer, but recent treatment approaches frequently utilize anticonvulsant medications for their mood-stabilizing properties (Keck et al., 1998). A more recent development has been the use of atypical antipsychotic drugs as mood stabilizers (Geddes and Miklowitz, 2013). While these treatment modalities are generally effective, they are not without their shortcomings. The need to find more effective, safe treatments is ever present.

In the quest for newer psychotherapeutic agents, the lack of an animal model founded in an appropriate, rational neurobiological basis restrains the development of specific treatments in BD (Berk et al., 2007). While the neurobiological basis of BD has been extensively investigated along with the mechanism of action of effective therapeutic agents, it is clear that both the underpinning biology of the disorder and the action of medications to attempt to normalize the behavioral abnormalities are far from simple (Goodwin and Jamison, 2007). While there is a strong genetic diathesis for BD a specific gene(s) has yet to be identified (Craddock and Sklar, 2013). Nevertheless, associations between genes and the occurrence of BDs in isolated populations have been identified (Shink et al., 2005). Wider associations between polymorphisms of candidate genes and BD have also been reported (Zhang et al., 2009). This gives rise to the possibility of using genetic engineering techniques to devise mouse models with abnormalities in these genes (knockout mice, provisional knockouts, overexpression) to examine their behavioral concomitants (Malkesman et al., 2009).

## Model considerations

No animal model so far devised has been able to reproduce the swing between behavioral states experienced by patients with BD. While it is clear that certain aspects of human psychiatric disorders cannot be replicated in animals, it has been suggested that an ideal bipolar animal model should exhibit face validity: it should exhibit oscillations between increases and decreases of the behavior being modeled (Goodwin and Jamison, 2007). The behavior should be normalized by chronic, but not acute, treatment with agents known to be effective in the human condition (i.e., lithium, anticonvulsants), i.e., it should show predictive validity. To fully establish such predictive validity antidepressant administration should tip the behavior in the manic direction (as occurs clinically). Construct validity, a common underlying abnormality between the human condition and the behavior in animals, is more difficult to establish since the cause or causes of BD are unknown. Given the unique difficulty of accomplishing the validity criteria, most animal models have focused on one pole of the disorder, depression or mania, alone. Currently more models of depressive disorder exist than for either mania or models which show oscillations between either of the two states. Increasingly it is recognized that an interaction between genes and environment is necessary in

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order to develop BD. Determining the types of environmental disturbances to pair with genetic alterations is a difficult task, but may be critical in producing useful models. An alternative notion is that of the so-called endophenotype in which models can provide useful insights into aspects of the disorder and its treatment (Malkesman et al., 2009). Endophenotypes are defined as well-characterized and readily quantifiable measures which are thought to involve fewer genes and fewer interactions between genes, although this remains an assumption. This approach is in its infancy, but using sound endophenotypes derived from clinical studies to develop preclinical animal models has the potential to be useful (Malkesman et al., 2009). In fact, animal modeling in psychiatry has relied almost exclusively on simpler phenotypes (Gould and Gottesman, 2006).

## Animal models of depression

It is clear that it is possible in animals only to model some symptoms of human depression. Symptoms such as guilt, depressed mood, and suicidal ideation are incapable of being "modeled" in another species. Nevertheless, some symptoms or clusters of symptoms can be modeled and provide useful insights into the etiological concomitants of depression. Further, the purpose for which the animal model is being utilized needs to be borne in mind. In the situation of drug discovery, for example, the notions of construct and face validity are likely to be less important than predictive validity: the extent to which activity in the behavioral test reliably and robustly predicts compound(s) which will be active in the clinic. Recently it has become apparent that some animal models are less reliable in this aspect than was previously believed (Kalueff et al., 2007).

Several well-known "depression" models have been developed in animals, primarily in rodents, but in earlier times utilizing other species as well. The utility of the models varies from screening tests, used to rapidly identify candidate molecules for further clinical development, to those which attempt to provide information about etiology of illness (or at least some symptoms of the disorder). A brief overview of some of the models is provided and their utility for the study of aspects of depression is assessed. A more detailed critique of specific animal models is beyond the scope of this limited review and is provided elsewhere (Cryan et al., 2002). Table 2.1 provides a summary of depression models and their validity based on various criteria.

