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REVIEW

Predictive animal models of mania: hits, misses and future directions

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Mania has long been recognized as aberrant behaviour indicative of mental illness. Manic states include a variety of complex and multifaceted symptoms that challenge clear clinical distinctions. Symptoms include over-activity, hypersexuality, irritability and reduced need for sleep, with cognitive deficits recently linked to functional outcome. Current treatments have arisen through serendipity or from other disorders. Hence, treatments are not efficacious for all patients, and there is an urgent need to develop targeted therapeutics. Part of the drug discovery process is the assessment of therapeutics in animal models. Here we review pharmacological, environmental and genetic manipulations developed to test the efficacy of therapeutics in animal models of mania. The merits of these models are discussed in terms of the manipulation used and the facet of mania measured. Moreover, the predictive validity of these models is discussed in the context of differentiating drugs that succeed or fail to meet criteria as approved mania treatments. The multifaceted symptomatology of mania has not been reflected in the majority of animal models, where locomotor activity remains the primary measure. This approach has resulted in numerous false positives for putative treatments. Recent work highlights the need to utilize multivariate strategies to enable comprehensive assessment of affective and cognitive dysfunction. Advances in therapeutic treatment may depend on novel models developed with an integrated approach that includes: (i) a comprehensive battery of tests for different aspects of mania, (ii) utilization of genetic information to establish aetiological validity and (iii) objective quantification of patient behaviour with translational cross-species paradigms.

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Abbreviations
ADHD, attention deficit hyperactivity disorder; AMP, amphetamine; BPRS, Brief Psychiatric Rating Scale; cAMP, cyclic adenosine monophosphate; CDP, chlordiazepoxide; CGI, Clinical Global Impression; CPT, Continuous Performance Task; CVLT, California Verbal Learning Task; DAT, dopamine transporter; DBP, D-box binding protein; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; ERK, extracellular-related signal kinase; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GluR6, glutamate 6 receptor; GSK-3, glycogen synthase kinase 3; IGT, Iowa Gambling Task; IMPase, inositol monophosphatase; MARCKS, myristoylated alanine-rich C kinase substrate, MDMA, 3,4-methylenedioxymethamphetamine; NMDA, N-methyl-D-aspartic acid; PKC, protein kinase C, PPI, prepulse inhibition; SADS-C, Schedule for Affective Disorders and Schizophrenia; YMRS, Young Mania Rating Scale

Mania: from clinical presentation to the challenges of validating animal models

Mania is typically defined as a distinct period characterized by elevated, expansive or irritable mood (APA, 1994). The word derives from the Greek term 'μανία', describing a madness or frenzy (Liddell and Scott, 1940), and literary descriptions of the phenomenon date back to antiquity (Jackson, 1986). Mania, as the very first word of Homer's epic saga, *The Iliad*, was used to describe the uncontained rage of Achilles against Agamemnon (Lattimore, 1961). This term was also defined as a mental illness by Hippocrates, the famed Hellenic physician and teacher (Luneberg, 1897). By the early 19th century, mania was considered to be part of the broad family of 'insanities' and was subcategorized into delusional and non-delusional states (Pinel, 1818). Other authors

described mania as a class of behaviours resembling schizophrenia, with subtypes such as simplex (pure rage), estatica (insane), ecnoa (rage with folly) and catholica (common rage) (Berrios, 1988). Near the end of the century, the concept of mania was associated with depression within the Kraepelin's terminology of manic–depressive insanity as distinct from dementia praecox, initiating the basis of modern psychiatric nosology (Kraepelin, 1899). Several decades later, Leonhard introduced the concept of polarity in the classification of affective disorders, reflecting the opposite extremes of depression and euphoria (Leonhard, 1957). Unipolar patients experienced only depressive episodes, while a bipolar diagnosis required the presence of a manic episode, a framework preserved by current diagnostic guidelines (APA, 1994).

Despite extensive efforts to categorize and define specific criteria that describe mania, manic states may include a variety of complex and multifaceted symptoms that challenge clear clinical distinctions (Grunze *et al.*, 2009). While mania may be precipitated by medical conditions that include viral infection, head trauma and neurological disorders (Arora and Daughton, 2007), this state is most commonly associated with bipolar disorder (BD), an illness with a worldwide lifetime prevalence of approximately 1% (Grunze *et al.*, 2009). According to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (APA, 1994), a manic episode as required for a BD diagnosis involves a distinct period of euphoric or irritable mood lasting at least 1 week (or less if hospitalized), concurrent with several other symptoms that may include grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased goal-directed activity and pleasurable risky activities (e.g. promiscuity, overspending; Figure 1). Some studies indicate that irritation is the most frequently exhibited mood symptom during a manic episode (occurring in 71% of patients; (Goodwin and Jamison, 2007), while psychotic symptoms such as delusions are observed approximately half the time. Hyperactivity is present in nearly all acute manic states (90%), followed by a decreased need for sleep (83%) and hyperverbosity (89%), while symptoms such as hypersexuality and religiosity appear less common (40–50%) (Goodwin and Jamison, 2007). Recent factor analyses of manic signs and symptoms (Cassidy *et al.*, 1998a,b) have identified between four and seven independent factors, including dysphoria (characterized by anxiety and depressed mood associated with mixed episodes), psychomotor acceleration (increased motor activity, pressured speech), psychosis (grandiosity, psychotic symptoms) and irritability/aggression. Despite the diversity of manic subgroups (irritable, euphoric, psychotic, depressed), psychomotor agitation appears to be a common denominator, leading some to hypothesize that increased activation or 'over-activity' represents the core underlying feature of mania (Depue *et al.*, 1987; Bauer *et al.*, 1991; Perry *et al.*, 2010).

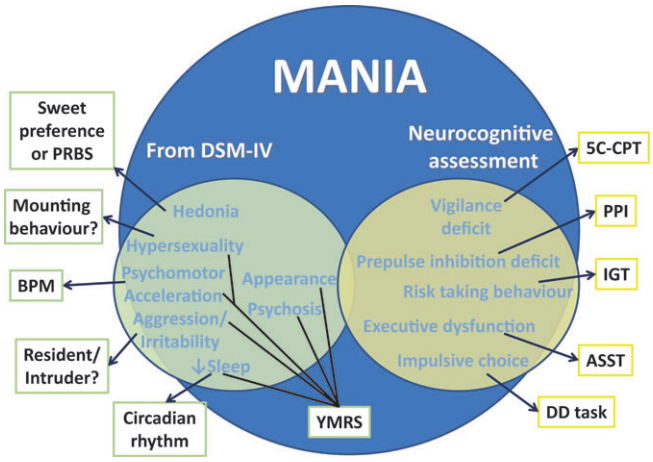

Figure 1

Symptoms and assays of mania. The symptoms of bipolar mania as described by DSM-IV rating scales (green circle). Also the neurocognitive symptoms associated with bipolar mania (yellow circle). The putative measurements of these symptoms (green and yellow rectangles respectively) are also provided. BPM = Behavioural Pattern Monitor, 5C-CPT = 5-choice continuous performance test, PPI = prepulse inhibition, IGT = Iowa gambling task, ASST = attentional set-shifting task, DD task = delayed discounting task.

Although classically conceptualized as a mood disorder, a considerable body of research indicates that BD mania is also associated with significant neurocognitive impairment across a broad array of domains (Burdick *et al.*, 2007; Goodwin *et al.*, 2008); Figure 1). While executive dysfunction appears to be the most salient aspect of BD mania (Savitz *et al.*, 2005), BD patients in manic states also exhibit deficits in vigilance, working memory, verbal fluency, inhibitory control and verbal recall and recognition (Sax *et al.*, 1999; Borkowska and Rybakowski, 2001; Fleck *et al.*, 2003; Martinez-Aran *et al.*, 2004). While most clinical trials for mania treatments have focused exclusively on the amelioration of mood symptoms, relatively little work has been done to examine the efficacy of various therapies on cognitive dysfunction linked with the disorder (Torres *et al.*, 2010b), despite close correlation of cognitive disruption with functional outcome (Green, 2006a; Torres *et al.*, 2010a). Inhibitory abnormalities are also observed in other domains such as in sensorimotor gating quantified as deficits in prepulse inhibition (PPI) (Perry *et al.*, 2001). PPI is a cross-species measure where a response to a startling stimulus (such as a loud noise) is inhibited by the prior presentation of a low intensity prepulse (Braff *et al.*, 1978; Swerdlow *et al.*, 2002; Geyer, 2006b). Thus, there are numerous behaviours beyond that of traditional mania rating scales that can be modelled in animals.

While animal models of human illness have proved to be a vital tool in the management and treatment of disease, developing cross-species paradigms of mania remains a challenging task. As with all animal models of psychiatric illness, it is difficult to infer affective states in rodents that mirror the clinical symptoms and cognitive deficits that characterize human psychopathology. Mania is a disorder marked by a variety of symptoms, including grandiosity and pressured speech, which are extremely difficult to derive from rodent behaviour. While increased motor activity remains the mainstay of animal models of BD, this measure has also been used as a proxy for other neuropsychiatric disorders such as schizophrenia and attention-deficit hyperactivity disorder (ADHD) (Young *et al.*, 2007). In addition, the aetiology and pathophysiology of mania remain unclear, limiting confidence in the construct validity of various animal models in the context of clinical medications whose therapeutic mechanism

remains unknown. Recent attempts to model mania in rodents have focused on assessing specific facets or individual symptoms associated with a manic episode, while a comprehensive multi-symptom model remains elusive. In this review, we will (i) outline clinical findings that support the efficacy of current treatments for BD mania; (ii) describe the pharmacological, environmental and genetic animal models of the illness; (iii) evaluate the utility of the available models in providing effective pharmacological predictive validity and developing treatment options for mania.

