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From Animal Models to Behavioral Treatment of Bipolar Disorder

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Bipolar disorder is difficult to capture in a single animal model, so far proving impossible. Animal models have evaluated the neurobiological, pharmacological and behavioral aspects, both in isolation and combination, but have yet to prove valid or lead to highly effective biologically based treatment. There has been some success in shaping behavioral treatment in humans. Third wave behavioral therapies and Applied Behavior Analysis (ABA) have shown decreased relapse and re-hospitalization in humans at one year follow up, increased medication compliance and increased family support. Cognitive Behavior Therapy (CBT), Dialectical Behavior Therapy (DBT) and Family Focused Treatment (FFT) that include problem solving, family education and self-management have shown success across school, home and community settings, especially when used as part of the overall treatment package with medication. While a single model is unable to encompass all areas of need for a diagnosis as complex as bipolar disorder, continued research may allow for new treatments to emerge.

Current lifetime rates of bipolar disorder (BD) range from 1-2% (Charney et al., 2017; Machado-Viera, Kapczinski, & Soares, 2004; Merikangas et al., 2007) to upwards of 4% when all forms of the disorder are considered including those subthreshold (Geddes & Miklowitz, 2013; Gould & Einat, 2007). Bipolar disorder has maintained grants and research interest within the scientific community over the last decade even in times of reduced funding and budget cuts (Insel, n.d.). This is possibly due to the prevalence and lifetime cost for treatment to the public estimated at over \$24 billion in 1998 (Begley et al., 2001). Even with continued research, meeting validity measures when using animal models has proven difficult. While aspects of symptomology are studied in great detail and specific brain regions have been implicated in those symptoms, understanding how to translate experimental work to applied treatment has proven slower and less efficacious than practitioners would like.

Bipolar disorder is characterized by cycling between mania and depression with periods of insomnia, hyper sexuality and euphoria during mania. During periods of mania, examples of manic behavior may include talking for hours jumping from topic to topic, purchasing high quantities of unneeded items, staying awake for multiple days at a time, making life altering decisions, painting and re-painting a home. At its most severe, the poor judgment that results from this combination of traits leads to hospitalization. Periods of mania can last weeks, months, or even years. Bipolar depression occurs between mania episodes with inconsistent durations across cycles. Rapidity of cycling is one dimension utilized to determine severity of the disorder with rapid cyclers being those who experience more than four episodes of mania or depression a year (Belmaker, 2004).

Bipolar depression may include decreased participation in once pleasurable activities, decreased appetite, weight loss, and feelings of worthlessness that last more than two weeks. This may include failure to get out of bed for days at a time, talk of suicide, the loss of a job, or failing out of school. While it is often described as cycling between depression and mania, it can also include quick changes between a calm state and anger or rage. Bipolar II is defined by hypomania and depression; though this version is not always less severe, it usually does not result in hospitalization (Belmaker, 2004). A person who has experienced full mania at least once is not diagnosed with bipolar II.

Those who have been diagnosed with BD have high rates of comorbidity to a myriad of disorders (Grant et al., 2005; Krishnan, 2005), health issues (Saunders et al., 2014) and high risk behaviors such as unprotected sex, suicide and alcohol use (Goldstein et al., 2015). In the 1960s, lithium carbonate became one of the most effective treatment options for BD with decreased symptoms in up to 60% of those treated (Rea et al., 2003). Even so, lithium decreases mania symptoms better than depressive symptoms (Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004). When treated with lithium alone, up to half of those with BD fail to respond significantly and up to 75% relapse within five years of treatment (Gitlin, Swendsen, Heller, & Hammen, 1995). Due to this lack of efficaciousness, other treatment options (pharmacological and otherwise) have been sought.

Animal Models of Bipolar Disorder

Animal models of psychiatric diseases have proven difficult to develop and, perhaps, even harder to validate. A major reason for this failure is the lack of full understanding regarding the biological basis of BD. Other reasons range from an inability to produce a strain of rats with all symptoms to behavioral tests that fail to translate into therapeutic models. Animal models for BD have been attempted with a focus on genetics (Falk et al., 2016; Le-Niculescu et al., 2008), brain kindling (Post, Weiss, Leverich, Smith, & Zhang, 2001), pharmacology (Shaldubina, Einat, Szechtman, Shimon, & Belmaker, 2002), neural manipulation (Phillips, Ladouceur, & Drevets, 2008), and brain lesions (Machado-Vieira et al., 2004). While each fell short of answering all questions, cumulatively they contributed to a better understanding of the etiology of BD.

One common option for an animal model involves selective breeding for traits that resemble either depression or mania. For example, Black Swiss mice exhibit higher rates of manic-like behaviors than other strains to include increased locomotion (Einat, 2007) and decreased rates of this locomotion following treatment with lithium. Another option is to induce a sleep deprivation state to induce manic-like behavior such as increased locomotion and agitation (Einat, Kofman, & Belmaker, 2000). Finally, transgenic mice with mutant deletions can come close to showing all behavioral requirements for BD (Kato, Kubota, & Kasahara, 2007) though most still fall short of displaying the repetitive natural cycling. A variety of other options have been studied and evaluated, and while a complete model has yet to surface, each leads to new answers.