**Table 2.1** Rodent models sensitive to the effects of antidepressant agents

| Behavioral test | Reliability | Specificity | Antidepressant response | References |
|---|---|---|---|---|
| Forced swim | High | High | Acute sensitivity; does not reliably detect SSRIs | Porsolt et al. (1977, 1978) |
| Modified forced swim | High | High | Acute sensitivity; differentiates antidepressants from different classes | Lucki (1997) |
| Tail suspension | High | High | Acute sensitivity; certain strains climb their tail | Mayorga and Lucki (2001) |
| Olfactory bulbectomy | High | High | Sensitive to chronic treatment only; mechanism of action not understood | Cryan et al. (1998); Song and Leonard (2005) |
| Learned helplessness | Medium | High | Sensitive to short-term treatments; ethical issues | Sherman et al. (1982); Willner (1984) |
| DRL-72 | Medium | Medium | Sensitive to short-term treatments | O'Donnell et al. (2005) |
| Neonatal clomipramine | Medium | ? | Limited testing conducted | Weiss and Kilts (1998) |
| Prenatal stress | ? | ? | Limited testing conducted | Dugovic et al. (1999); Alonso et al. (2000) |
| Chronic mild stress | Low | High | Sensitive to chronic treatment only; reliability between labs has been questioned | Willner et al. (1992); Forbes et al. (1996); Harris et al. (1997); Willner (1997) |
| Resident intruder | ? | Medium | Sensitive to chronic treatment only; requires further validation | Mitchell and Redfern (1997) |
| Drug withdrawal-induced changes in ICSS | High | Medium | Requires further validation | Kokkinidis et al. (1980); Harrison et al. (2001); Barr et al. (2002) |

Modified from Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs, *Trends Pharmacol Sci.* 2002: 23, 238–245.
DRL-72, differential reinforcement of low-rate 72 second schedule; ICSS, intracranial self-stimulation; SSRI, selective serotonin reuptake inhibitor.

## Behavioral models of depression

One of the earliest exemplars of the etiological/neurochemical type was the primate separation model which consisted of rearing monkeys apart from other animals in the first 6–12 months of life (Seay and Harlow, 1965). In social contact with conspecifics, separation-reared animals manifest a despair-like syndrome which was responsive to some medications and electroconvulsive shock. Studies in primates may be capable of uncovering interactions between genes, environmental challenges, and development, resulting in altered risk for psychopathology. Findings from primate models and their limitations have been reviewed (Nelson and Winslow, 2009). Use of non-human primates is limited by ethical and legal considerations but the separation models have been continued using rodent species. Prenatal stress, maternal deprivation, and early postnatal handling all seem to produce biochemical and behavioral changes in rodents that persist into adulthood. Furthermore, they exhibit a hyperactive hypothalamic–pituitary–adrenal (HPA) axis evident in the endocrine responses to stress. Whether such changes represent a strong factor for adult mental illness is unclear.

The forced swim or Porsolt test (FST) is mostly used as a screen for antidepressant-like effects of new molecules and is widely regarded as a standard test, at least as a first screen (Porsolt et al., 1977). The FST is more appropriately considered a model of antidepressant action rather than model of depression *per se*. The FST is reproducible and is sensitive to both acute and repeated doses of antidepressants. Animals are placed in a tank of water and the amount of time spent immobile is recorded. The posture of immobility was regarded as a measure of "behavioral despair," primarily because of the assumption that the animals have "given up hope of escaping" (Porsolt et al., 1978). Immobility can be considered a failure of persistence in escape-directed behavior. Others contend that the behavior may be evolutionarily conserved (Cryan et al., 2005). In any event, antidepressants decrease the immobility time. A variant of the test used primarily in mice is the tail suspension test (TST), which has been reviewed in detail elsewhere (Cryan et al., 2005). Of interest is that interventions linked to the susceptibility or induction of major depression in humans can induce the depression-like effect in the TST, i.e., increased immobility (Cryan et al., 2005).

Antidepressants in the clinic require chronic administration for efficacy and some animal tests which also depend on repeated administration have been developed. One test relies on the development of hyperactivity of rats or mice in an open field following bilateral removal of the olfactory bulbs (Cairncross et al., 1978). Bulbectomy has been extensively evaluated with respect to its predictive and face validity, although construct validity remains problematic (Song and Leonard, 2005). Chronic administration of antidepressant drugs reverses the hyper-locomotion due to bulbectomy, but acute doses are without effect. Antidepressants across all classes are active in the model and the predictive value is high even for molecules which do not rely exclusively on monoamine mechanisms for their antidepressant effects (Norman et al., 2012). Empirically bulbectomized animals exhibit many of the same biological features which have been demonstrated in patients with depression, such as alterations in receptor binding, sensitivity to neuroendocrine challenge, and circadian rhythm disturbance (Song and Leonard, 2005). Recently it has been shown that the model demonstrates disturbances in immune function similar to those found in clinical populations (Song and Leonard, 2005). Heuristically the bulbectomized model has much to recommend it for the study of some symptoms and biological features of depression.

Prolonged exposure to stressors has long been considered a precipitating factor in the development of depression in humans (Vinkers et al., 2014). While there is no doubt that chronic stresses in rodents produce demonstrable biological changes, which are reversible with antidepressant drugs, the relevance to depressive states may be less certain (Duman et al., 1999). The exposure of rodents to unpredictable mild stressors over an extended period (up to 6 weeks or more) produces a behavioral syndrome that resembles certain aspects of human depression. This so-called chronic mild stress model has been proposed as a valid model of human depressive conditions (Willner et al., 1992; Willner, 1997). This model relies on measuring a decrease in the preference for a sweetened solution (usually 1% sucrose or saccharin) in animals previously trained to prefer the solution instead of water. This is suggested as a model of the symptom of anhedonia. Restoration of sucrose preference can be taken as a measure of the extent to which a novel agent possesses antidepressant-like behavior. The model is generally regarded as having good face validity, although