Pharmacological treatments for mania

While the number of drugs licensed for treatment of manic episodes has grown substantially over the past decade (Smith *et al.*, 2007), there remains a dearth of consensus in current clinical practice regarding the optimal treatment for mania (Bourin *et al.*, 2005). Some groups recommend monotherapy with a mood stabilizer or atypical antipsychotic as a first-choice treatment option for BD mania (Suppes *et al.*, 1995; Bauer *et al.*, 1999), while others advocate combination treatment with these two classes of drugs, especially in the case of severe manic episodes (APA, 2002). While older clinical trials for mania medications were conducted with less rigorous methodological requirements and did not necessarily satisfy current scientific criteria (comparative, randomized, double-blind design), more recent studies have validated the efficacy of a variety of anti-manic drugs (Grunze *et al.*, 2009). It is relevant to note, however, that treatment efficacy is most commonly defined as a 50% improvement on subjective measures such as the Young Mania Rating Scale (YMRS) (Smith *et al.*, 2007), while objective quantification of manic symptoms such as motor hyperactivity is rarely assessed (Henry *et al.*, 2010). Recent investigations indicate that genetic variation in BD could also play a important role in treatment effects; the response to lithium therapy may relate to variants in genes that code for the serotonin transporter, glycogen synthase kinase 3 (GSK-3) and inositol monophosphatase (IMPase) proteins (Cruceanu *et al.*, 2006). To provide a context for the challenges associated with designing optimal animal models and interpreting the preclinical effects of anti-manic agents, this section will outline a brief history of the clinical work supporting currently accepted treatments for BD mania (Table 1). Following a review of the clinical measures requisite for validation of animal models, we will describe and critique the preclinical assays utilized to assess potential therapeutics.

Lithium

Long considered to be the gold standard of treatment for bipolar disorder, lithium is one of the oldest psychotropic agents prescribed today (Grandjean and Aubry, 2009). Originally discovered in 1817, the drug has been used since the mid-19th century to treat conditions such as gout and rheumatism (Atack, 2000). In 1949, the Australian physician John Cade, who was investigating the toxicity of urine samples from psychotic patients (stored on the top shelf of his kitchen refrigerator), observed that injections of lithium urate induced lethargic behaviour in guinea pigs (Cade, 1978). After injecting himself with lithium carbonate to assess the safety of the drug, Cade observed that the compound reduced or eliminated manic symptoms (such as being restless and euphoric) in a sample of 10 manic patients but did not ameliorate psychotic symptoms in a group of schizophrenia patients (Cade, 1949). No clear diagnostic or assessment criteria were reported in this study, which consisted of a series of very brief case histories.

Following Cade's pioneering study, several reports provided independent but poorly controlled observations supporting the efficacy of lithium in mania. Schou and colleagues examined the effect of two weeks of lithium treatment on 38 manic patients using a within-subjects design, evaluating clinical response with a three-point global severity scale (Schou *et al.*, 1954). While 37% of patients showed a 'positive response' to the drug, another 47% exhibited a 'possible response', but these criteria were vague and specific symptom improvement remained undefined. A subsequent review of 45 manic patients treated with lithium indicated that the majority showed an 'entirely satisfactory' or 'considerably improved' condition but again failed to provide an adequate description of the assessment criteria (Hartigan, 1963). A concurrent study examined the effect of 2 weeks of lithium therapy or placebo on manic symptoms using the Wittenborn scale for Manic State and Schizophrenic Excitement (Maggs, 1963). Although the diagnostic criteria for patient selection were not clear and alterations in specific symptoms were not reported, the results indicated that the drug was superior to placebo in reducing the severity of manic episodes.

In the decade following these initial reports, a series of larger controlled studies confirmed the efficacy of lithium therapy for mania, culminating in Food and Drug Administration (FDA) approval for treatment of acute manic episodes (1970) and as a prophylactic agent (1974) (Bourin *et al.*, 2005). Baastrup and colleagues observed the effect of chronic lithium treatment on 88 bipolar subjects over a 6 year duration, concluding that the drug significantly reduced the number of manic and depressive episodes (Baastrup and Schou, 1967). Goodwin *et al.* (1969) conducted a double-blind placebo-controlled study, demonstrating that lithium reduced manic symptomatology on the Bunney–Hamburg Scale, a 25-item rating instrument used to quantify mania and depression (Bunney *et al.*, 1968; Goodwin *et al.*, 1969). Several additional reports indicated that lithium exhibited an anti-manic effect comparable to the antipsychotic chlorpromazine as assessed by measures such as the Brief Psychiatric Rating Scale (BPRS) (Johnson *et al.*, 1968; Spring *et al.*, 1970; Johnson *et al.*, 1971). One study observed that both drugs reduced sleep disturbance and grandiosity, but lithium was superior in controlling behaviours such as motor hyperactivity, flight of ideas, euphoria and pressured speech (Spring *et al.*, 1970). In 1972, the Veterans Administration (VA) and National Institute of Mental Health (NIMH) conducted a collaborative 18-site study, reporting that 3 weeks of treatment with both drugs significantly reduced BPRS-rated symptoms such as excitement, elevated mood, grandiosity and hostility in manic and schizoaffective patients (Prien *et al.*, 1972). Finally, more recent randomized, multicentre, double-blind studies (Bowden *et al.*, 1994; Poolsup *et al.*, 2000) have conclusively demonstrated that

Table 1

Drugs approved/ not approved for treatment of mania

Drug	Measure	Outcome	Reference
US Food and Drug Administration approved agents for mania			
Lithium	BPRS IMPS	Significant reduction in elevated mood, excitement, grandiosity and hostility	Prien *et al.*, 1972
	SADS	Half of lithium-treated subjects demonstrated a 50% reduction in mania scale ratings	Bowden *et al.*, 1994
Valproate	BPRS YMRS	Reduction in conceptual disorganization, tension, hostility, excitement and motor activity;	Pope *et al.*, 1991
	SADS	Half of valproate-treated subjects demonstrated a 50% reduction in YMRS score	Bowden *et al.*, 1994
Carbamazepine	BPRS YMRS BRMS	Pooled data from randomized controlled trials indicate that approximately 52% of mania patients show reduction in manic symptoms	McElroy *and* Keck, 2000
Aripiprazole	YMRS	Significant reduction in YMRS scores compared with placebo	Keck *et al.* (2003)
Asenapine	YMRS	Significant reduction in YMRS scores compared with placebo	McIntyre *et al.*, 2009
Olanzapine	YMRS	Significant reduction in YMRS scores compared with placebo	Tohen *et al.*, 1999
Quetiapine	YMRS	Significant reduction in YMRS scores compared with placebo; similar efficacy to haloperidol	McIntyre *et al.*, 2007
Resperidone	YMRS CGI PANSS	Significant reduction of manic symptoms and diminished excitement/hostility on the PANSS compared with placebo	Khanna *et al.* (2005)
Ziprasidone	YMRS CGI PANSS SADS	Significant reduction of manic and psychotic symptoms compared with placebo on multiple rating scales	Keck *et al.* (2003)
Potential mania agents not approved for treatment			
Lamotrigine	YMRS	No significant difference between drug treatment and placebo for treatment of acute manic episodes	Goldsmith *et al.*, 2003
Oxcarbazepine	YMRS	Inconsistent effects on manic symptoms, may have little effect on severe psychotic mania	Hummel *et al.* (2002) Mazza *et al.*, 2007
Tiagabine	YMRS BRMS	No significant effects of drug treatment reported in some studies; data are limited by lack of randomized controlled trials	Young *et al.*, 2006
Gabapentin	YMRS	No significant difference between drug treatment and placebo for treatment of acute manic episodes	Pande *et al.* (2000) Fullerton *et al.* (2010)
Topiramate	YMRS	No significant difference between drug treatment and placebo of acute manic episodes	Kushner *et al.*, 2006

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; BRMS = Beach–Rafaelsen Mania Scale; IMPS = Inpatient Multidimensional Psychiatric Scale; PANSS = Positive and Negative Syndrome Scale; SADS = Schedule for Affective Disorder and Schizophrenia; YMRS = Young Mania Rating Scale.

lithium is superior to placebo in reducing acute manic symptoms as assessed by multiple rating scales, including the BPRS, the YMRS and the Schedule for Affective Disorders and Schizophrenia (SADS-C).

Anticonvulsants

Anticonvulsant medications have been evaluated as mood stabilizers since the early 1970s, buttressed by the proposal that epilepsy and BD may share similar underlying features such as kindling, a phenomena involving repeated subthreshold neuronal stimulation (Post and Uhde, 1983; Brambilla and Soares, 2005). Substantial evidence supports the use of anticonvulsants such as valproate and carbamazepine in the treatment of mania, while more recent studies have examined the effectiveness of newer compounds such as lamotrigine, oxcarbazepine and topiramate (Singh *et al.*, 2005). Valproate, originally developed as an organic solvent in 1881, was recognized serendipitously as an anticonvulsant in the 1960s and first observed to exert clinical benefit in BD in a 1966 French study (Lambert *et al.*, 1966). Two pivotal reports

in the early 1990s led to regulatory approval in the United States in 1995 (Bowden and Singh, 2006). Pope and colleagues conducted a double-blind placebo-controlled study of valproate treatment in 36 acute manic patients, reporting that the drug reduced YMRS-rated manic symptoms by an average of 54% and significantly mitigated BPRS-evaluated symptoms such as conceptual disorganization, tension, excitement and hostility relative to placebo (Pope *et al.*, 1991). A subsequent randomized, multicentre study (Bowden *et al.*, 1994) reported that valproate significantly improved manic symptoms as assessed by the SADS-C scale, decreasing elevated mood, motor hyperactivity and sleep disturbance compared with the placebo group. More recent studies indicated that valproate may be superior to lithium in treating mania characterized by co-morbid depressive symptoms, marked irritability or a higher number of lifetime manic episodes (Bowden and Singh, 2006).

Similar to valproate, the efficacy of carbamazepine treatment for mania has been demonstrated primarily through the use of rating scales (Bourin *et al.*, 2005). Carbamazepine, the first anticonvulsant drug widely used for the treatment of BD, has been assessed as a therapy for mania in at least 16 controlled trials (Singh *et al.*, 2005), although many of these studies were limited by small sample size, the absence of a placebo group and concurrent use of other anti-manic drugs (Keck *et al.*, 2000). Pooled data from five studies with carbamazepine monotherapy indicates that the drug is superior to placebo and comparable with lithium and typical antipsychotics in treating BD mania (McElroy *and* Keck, 2000) and alleviating manic symptoms assessed by the BPRS, the Manic State Rating Scale and the Bunney–Hamburg Scale (Keck *et al.*, 2000).

In contrast, a number of so-called 'third-generation' or atypical anticonvulsants have failed to effectively treat acute manic episodes of BD, including oxcarbazepine (Mazza *et al.*, 2007), tiagabine, gabapentin, topiramate and lamotrigine (Yatham *et al.*, 2002; Kushner *et al.*, 2006). While a series of open-label and pilot studies reported that oxcarbazepine reduces manic symptoms on measures such as the YMRS and Bech–Rafaelson Mania Scale (Hirschfeld and Kasper, 2004; Popova *et al.*, 2007), these results were not confirmed by subsequent controlled studies (Mazza *et al.*, 2007). Administration of topiramate was indicated to decrease YMRS scores in BD patients as an adjunctive treatment or monotherapy (Yatham and Kusumaker, 2003), but more recent double-blind placebo-controlled trials did not observe significant effects of the drug (Kushner *et al.*, 2006). While initial results indicated lamotrigine decreased manic symptoms as measured by the YMRS in a within subjects design (Bowden *et al.*, 1999), these effects were not robust in two large placebo-controlled clinical trials (Bowden, 2002; Goldsmith *et al.*, 2003; Singh *et al.*, 2005; Ghaemi *et al.*, 2008; Weisler *et al.*, 2008). Despite these findings and lack of FDA approval, some of these drugs have been used as off-label treatment for BD mania (Grunze *et al.*, 2009). In comparison, older drugs such as lithium have retained their clinical efficacy even when assessed in more recent and rigorous clinical trials (Bowden *et al.*, 1994; Sachs *et al.*, 2007). In addition, in the case of lamotrigine, inadequate description of the clinical findings (e.g. a dearth of details regarding drug efficacy on symptoms such as aggression, sleep disturbance or cognition) (Goldsmith *et al.*, 2003) complicates interpretation of drug effects in animal models.

Antipsychotics

Antipsychotic medications have been utilized as a primary or adjunctive treatment for mania for over 50 years (Cookson, 2006). Clinical use of antipsychotic agents such as chlorpromazine began in the 1950s, predating widespread use of lithium (Tohen and Vieta, 2009). For decades, haloperidol was often the drug of first choice to rapidly tranquilize agitated or aggressive acutely manic patients, in contrast to the delayed response to lithium (Cookson, 2006). While typical antipsychotic drugs such as chlorpromazine and haloperidol were comparable with lithium in reducing manic symptomatology as assessed by the BPRS (Shopsin *et al.*, 1975), more recent studies suggested that the atypical antipsychotic clozapine could have potential therapeutic efficacy in mania (Keck and McElroy, 2006). Over the past 10 years, a series of atypical antipsychotics have gained FDA approval to treat mania, including aripiprazole, asenapine, olanzapine, quetiapine, risperidone and ziprasidone (McIntyre *et al.*, 2009; Tohen and Vieta, 2009). The efficacy of these drugs as monotherapy or adjunctive treatments to lithium or valproate has again been demonstrated primarily with the use of rating scales, including the YMRS, BPRS and Clinical Global Impression (CGI) (Cookson, 2006; Smith *et al.*, 2007; Fountoulakis and Vieta, 2008; Grunze *et al.*, 2009). While some reports include symptom-specific data (e.g. improvement in elevated mood with olanzapine, a reduction in hostility with risperidone and aripiprazole, or a general improvement across all the YMRS categories with quetiapine; (Tohen *et al.*, 1999; Hirschfeld and Kasper, 2004; McIntyre *et al.*, 2007; Keck *et al.*, 2009b), data from many recent clinical trials are limited to assessing the overall change in the total YMRS score (Fountoulakis and Vieta, 2008). Although potential mechanisms of action remain unknown, this class of drugs does appear to exert a specific anti-manic effect independent of the presence of co-morbid psychosis or the degree of sedation induced by the agent (Keck and McElroy, 2006; McIntyre *et al.*, 2007; Sachs and Gardner-Schuster, 2007; Tohen *et al.*, 1999).

Investigational agents

Despite numerous anti-manic medications now available, identifying the neurobiological factors underlying manic episodes and the therapeutic targets of efficacious treatments remains a challenge. Numerous biochemical effects of lithium have been identified as potential mediators of the therapeutic response, including inhibition of IMPase, inhibition of GSK-3, inhibition of NMDA receptor–mediated signalling, alterations in cyclic adenosine monophosphate (cAMP) signalling and guanine nucleotide binding protein (G-protein) function, inhibition of protein kinase C (PKC) and augmentation of cholinergic activity (Manji *et al.*, 2000; Chiu and Chuang, 2010). Anticonvulsants such as valproate may also exert anti-manic properties through a variety of mechanisms, including increased gamma-aminobutyric (GABA) release, inhibition of GSK-3 and PKC and activation of extracellular-related signal kinase (ERK) (Bowden and Singh, 2006). Both typical and atypical antipsychotic medications are hypothesized to not only reduce manic symptoms

via dopamine D2 receptor blockade but to also impact multiple neurotransmitter systems crucial to regulating affect (Tohen and Vieta, 2009). Several recent clinical trials (NCT00026585, NCT00206544, NCT00411203 on http://www.clinicaltrials.gov) have focused specifically on PKC as a molecular target by assessing the effect of the PKC inhibitor Tamoxifen, a non-steroidal anti-oestrogen agent used in the treatment of breast cancer (DiazGranados and Zarate, 2008). PKC is an intracellular enzyme that coordinates the neuronal response to the activation of multiple neurotransmitter receptors, playing a key role in regulating pre- and post-synaptic transmission (Zarate *et al.*, 2007). Data from four published studies indicate that tamoxifen reduces BD manic symptoms relative to placebo as indicated by decreased YMRS scores, including a reduction in elevated mood, motor hyperactivity and sexual interest (Bebchuk *et al.*, 2000; Kulkarni *et al.*, 2006; Zarate *et al.*, 2007; Yildiz *et al.*, 2008).

While almost all clinical studies focus on the psychiatric symptoms associated with mania, there is a growing awareness that treatments for disorders such as BD should also address the neurocognitive deficits coupled with the illness. Bipolar mania is characterized by significant impairment in several cognitive domains, including attention, memory and executive functioning (i.e. planning, abstract concept formation, set shifting, decision making and inhibitory control) (Doyle *et al.*, 2005; Green, 2006b; Burdick *et al.*, 2007; Bora *et al.*, 2009). Current clinical trials are assessing the efficacy of several agents, including ashwaganhda (Withania somnifera), L-carnosine, memantine, methylene blue, intranasal insulin, pramipexole and galantamine on cognitive function in BD (see http://www.clinicaltrials.gov, trial identifiers NCT00761761, NCT00177463, NCT00586066, NCT00214877, NCT00314314, NCT00597896, NCT00741598). Outcome measures include performance in the domains of attention, executive function, working memory and verbal and visuospatial memory. Neuropsychological paradigms utilized to quantify cognition include Cogtest, the California Verbal Learning Task (CVLT), Trail Making Test A (insulin), Trail Making Test B and the Connors Continuous Performance Task (CPT). While much of this information has yet to be published, one recent study reported that 4 months of treatment with galantamine-ER improved attentional deficits (better CPT performance) and normalized lipid membrane metabolism in the left hippocampus of BD participants (Iosifescu *et al.*, 2009). Finally, memantine is not only an agent used to treat Alzheimer's disease but is also being investigated as a potential treatment for BD mania (Zdanys and Tampi, 2008; Agarwal and Tripathi, 2009; Koukopoulos *et al.* 2010), despite a lack of preclinical testing with putative animal models of mania. Preliminary work suggests the drug may reduce BD manic symptoms (as assessed by YMRS) and improve cognitive function (Teng and Demetrio, 2006; Keck *et al.*, 2009a). Memantine may also prevent amphetamine- or MDMA-induced neurotoxicity or cognitive impairment (Chipana *et al.*, 2008a,b; Camarasa *et al.*, 2010).

Assessing models of mania

It is evident that until recently, most clinical trials investigating anti-manic treatments have focused on reducing scores on BPRS and YMRS scales in patients. Widespread use of these measures has limited opportunities for assessing these agents in tasks with cross-species translational validity (Young *et al.*, 2007). As discussed in the following sections, hyperactivity is frequently used as the primary outcome to assess the validity of many animal models of mania, while objective quantification of motor activity in clinical studies is rare. Recognition of the multi-faceted nature of mania has stimulated research in other domains (Gould and Einat 2007; Young *et al.*, 2007), but the validation of models in these domains remain limited to date.

Pharmacological models of mania

Animal models of BD mania began with observational evidence. Psychostimulants (such as amphetamine) can produce mania-like symptoms in normal healthy subjects (Meyendorff *et al.*, 1985; Peet and Peters, 1995; Hasler *et al.*, 2006) and exacerbate symptoms or induce a manic episode in patients. Thus, the effects of pharmacological agents (stimulants) on behaviour have been widely used as an animal model of mania (Table 2; (Frey *et al.*, 2006; Kato *et al.*, 2007). Because psychomotor agitation is commonly observed during mania and locomotor activity is easily measured in rodents, activity level is most often the behavioural measure used in animal models of mania. Amphetamine-induced hyperactivity is considered to be the 'gold-standard' rodent model of mania (Davies *et al.*, 1974; Berggren *et al.*, 1978; Gould *et al.*, 2001), despite detailed inspection of amphetamine-induced alterations of behaviour in humans revealing differences in behaviours (Silverstone *et al.*, 1998). Amphetamine-induced hyperactivity has been reversed by acute lithium in some mouse strains but not others (Davies *et al.*, 1974; Gould *et al.*, 2001), although this effect is often confounded by lithium-induced reductions in activity alone (Berggren *et al.*, 1978), especially when studies are done in habituated animals during their sleep cycle. Chronic lithium does not appear to reverse amphetamine-induced hyperactivity (Fessler *et al.*, 1982; Cappeliez and Moore, 1990). The use of amphetamine as a model of BD mania does have a number of limitations, including the following: (i) amphetamine hyperactivity has been interpreted as a model for a number of distinct disorders besides BD (including schizophrenia, drug abuse and tardive dyskinesia); (ii) mania is characterized by a broad set of symptoms that may not always include motor hyperactivity; (iii) most models utilize acute doses, while mania is a chronic disease with long-term alterations in behaviour.

The adenosine triphosphotase inhibitor ouabain induced hyperactivity in the open field has also been proposed as a model of BD mania (el-Mallakh *et al.*, 1995). The predictive validity for ouabain-induced increased activity has been investigated using antipsychotic medication approved for the treatment of BD mania. The typical antipsychotic haloperidol decreased ouabain-induced hyperactivity in rats, an effect confounded by haloperidol-induced reduction in activity alone (El-Mallakh *et al.*, 2006). The atypical antipsychotic olanzapine did not significantly reduce activity alone, nor did it attenuate ouabain-induced hyperactivity (El-Mallakh *et al.*, 2006). The effects of ouabain may be related to alterations in

Table 2

Pharmacological animal models of mania

Manipulation	Spp.	Treatment	Outcome	Strengths	Weaknesses	Reference
Acute AMP-induced ↑ in activity	Mice	Acute lithium (150 and 300 mg·kg^{-1})	Attenuated AMP-induced hyperactivity	Approved mania treatment attenuated manipulation effects	Acute manipulation and treatments, and lithium decreased activity alone – additive effects?	Berggren *et al.* (1978)
Acute AMP + CDP–induced ↑ in head dips	Mice	Acute lithium (3 mEq·kg^{-1})	Reversed the AMP + CDP–induced ↑ in head dips	Approved mania treatment reversed manipulation effects	Acute manipulation & treatments. Full controls not assessed (see text)	Davies *et al.*, (1974)
Acute AMP-induced ↑ in activity	Mice	Acute lithium (4 mEq·kg^{-1})	Attenuated AMP-induced hyperactivity in C57 but not C3H mice	Approved mania treatment attenuated manipulation effects, genetic differences between strains may yield interesting evidence for lithium effects	Acute manipulation and treatments, and lithium decreased activity alone – additive effects?	(Gould *et al.*, 2001)
AMP-induced stereotypy	Rats	Chronic lithium mash (2.3 g·kg^{-1}) for 14 days	No effect of AMP-induced stereotypy	Used chronic treatment of lithium, reduced weight of treated rats indicative of biological effect of treatment	No effect of treatment alone or on manipulation	(Fessler *et al.*, 1982)
Chronic AMP-induced hyperactivity	Rats	Chronic lithium injections (1.5 mEq·kg^{-1}) for 21 days	No effect on AMP-induced hyperactivity	Used chronic treatment of lithium, reduced weight of treated rats indicative of biological effect of treatment	No effect of treatment on behaviour during or after removal	Cappeliez and Moore, 1990
Acute ouabain i.c.v.-induced hyperactivity	Rats	Chronic lithium 7 days (2.5 mEq·kg^{-1})	Lithium reversed ouabain-induced hyperactivity	Chronic approved mania treatment attenuated manipulation effects	Animals were habituated to environment so minimum activity levels may have masked lithium-induced decreases in activity	Li *et al.*, 1997
Acute quinpirole-induced hyperactivity	Rats	Chronic valproate (12 g·L^{-1}), phenytoin (6 g·kg^{-1}), carbemazepine (8 g·kg^{-1}), & topiramate (30 mg·kg^{-1}), each for 11 days	Quinpirole-induced hyperactivity was only attenuated by topiramate treatment	Chronic treatment examined	Approved mania treatments ineffective in paradigm, while agents not approved were effective	Shaldubina *et al.*, 2002
Acute AMP + CDP–induced hyperactivity	Rats and mice	Acute lithium, retigabine, lamotrigine and levetiracetam	All drugs were efficacious in reversing AMP + CDP effects	Approved mania treatment attenuated manipulation effects	Acute dosing only. Drugs not approved for mania were efficacious (lamotrigine and levetiracetam)	Dencker *et al.*, 2008; Lamberty *et al.*, 2001; Redrobe and Nielsen, 2009
Repeated ouabain i.c.v. induced hyperactivity, measured at 0, 6 and 7 days post injection	Rats	Chronic olanzipine 7 days twice daily (1 or 6 mg·kg^{-1}) or haloperidol twice at 21 mg·kg^{-1} last 7 days prior to testing	Haloperidol attenuated ouabain-induced hyperactivity, no effect of olanzapine	Approved mania treatment attenuated manipulation effects	Haloperidol decreased effects alone – additive effects? No differentiation between mania and schizophrenia, repeated testing may attenuate evidence of drug alone-induced reduction in activity	El-Mallakh *et al.*, 2006

AMP = amphetamine, CDP = chlordiazepoxide

the phosphorylation of mitogen-activated protein kinase kinase1/2–ERK 1/2 pathway (Kim *et al.*, 2008).

To assess the generalizability of ouabain-induced effects on activity, one study compared behaviour in an open field (86 × 86 cm and well lit) and an activity chamber (41.5 × 41.5 cm and dark) (Decker *et al.*, 2000); the results indicated that ouabain increased activity only in the open-field test. Thus, the environment appears to be important for observing behavioural changes associated with mania, even in 'simple' hyperactivity. Environmental factors are also important in BD mania because complex environments can increase manic symptoms, while 'quiet rooms' can reduce symptoms (Fisher *et al.*, 1991). Environmental novelty may disrupt a subject's circadian rhythm, resulting in manic episodes in predisposed subjects (Ehlers *et al.*, 1988; Malkoff-Schwartz *et al.*, 1998; 2000), while events that disrupt social rhythm can predict episodes of hypomania (Sylvia *et al.*, 2009). Maintaining environmental consistencies and managing rhythm dysregulation may buffer against future manic episodes (Frank *et al.*, 2005).

Environmental novelty can therefore be a critical factor when interpreting the effects of drugs on activity levels alone. For example, for a drug to treat symptoms, it should reverse a psychostimulant-induced effect (e.g. normalization of activity) rather than simply exerting an additive effect (e.g. reducing activity irrespective of prior treatment). The only way to assess whether a drug effect represents a reversal or additive finding is to include a drug-only group as a control (Figure 2). For example, haloperidol (El-Mallakh *et al.*, 2006), valproate (Dencker and Husum, 2010), asenapine, olanzapine (Marston *et al.*, 2009) and carbamazepine (Arban *et al.*, 2005) all reduce activity alone, confounding the interpretation of their antagonism of amphetamine-induced hyperactivity. A second issue to consider is the degree of habituation to the testing chamber. Repeated exposure to an open-field chamber may induce a 'floor effect', where activity levels are so low that a drug effect alone could not lower them further. This condition may confuse data interpretation, suggesting a reversal effect when identification of additive effects is not possible. For example, Li *et al.* (1997) assessed the activity of rats for several days prior to quantifying ouabain-induced hyperactivity and acute lithium 'reversal' of effects. In this study, lithium failed to decrease activity levels that were already minimal due to environmental familiarity.

Antipsychotic drugs developed for the treatment of schizophrenia are typically assessed in preclinical studies that quantify their ability to reduce amphetamine-induced hyperactivity or stimulant-induced disruption in PPI, two paradigms also used to assess the effects of anti-manic drugs. Using a dopamine D2 receptor antagonist (the primary mechanism of action of antipsychotics is binding to the D2 receptor) to inhibit or block the effects of a dopamine agonist-induced change in behaviour has been referred to as receptor tautology (Geyer, 2006a). Although utilizing the same behaviour and stimulants that are used to model mania, these models appear primarily useful at identifying efficacious antipsychotics. The use of this model for developing antipsychotic treatment in schizophrenia has been covered elsewhere (Geyer and Moghaddam, 2002). A recent example, however, is the new atypical antipsychotic asenapine, initially approved for schizophrenia and now also approved for

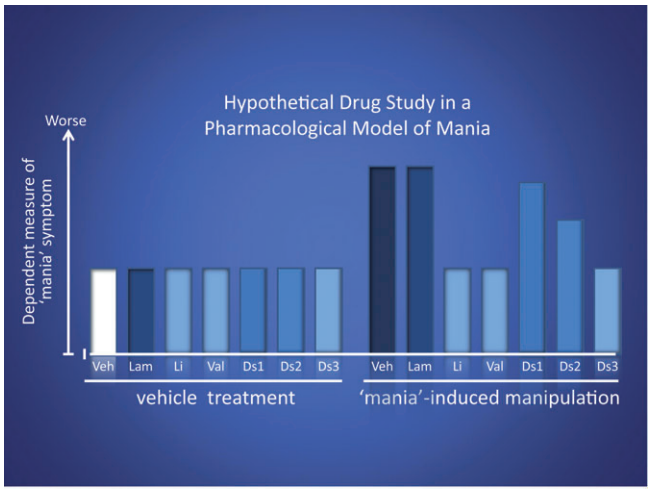

Figure 2

Hypothetical results of a putative treatment study in a pharmacological animal model of mania. The dependent measure of mania-like activity is on the *y*-axis and the seven treatment group by two pre-treatment groups are depicted on the *x*-axis. Veh = vehicle, Lam = lamotrigine (used here as a negative control), Li = lithium, Val = valproate (both used here as positive controls), Ds1 = dose 1, Ds2 = dose 2, Ds3 = dose 3 of the drug studied. Each of the treatment groups in the vehicle pretreatment arm would not affect 'mania'-like behaviour. The 'mania'-inducing pretreatment would increase the 'mania' symptoms of each treatment group in comparison with the corresponding treatment group in the vehicle pretreatment arm. Given that lamotrigine does not treat bipolar mania while lithium and valproate do, one would expect no improvement in mania with lamotrigine, but improvements are observed for lithium and valproate in the mania model. For the test therapeutic, a dose–response effect would be observed. Ideally, treatment effects would be assessed after a chronic 4 week plus treatment duration.

treating mania in BD (Minassian and Young, 2010). Early studies indicated that asenapine reversed the dopaminergic-induced hyperactivity model of schizophrenia, consistent with other antipsychotics (Ellenbroek, 1993; Moore *et al.*, 1997; Geyer and Ellenbroek, 2003; Sun *et al.*, 2009). The effects of asenapine alone were not presented (Costall *et al.*, 1990); thus, it was unclear whether the asenapine reversal of dopamine-induced hyperactivity was simply due to a non-specific reduction in activity. Recently, it was demonstrated that systemic administration of asenapine did reduce spontaneous activity alone (Marston *et al.*, 2009) – consistent with other antipsychotics. For example, the pattern of reduced activity in normal animals and amphetamine-induced hyperactivity has also been observed for aripiprazole (Mavrikaki *et al.*, 2010). Asenapine also reversed apomorphine-induced disruption of prepulse inhibition (PPI; (Marston *et al.*, 2009), consistent with other antipsychotics (Swerdlow *et al.*, 1994) and an effect linked to dopamine D2 receptor binding levels. Topiramate, the failed putative anti-manic agent, was also efficacious in apomorphine-induced disruption in PPI (Frau *et al.*, 2007). Ketamine- but not amphetamine-induced reduction in PPI in mice was attenuated by the failed putative anti-manic lamotrigine (Brody *et al.*, 2003), suggesting that ketamine-induced disruption in PPI may not be an

appropriate animal model of mania. Acute lithium attenuated amphetamine- but not ketamine-induced disruption in PPI in mice, but the opposite was true for carbemazapine, while valproate reversed neither effect (Ong *et al.*, 2005). Other NMDA antagonist models of mania include phencyclidine-induced stereotypy and hyperactivity, with the former but not the latter being reversed by subchronic lithium treatment (Fessler *et al.*, 1982). Phencyclidine-induced changes in behaviour are used more often as models of schizophrenia, however (Neill *et al.*, 2010), and have not received much investigation in the context of treatments for BD mania.

Acute administration of the dopamine agonist quinpirole induces a pattern of hyperactivity also utilized as an animal model of mania. Shaldubina *et al.* (2002) observed that chronic administration of the anti-manic drugs valproate and carbamazepine successfully reversed quinpirole activation. The attenuation of quinpirole-induced hyperactivity was also observed however for topiramate (Shaldubina *et al.*, 2002), which is not indicated for mania treatment (Kushner *et al.*, 2006; Vasudev *et al.*, 2006; Correll *et al.*, 2010) and may in fact induce a manic episode in some patients (Jochum *et al.*, 2002). It is relevant to note that topiramate was not assessed in animal models of mania prior to clinical studies (see above). Behavioural sensitization to psychostimulants that induce dopamine release (such as amphetamine) is also used as an animal model of mania (Cappeliez and Moore, 1990). Acute administration of lamotrigine, lithium, valproate, retigabine and carbamazepine all reversed the amphetamine-induced sensitization hyperactivity model of mania (Dencker and Husum, 2010), although valproate alone also reduced activity in vehicle-treated mice. These data suggest that false-positive effects are also observed for psychostimulant sensitization models of mania since lamotrigine has not proven effective to treat acute manic episodes (Bowden, 2002; Singh *et al.*, 2005). In summary, the data from these studies indicate that the efficacy of putative mania treatments in preclinical models is not always maintained in clinical trials.

Another animal model of mania has sought to go beyond the simplicity and putative receptor tautology of single psychostimulant administration. The benzodiazepine derivative chlordiazepoxide, which has anxiolytic and sedative effects alone, has been used in combination with amphetamine as a rodent model of mania (Poitou *et al.*, 1975; Arban *et al.*, 2005). The most common behavioural output measure used is still activity level, as the amphetamine and chlordiazepoxide (AMP + CDP) model increases activity in both rats and mice. Consistent with amphetamine alone, AMP + CDP–induced hyperactivity is reversed by acute lithium, retigabine, lamotrigine and levetiracetam (Lamberty *et al.*, 2001; Dencker *et al.*, 2008; Redrobe and Nielsen, 2009). Similar to amphetamine alone, the predictive validity of the AMP + CDP model is questionable, based on evidence that both lamotrigine and levetiracetam have limited efficacy for treating mania (Goldberg and Burdick, 2002; Grunze *et al.*, 2003; Kruger *et al.*, 2008).

One of the major difficulties of the AMP + CDP model of mania is the number of control groups required for each study (vehicle alone, amphetamine alone, chlordiazepoxide alone, AMP + CDP in combination, AMP + CDP plus each treatment, amphetamine plus each treatment and chlordiazepoxide plus each treatment). Arban *et al.* (2005) conducted a full control comparison study utilizing the AMP + CPD model in conjunction with several anti-manic agents. Chlordiazepoxide alone often potentiated the activity-suppressant effects of anti-manic agents (Arban *et al.*, 2005), a finding also observed for lamotrigine (Redrobe and Nielsen, 2009). It was unclear whether the combined model provided meaningful data on the action of anti-manic agents or whether alterations in activity simply represent a combination of additive drug effects. This work was supported recently by (Kelly *et al.*, 2009), who describe a more complete dose–response interaction and highlight the difficulties in interpreting putative anti-manic responses based on this mixture of drug effects. Thus, the complexity of controls required in the AMP + CPD model of mania makes it difficult to interpret the responses to novel putative anti-manic agents. For example, Kozikowski *et al.* (2007) assessed the effects of a newly synthesized GSK-3β inhibitor in the AMP + CPD model of mania, observing that consistent with valproate, the novel inhibitor attenuated but did not reverse AMP + CDP–induced hyperactivity. The findings of the study were limited by several factors, including the use of a high dose of valproate (400 $mg \cdot kg^{-1}$); in addition, the authors did not assess the effects of valproate treatment alone or in combination with either amphetamine or chlordiazepoxide, nor did they provide statistics on the inhibitor effect compared to a vehicle treatment that itself appeared to reduce activity. In summary, the complexity and false positives observed for the AMP + CDP model of mania may limit its utility in the future.

The predictive validity of many of the models described above may be further limited given that efficacious treatment effects are often observed with acute treatment. Acute administration of anti-manic agents does not treat BD mania; in fact, in randomized controlled trials patients often still exhibit mania rating scores high enough to meet criteria for enrolling in the study even after 3 weeks of treatment (Sachs and Gardner-Schuster, 2007). Thus, it has been suggested that treatment predictive validity should be assessed in chronic not acute studies (Harrison-Read, 2009).

More recently, researchers have highlighted the need to develop animal models of mania that assess more than just levels of activity (Einat, 2006; Young *et al.*, 2007; Einat, 2007b; Geyer, 2008). One technique would be to develop a battery of tests that putatively assess different facets of quantified mania symptoms, such as sleep deprivation, aggression (see below also), strain differences, reward-seeking behaviour or impaired cognition (Einat, 2007b; Geyer, 2008; Flaisher-Grinberg *et al.*, 2009). This premise of using multiple techniques may filter out drugs with false positives in some assays in the hope of identifying effective agents that will treat mania (Einat, 2007b). One must be wary of focusing on 'aspects of animal behaviour that bear a *superficial resemblance* to at least one of the clinical features of mania' (authors' own italics) (Harrison-Read, 2009), or what is known as 'face validity'. Therefore, another tactic has been to reverse translate the quantification of spontaneous exploration in rodents so that it can also be assessed in humans, thus producing behavioural profiles that can be modelled directly in animals (Young *et al.*, 2007). This latter technique has led to the identification of a unique pattern of exploration in patients with mania that includes increased activity, more specific

Table 3

Environmental models of mania

Manipulation	Spp.	Treatment	Outcome	Strengths	Weaknesses	Reference
Sleep deprivation (72 h)	Rats	Subchronic lithium (60 mmol·kg^{-1}) 10 days	↓ sleep latency and hyperactivity	Sleep disruption can induce manic episodes and ↓ sleep seen in mania	Performed in normal animals, other stressors also used may interfere with effects	Gessa *et al.*, 1995
Sleep deprivation (4 h in dark cycle)	Rats	Chronic lithium (2.4 g·kg^{-1}) 4 weeks	↓ forebrain PKC expression	↓ PKC implicated in BD disorder affected by lithium and valproate	Performed in normal animals. Behavioural symptoms have not been assessed	Szabo *et al.*, 2009
Resident/intruder	Mice	Chronic lithium (2.4 g·kg^{-1}) or valproate (20 g·kg^{-1}) 4 weeks	↓ resident aggressive attacks with lithium and valproate	Approved mania treatments ↓ mania-like behaviour (aggression)	Performed in normal animals, assay sensitive to non-mania treatments, antidepressants, anxiolytics etc	Einat, 2007a,b
Food competition	Rats	Chronic daily lithium (100 mg·kg^{-1}), carbemazepine (20 mg·kg^{-1}) or valproate (30 mg·kg^{-1}) 7 weeks	↓ dominant behaviours	Approved mania treatments ↓ dominant-like behaviour, observed only with chronic treatment	Performed in normal animals, assay sensitive to non-mania treatments, antidepressants, anxiolytics etc, multiple injections problematic	Malatynska and Knapp, 2005; Malatynska *et al.*, 2007
Footshock stress	Rats	Subchronic lithium (20 mEq·L^{-1}) 14 days	Lithium ↓ shock-induced aggression	Approved mania treatments ↓ aggression	Performed in normal animals, assay sensitive to non-mania treatments, antidepressants, psychstimulants etc,	Prasad and Sheard, 1982

PKC = protein kinase C

exploration and straighter line movement from location to location (Minassian *et al.*, 2009; Perry *et al.*, 2009; 2010). This technique also led to the development of novel animal models of mania including dopamine transporter (DAT) knockdown mice (discussed in greater detail below) and the effects of the selective DAT inhibitor GBR 12909 on spontaneous exploration. This methodology has also provided quantifiable evidence (Perry *et al.*, 2009; Young *et al.*, 2010a,b) to support self-report data in humans (Silverstone *et al.*, 1998), questioning the validity of acute amphetamine as a model for BD mania. Extensive tests have yet to be completed on the predictive validity of these reverse-translational models, while assessment of cognitive performance should be carefully designed to account for potential impairment induced by anti-manic medications (Goldberg and Burdick, 2001; Gualtieri and Johnson, 2006).

Environmental models of BD mania

In contrast to pharmacological models of mania, some groups have attempted to use environmental manipulations to induce behaviour in animals that resembles human symptoms associated with the disorder. These environmental model challenges often use stimuli that can provoke a manic episode (e.g. sleep deprivation, stress – see below). Despite the use of such challenges, the animals being investigated in these models are not perturbed in any way, which equates to mania (non-mania prone subjects do not become manic under similar environmental challenges). Treatments identified using these models may not therefore be specific to mania but represent symptomatic treatment only (Table 3).

The rodent sleep deprivation model purports to examine a cluster of behavioural markers germane to manic episodes and also exhibits significant clinical relevance, because sleep disruption constitutes one of the most frequent prodromes of mania (Gessa *et al.*, 1995; Mansell and Pedley, 2008). The paradigm involves placing a rat or mouse on a small platform (3–7 cm) surrounded by water for an extended period, typically 72 h (Gessa *et al.*, 1995). Muscle relaxation associated with sleep results in the animal falling into the water, thereby waking the animal. When rodents are placed back into their home cage after the sleep deprivation period, they exhibit a series of mania-like behaviours that include insomnia, hyperactivity, aggressive actions towards other animals, hypersexuality (an increase in mounting behaviour) and stereotypy (sniffing and rearing) (Morden *et al.*, 1967; Hicks *et al.*, 1979; Fratta *et al.*, 1987). This pattern of over-activity is maximal during a 30–40 min period immediately after the sleep deprivation treatment (Einat, 2007a). Gessa *et al.* (1995) reported that 10 days of lithium treatment (60 mmol·kg^{-1} of lithium salt added to food) significantly reduced motor hyperactivity

and decreased the latency to fall asleep compared with vehicle in 72 h sleep-deprived rats (Gessa *et al.*, 1995). Rats administered four injections of haloperidol in the last hour of the sleep deprivation period also demonstrated a decreased latency to fall asleep relative to saline-treated animals, which was interpreted as a reduction in mania-like insomnia. These data support the contention that this model has pharmacological predictive validity, but it is relevant to note that the paradigm includes several stressors aside from simple sleep deprivation, including isolation, immobilization and the experience of falling into water. A more recent study administered intervals of 24 h sleep deprivation to CD1 mice while also including a stress control group with a larger stable platform enabling sleep, but enforcing isolation and immobilization (Benedetti *et al.*, 2008); only the sleep-deprived mice exhibited increased locomotion and aggressive behaviour relative to control, indicating that lack of sleep is key to the mania phenotype observed.

One report examined the effect of lithium and sleep deprivation on brain PKC activity, a pathway implicated in the motoric hyperactivity, risking taking and excessive hedonic drive associated with mania (Szabo *et al.*, 2009). Male Wistar-Kyoto rats subjected to a relatively short period of sleep deprivation (4 h during the light cycle) exhibited evidence of increased PKC signalling as assessed by elevated PKC phosphorylation of AMPA receptors, neurogranin and myristoylated alanine-rich C kinase substrate (MARCKS) in frontal cortex relative to rested animals. In contrast, C57BL/6 mice treated with lithium in food for 4 weeks showed significantly reduced phosphorylation of these PKC molecular targets compared with animals fed a drug-free diet. While behavioural symptoms such as hyperactivity or aggression were not assessed in this paper, the data indicate that a sleep deprivation paradigm may have construct validity in representing the neurobiological alterations that may mediate manic episodes.

Manic individuals are frequently characterized by provocative, intrusive or aggressive actions, behaviours that are frequently modelled in animals using variants of the resident–intruder test (Einat, 2007a). This task typically consists of introducing a group-housed intruder rodent into the home cage of an isolated mouse or rat and quantifying the aggressive acts committed by the resident and the defensive acts and postures exhibited by the intruder (Miczek *et al.*, 2001). Resident aggressive behaviours, including biting, threatening postures and tail rattling, can be augmented by prolonged isolation or exposure to acute stressors such as foot shock (Legrand and Fielder, 1973; Miczek and O'Donnell, 1978). While the resident–intruder test has been utilized as a model of depression by assessing social defeat characteristics demonstrated by the intruder, treatment with anti-manic medications such as lithium has also been demonstrated to reduce resident aggression in both rats and mice (O'Donnell and Gould, 2007). Lithium administration has consistently reduced aggression induced by mild electric foot shock in rats, as well as attenuate combative behaviour augmented by stimulants such as D-amphetamine (Eichelman *et al.*, 1973; Mukherjee and Pradhan, 1976; Prasad and Sheard, 1982). The drug also diminishes conspecific isolation-induced fighting outside the home cage, as well as resident–intruder fighting within the home cage (Brain and Al-Maliki, 1979; Oehler *et al.*, 1985). One recent study examined the effect of both lithium and valproate on aggression using a resident–intruder paradigm in C57BL/6 mice (Einat, 2007b). Resident mice treated with either mood-stabilizer for 4 weeks before the test exhibited a significant reduction in the number of attacks against intruder mice compared with control but did not show any difference in non-aggressive interactions such as rearing or sniffing. Finally, it is also worth noting that chronic treatment with a variety of antidepressant drugs increases aggression in the resident–intruder paradigm (Mitchell, 2005), suggesting that this may constitute a model of antidepressant-induced mania in BD individuals (Koszewska and Rybakowski, 2009).

While the resident–intruder test has been in use for several decades (Miczek *et al.*, 2001), a recent representation of dominant–submissive behaviour has also been proposed to model symptoms of both depression and mania (Malatynska and Knapp, 2005). This paradigm is based on the concept that subordinate animals, similar to depressed humans, show increased defensive behaviour and reduced activity; in contrast, dominant animals, similar to manic states, are characterized by self-confident, assertive and aggressive behaviour (Gardner, 1982). In this paradigm, two rats are placed in opposite chambers connected by a narrow tunnel allowing only one animal at a time access to a food source. When tested over 2 weeks in 5 min daily sessions, approximately half the animal pairs develop a dominant–submissive relationship, where one dominant animal monopolizes access to the food, defined as spending 40% more time at the feeder compared with the submissive rodent. When treated with antidepressant medications such as imipramine, desipramine and fluoxetine (daily dose of 10 $mg \cdot kg^{-1}$ i.p.), submissive rats become more assertive, resulting in a significantly greater access to the food after 2 to 4 weeks of treatment. Conversely, dominant rats injected with lithium (100 $mg \cdot kg^{-1}$), carbamazepine (20 $mg \cdot kg^{-1}$) or sodium valproate (30 $mg \cdot kg^{-1}$) become less aggressive and lose their dominant status (Malatynska and Knapp, 2005; Malatynska *et al.*, 2007). In addition, the mood stabilizers exert an effect over a time course relatively similar to that observed in BD patients; lithium and carbamazepine treatment reduced rodent dominance only after 2–3 weeks of treatment. It is relevant to note, however, that resident–intruder paradigms are also sensitive to the effects of anxiolytic and anxiogenic drugs, suggesting that behavioural changes in this model could be interpreted as representing different behavioural constructs such as anxiety, limiting the predictive validity of this model for mania (Vassout, *et al.*, 2000).

Genetic models

Genetic models of mania can assume any of several forms. One technique is to compare strains where the behaviour of one strain is akin to that of other models of mania, or is more susceptible to treatment-induced alterations in behaviour. Another technique is to examine the behaviour of mice with genetic mutations in genes that have been linked to BD mania. Finally, a third technique is the creation of mice with specific genetic alterations designed to recreate those observed in BD mania. Gould and Einat (2007) emphasize

that greater understanding of the genes that contribute to BD mania will assist in the identification of endophenotypes of the disorder and increase the utility of mutant mice as useful models. Malkesman *et al*. (2009) describes the creation of genetic mouse models of BD that may provide greater etiological validity compared with models based on behavioural abnormalities observed in BD mania (for the predictive validity of such models, see Table 4).

Flaisher-Grinberg *et al*. (2009) compared the sweet solution preference of four mouse strains (Black Swiss, C57BL/6, CBA/J and AJ) as a putative method to model reward-seeking behaviour in mania. It was observed that Black Swiss mice exhibited the greatest preference for sweet solution, which was antagonized by twice daily injections of valproate (200 mg·kg^{-1}) or lithium (200 mg·kg^{-1}), but not the antidepressant imipramine (Flaisher-Grinberg *et al*., 2009). Further investigations with this model are warranted, especially because it is not clear why other strains did not exhibit a strong preference for sweet solutions, as well as the possibly confounding effect of polydipsia induced by these treatments. The Brattleboro rat, characterized by an inability to synthesize vasopressin, has been used commonly as an animal model of schizophrenia because they exhibit reduced PPI when compared with Long Evans rats (Feifel *et al*., 2004; Cilia *et al*., 2010). Because deficient PPI is observed in BD mania as well as in schizophrenia (Braff *et al*., 2001; Perry *et al*., 2001), this animal model may have relevance to mania. Treatments used for both mania and schizophrenia are effective in this model. Specifically, acute or subchronic clozapine, risperidone or haloperidol improved PPI in Brattleboro rats to levels comparable with Long Evans rats (Feifel *et al*., 2004; Feifel *et al*., 2007; Cilia *et al*., 2010). Brattleboro rats also exhibit increased activity in response to a novel test environment (Cilia *et al*., 2010). The effect of anti-manic medications has not yet been assessed in these animals, but such studies would prove useful to determine the specificity of this model for identifying novel treatments for the disorder. In mice exhibiting lower PPI than other strains (DBA mice), acute administration of lithium (30 mg·kg^{-1}), carbamazepine (30–100 mg·kg^{-1}), topiramate (100 and 300 mg·kg^{-1}), valproate (178 and 316 mg·kg^{-1}) and lamotrigine (3–30 mg·kg^{-1}) increased PPI (Flood *et al*., 2009). These results demonstrate that PPI may be affected non-selectively by drugs both efficacious and ineffective in treating BD mania, limiting the specific applicability of this measure. Therefore, although using strain differences to investigate putative treatments for BD mania may prove useful, it is likely that any drug developed will not only specifically 'treat' the underlying causes but also exhibit subtractive effects on behaviour that would be observed in non-BD as well as BD patients (Harrison-Read, 2009). Models developed specifically to mimic neurobiological abnormalities observed in patients with BD mania are consequently more likely to enable BD mania-specific treatments.

There are several examples of genetically manipulated mice that could serve as models of BD mania, characterized by links to potential underlying mechanisms of the illness. Examples include genes that have been associated with BD, such as CLOCK, DAT, Glutamate 6 receptor (GluR6) and DISC1. GluR6 knockout (KO) mice exhibit hyperactivity, aggression and reduced anxiety, which were reversed with chronic lithium treatment (4 week 2.4 g·kg^{-1} chow), with modest effects in wild-type (WT) mice (Shaltiel *et al*., 2008). Given that lithium was so effective in these mice, but fails to effectively treat all patients with mania, other treatments should also be assessed, including antipsychotics, as well as failed therapeutics such as lamotrigine. The behaviours described in GluR6 KO mice differed from WT littermates, but the similarity to behaviours in BD mania is largely superficial.

As discussed above, one technique to generate models of mania based on the quantification of behaviour in patients with BD mania was to create a human exploratory paradigm that mimics a rodent exploratory paradigm, the behavioural pattern monitor (BPM) (Geyer *et al*., 1986; Young *et al*., 2007). This multivariate approach to assessing spontaneous exploration in the human BPM has resulted in the identification of a unique exploratory profile of patients with BD (increased motor activity, exaggerated specific exploration and more linear patterns of movement) that differed from control subjects, patients with schizophrenia and adult ADHD subjects (Paulus *et al*., 2007; Perry *et al*., 2009).

The BPM has been instrumental in the development of DAT KD mice as a model of BD mania. The DAT has been linked to BD mania across several genetic linkage studies (Kelsoe *et al*., 1996; Greenwood *et al*., 2001; Greenwood *et al*., 2006), with functional consequences of DAT mutation leading to reduced cell surface expression of the transporter (Horschitz *et al*., 2005). These findings support observations of lower levels of DAT reported in BD patients (Amsterdam and Newberg, 2007). DAT KO mice were reported as a putative model of mania because these mice exhibit increased motor activity (Giros *et al*., 1996) and impaired PPI (Ralph *et al*., 2001). Moreover, PPI deficits in these mice were reversed with acute treatment with the atypical antipsychotics clozapine and olanzapine (Powell *et al*., 2008). Given that the poor physical condition of these mice limits their usefulness in assessing novel therapeutics, a line of DAT KD mice was subsequently developed (Zhuang *et al*., 2001). Because DAT KD mice exhibit only 10% DAT compared with WT littermates, their spontaneous exploration was assessed in the mouse BPM to assess their possible utility as a model of mania. DAT KD mice exhibited a profile that is (i) consistent with that of patients with BD mania (Ralph-Williams *et al*., 2003; Perry *et al*., 2009); (ii) attenuated with environmental familiarity (Young *et al*., 2010c); (iii) reinstated with environmental novelty or stimulants at doses that do not affect WT littermates (Young *et al*., 2010c); and (iv) partially attenuated by chronic valproate treatment (Young *et al*., unpubl. obs.). Interestingly, *in vitro* studies suggest that valproate treatment may increase DAT expression (Wang *et al*., 2007), thus providing a putative mechanism for the valproate-induced treatment effects observed in these mice. Increased activity and straighter linear movement through the environment (as measured by reduced spatial d, also observed in patients with mania) are also observed in these mice when assessed in a smaller open-field test, both of which were attenuated by acute valproate treatment (200 mg·kg^{-1}) (Ralph-Williams *et al*., 2003). DAT KD mice also exhibit hedonia-like behaviour in terms of food motivation behaviour (Cagniard *et al*., 2006), as well as increased risk preference in a mouse version of the IGT (Young *et al*., 2011). DAT KD mice therefore mimic several features that are observed in BD mania in terms

Table 4

Genetic models of mania

Manipulation	Spp.	Treatment	Outcome	Strengths	Weaknesses	Reference
Assessing sweet preference of four strains	Mice	Subchronic lithium (200 mg·kg^{-1}) or valproate (200 mg·kg^{-1}) for 2–4 days	Both treatments reduced sweet preference of Black Swiss mice but not other strains	Approved mania treatment attenuated manipulation effects, genetic differences between strains may yield interesting evidence for lithium effects	Effects are on normal behaviour, thus additive and not specific to mania. Not all strains exhibited a sweet preference	Flaisher-Grinberg *et al.*, 2009
Reduced PPI of DBA vs. C57 mice	Mice	Acute lithium (30 mg·kg^{-1}), carbemazepine (30–100 mg·kg^{-1}), topiramate (100 and 300 mg·kg^{-1}), valproate (178 and 316 mg·kg^{-1}) and lamotrigine (3–30 mg·kg^{-1})	All treatments ↑ PPI in DBA mice	Approved mania treatments ↑ PPI except lithium	Effects are on normal behaviour, thus additive and not specific to mania. False positives of topiramate and lamotrigine limit the predictive validity of effect	(Flood *et al.*, 2009
Glutamate receptor 6 knockout mice hyperactivity, aggression and low anxiety	Mice	Chronic lithium (2.4 g·kg^{-1})	Lithium reversed the abnormal behaviour of the mice	Approved mania treatment reversed the mania-like behaviour without the need to antagonize an acute drug effect	Modest effects of lithium on wild-type mice, common polydipsea side effect not discussed, mania patients not null for glutamate receptor 6	Shaltiel *et al.*, 2008
Hyperactivity in dopamine transporter knockdown mice	Mice	Acute valproate (200 mg·kg^{-1})	Lithium attenuated the hyperactivity of the mice	Approved mania treatment reversed the mania-like behaviour without the need to antagonize an acute drug effect, links of reduced DAT expression in mania patients	Mania-like behaviour reversed via acute not chronic treatment	Ralph-Williams *et al.*, 2003
D-box binding protein knockout mouse stress-induced hyperactivity	Mice	Subchronic lithium (0.6 g·L^{-1}) for 10 days	Lithium attenuated some mania-like behaviours	Approved mania treatment reversed the mania-like behaviour without the need to antagonize an acute drug effect	Mania-like behaviour only induced via long-term stressors including isolation rearing	Roybal *et al.*, 2007

of behaviour, cognition and putative neurobiological abnormalities.

Another gene putatively, although not consistently, linked to BD is GSK-3. Interest in this gene is motivated by the possibility that lithium and valproate may exert their effects via the pathway in which this gene acts. Heterozygous GSK-3 mutant mice have been created and exhibit reduced hole-poking behaviour and increased immobility in the forced swim test as well as other changes that resemble lithium-treated mice (O'Brien *et al.*, 2004). Overexpression of GSK-3β in mice results in hyperactivity and reduced habituation, which may mimic some of the features of mania (Prickaerts *et al.*, 2006). Therefore, GSK-3 mice may be useful as a screen for lithium-like compounds. Moreover, there appears to be greater evidence linking GSK-3 inhibition with antidepressant-like activity than with mania-reducing effects.

Finally, there are several circadian gene mutants that may prove to be useful animal models of mania. The circadian gene D-box binding protein (DBP) was identified as a putative candidate gene for BD (Le-Niculescu *et al.*, 2008). DBP KO mice exhibit lower activity and a blunted response to stimulants, but after a chronic stress paradigm, these mice become hyperactive and sensitive to stimulant treatment, with sleep deprivation–induced hyperactivity that was attenuated by acute valproate (200 mg·kg^{-1}) treatment (Le-Niculescu *et al.*, 2008). The hyperactivity exhibited by these DBP KO mice only occurred after exposure to long-term stressors such as isolation housing, chronic unpredictable stress and foot shock testing over a 1 month period. If this stress manipulation is required in every study, these mice may not prove the most desirable as an animal model for assessing novel therapeutics. Polymorphisms in BMAL1, a binding partner of CLOCK, have been observed in BD patients, and mice with a mutation of the CLOCK gene were created (Roybal *et al.*, 2007). These CLOCK mutant mice exhibited mania-like behaviours including reduced sleep, hyperactivity that wanes with time but is reinstated with novelty (consistent with DAT KD mice above), increased reward sensitivity to cocaine as well as sucrose preference, increased dopaminergic activity and subchronic lithium-induced (600 mg·L^{-1} for 10 days) reversal of some behaviours (McClung *et al.*, 2005; Roybal *et al.*, 2007). More studies are required for these CLOCK-related mutants, not only in other behaviours but also in investigating additional proven and ineffective treatments (see Figure 3).

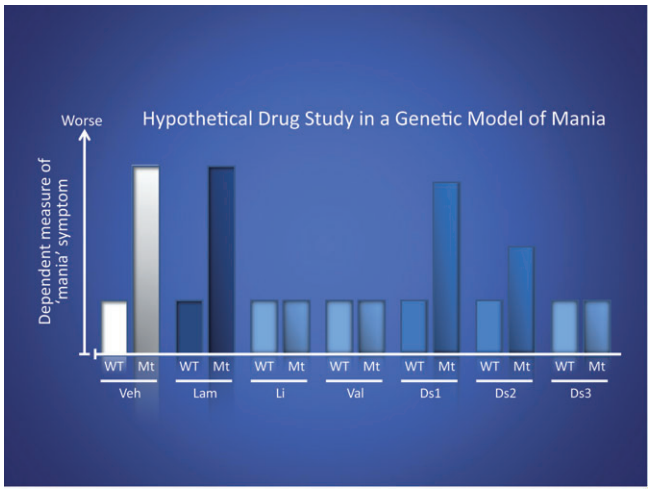

Figure 3

Hypothetical results of a putative treatment study in a mutant animal model of mania. The dependent measure of mania-like activity is on the *y*-axis, and the treatment groups are depicted on the *x*-axis. WT = wild-type littermate mice, Mt = genetically modified mouse model of mania. Veh = vehicle, Lam = lamotrigine (used here as a negative control), Li = lithium, Val = valproate (both used here as positive controls), Ds1 = dose 1, Ds2 = dose 2, Ds3 = dose 3 of the drug studied. The Mt mice would exhibit more 'mania' symptoms in comparison with WT mice. Given that lamotrigine does not treat Bipolar mania while lithium and valproate do, one would expect no improvement in mania with lamotrigine in either group, but improvements/normalization are observed for lithium and valproate treated mutant mice. For the test therapeutic, a dose–response effect would be observed in treating Mt mice. Ideally all treatments would be assessed using a chronic 4 week plus study.

Summary of findings

While manic states may include a diverse variety of multifacted symptoms that include euphoria, irritation, grandiosity and increased goal-directed activity, it is clear that the majority of the animal models of BD mania rely predominantly on motor activity levels as their primary behavioural outcome measure. Many factors can influence the effect of the inducing agent and/or treatment in this univariate approach to modelling BD mania, including the size of the chamber used, whether it is an open field or activity chamber, assessed in the dark or light and the familiarity of the testing environment. Moreover, treatment attenuation of stimulant-induced hyperactivity can be confounded by the selection of a hypoactive strain of animals, even in the absence of treatment effects on stimulant-naive subjects. These factors may contribute toward the large variety of effects of anti-manic agents and treatment regimens on these models. Acute stimulant-induced effects on behaviour reversed by drugs that act on the same receptors (e.g. amphetamine, an indirect dopamine agonist, and antipsychotics, dopamine D2 receptor antagonists) may be confounded by receptor tautological effects. Unfortunately, the combination of amphetamine and chlordiazepoxide produces so many possible interactions that the data produced can be unreliable unless all possibilities are addressed. The false-positive data generated by drugs that are effective in these models as well as in the ouabain-induced hyperactivity model, but not in BD mania, further highlight the limitation of these approaches for generating novel anti-manic treatments. Finally, many studies listed here examined the effects of acute administration of an 'inducing' agent as well as acute treatment-induced reversal of effects. While these studies are useful in behavioural pharmacological terms, mania is a long-term disease in which chronic treatment is required to alleviate symptoms. Studies that utilize chronic treatment are therefore more likely to exhibit predictive validity for treatment in patients. Care must be taken in chronic studies however, because the side effects of chronic lithium treatment in rodents may interact with mania-like behaviour in animals, limiting the predictive validity of the study.

Neither environmental models nor genetic models are limited by receptor tautological or by drug interaction confounds. Environmental models involve using manipulations such as sleep deprivation, competition or stressors to induce behavioural changes in an otherwise normal animal to recreate behaviours that may have relevance to BD mania. These models may mimic aspects of the disorder but care must be taken when assessing treatments in these models given their use in other diseases such as sleep disturbance and anxiety. Given that animals tested in these paradigms may not necessarily have links to the aetiology of BD mania, any treatments developed may have limited efficacy for specifically treating this disorder.

Genetic models appear under several guises, including assessing strain differences on behaviour. The concern arising from environmental models can also be levelled at strain difference models, because any treatment developed in such normal animals may not have specificity to BD mania. Genetic models that are created with reference to the aetiology of BD mania may provide greater validity for treatment in acute mania if that model is based on abnormalities observed in patients. Such investigations may offer the opportunity to develop pharmacogenomic treatments in psychiatry as has occurred for other disease populations (Moller and Rujescu, 2010; Serretti and Drago, 2010). There is only a limited number of treatment predictive validity studies performed on genetic models to date; thus, more are required to validate these models across treatments for a variety of psychiatric disorders, including mania and schizophrenia. Evaluation of a diverse group of drugs, including both efficacious medications and agents proven clinically ineffective, will enable improved development and validity of high-utility preclinical models.

Future directions

There are multiple treatments approved for BD mania, including lithium, valproate and carbamazepine, as well as several antipsychotics. A number of potential treatments have also failed to gain approval, including lamotrigine and gabapentin. Using these drugs as positive and negative controls would enable the pharmacological predictive validation of animal models of BD mania. One problem is the difficulty in identifying drugs that do not attain approval for the treatment of BD mania for further comparisons. Moreover, the lack of details in these failed studies also impedes interpretation of the effects of these drugs on animal models of BD and constrains future directions of research. Thus, greater detail should be provided from clinical studies to delineate specific aspects of mania impacted by novel agents under investigation.

The majority of approaches employed in modelling BD mania have also been limited in focusing on simple behaviours that may have only limited validity with respect to the self-report and observer-rated human behaviours they are supposed to model (Harrison-Read, 2009) (e.g. activity levels and psychomotor agitation, resident–intruder and aggression). Given the wide range of psychiatric conditions these paradigms are designed to model, their selectivity for identifying treatments for BD mania may be limited.

BD mania is characterized by extensive behavioural and cognitive dysfunction that could be modelled with a variety of preclinical paradigms (Einat, 2007b). Some abnormalities during manic episodes that can be detrimental to their overall functioning include attentional deficits, disinhibited responses and increased risk taking. These behaviours can be quantified in laboratory settings and assessed in rodents using cross-species tasks with translational validity, including measures of vigilance (Young *et al.*, 2009a,b), stop-signal reaction time (Eagle and Baunez, 2010) and delay-discounting (Reynolds, 2006; Madden *et al.*, 2007). Moreover, attempts have been made to objectively quantify the hyperactivity and goal-directed activity in these patients (Young *et al.*, 2007; Minassian *et al.*, 2009; Perry *et al.*, 2009; 2010), resulting in novel animal models that may mimic some of the underlying behavioural abnormalities observed in BD mania (Perry *et al.*, 2009; Young *et al.*, 2010a,b). Combining the approaches of (i) using a comprehensive battery of tests for different aspects of mania (Einat, 2007b), (ii) utilizing genetic information on developing models with greater etiological validity (Gould and Einat 2007; Malkesman *et al.*, 2009) and (iii) objective quantification of patient behaviour with cross-species paradigms (Young *et al.*, 2007) will enable the development of models producing drug treatments that are specialized for treating BD mania. The validity of these models can be effectively assessed by testing a diverse group of drugs, including treatments approved for BD mania as positive controls, as well as using clinically ineffective agents as negative controls.

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Conflict of interest

The authors report no conflict of interest with the current manuscript.

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