Three requirements for a model to be considered relevant are construct, face and predictive validity (Ellenbroek & Cools, 1990). Construct (or etiologic) validity is the evaluation of how the model is developed (e.g., knock out species, teratogens on pregnant females, or exposure to other environmental toxins). Face validity requires that the animal display the symptoms of the disorder in their own behavior; that the species engages in behaviors that ‘look’ like the disorder. One of the most difficult aspects of an animal model for BD is a way to induce or replicate natural cycling between mania and depression. Finally, predictive validity is the response of the model to treatment. It needs to follow a similar pattern as the treatment found in human models such as decreased mania symptoms following trials with Lithium and Valproate (Cappeliez & Moore, 1990; Frey et al., 2006). Overall, animal models have trouble meeting at least some, and sometimes all, of these requirements for psychiatric disease and therefore development of pharmacological and therapeutic options has proven slow. Many of the current treatments for BD were found while researching other disorders (Gould & Einat, 2007) and the effectiveness of new ones has been slow to emerge. The better option may continue to be evaluating combinations of models to increase overall validity (Einat, 2007).

Behavioral Treatment for Bipolar Disorder

Overall, the behavior treatments for BD range from treating individual symptoms to tackling the disorder as a whole. Behavioral treatment spans family focused treatment (Rea et al., 2003) and applied behavior analysis to cognitive behavior therapy, dialectal therapy (Marra & Thomas, 2005) and other third wave behavior therapies. Treatment for BD rarely only includes a behavioral element; it is usually a small piece within an overall package that includes daily medication and outpatient therapy. One reason for the variety in treatment modalities is the wide range of topographies those with BD may display. Pharmacological modalities may be combined with therapy for various aspects of the disorder, but even then different medications may be selected for different aspects of the cycle.

Each of the behavioral treatments discussed below evolved from the animal work of Skinner and Pavlov and from animal studies published in *The Journal of the Experimental Analysis of Behavior*. And early behavioral treatment models of mood disorders started with the work of “learned helpfulness” based on experimental work involving dogs. Behavior analysis, whose early days involved almost exclusively animal research, led to behavior analytic principles applied for treatment approaches and that subsequently led to cognitive-behavior therapy. Animal research was almost exclusively what started the behavioral fields that became cognitive-behavior therapy and the other behavioral treatments discussed here. So, although animal neuroscience models of bipolar disorder are limited at best, animal models play a very significant role in developing treatment modalities for bipolar disorder.

Family Focused Treatment

Treatment that includes interpersonal and family components for mood disorders originally gained momentum after showing those with schizophrenia had better outcomes when family therapy was part of the overall treatment package (Rea et al., 2003). When comparing a family based intervention package to an individual based intervention package, there was a greater reduction in relapse and rehospitalization for those receiving family based interventions (Goldstein, Axelson, Birmaher, & Brent, 2007). Individualized therapy appears to be less effective because the symptoms of BD are only evaluated from the perspective of individualized problem behaviors (Weisz & Kazdin, 2010) ignoring the depth of problems found within families of those with BD.

Family Focused Treatment (FFT) includes psychoeducation, communication training, and problem-solving skills training usually over a 6 -9 month period (Miklowitz, George, Richards, Simoneau, & Suddath, 2003; Miklowitz et al., 2000). FFT has been used with success in both adult and adolescent (FFT-Adolescents) populations to include shorter durations of both mania and depressive symptoms as well as better outcomes up to 2 years post treatment (Miklowitz et al., 2008). As with most behavioral treatments, FFT and FFT-A is most effective when used in combination with pharmacological treatment to stabilize or decrease depressive symptoms (Sullivan, Judd, Axelson, & Miklowitz, 2012). Given the high rate of heritability (McGuffin et al., 2003), a possible reason for the effectiveness for family based treatment is to teach all family members the skills needed for emotional regulation, stress reduction and symptom awareness.

Applied Behavior Analysis

Applied Behavior Analysis (ABA) is the scientific study of behavior using evidence based treatment to change socially significant behaviors (Cooper, Heron, & Heward, 2007). Similar to FFT, when ABA is used in treatment for individuals diagnosed with BD, a behavior analyst would evaluate the objective topography of each displayed behavior. Carr and Durand (1985) explain that behavior is communicative, both those displayed in a socially appropriate and inappropriate manner. The environment can be altered to decrease inappropriate behavior to include changing the motivating operations (McGinnis, Houchins-Juárez, McDaniel, & Kennedy, 2010) and teaching self-control skills (Dixon & Holcomb, 2000) or functionally equivalent replacement behaviors (Carr & Durand, 1985).

Treatment using ABA can be applied to specific BD symptoms, such as sleep dysregulation, that often accompanies mania episodes. Complicating pathology is that a lack of sleep can increase the severity of symptoms and induce those that were not already present (Carskadon, Acebo, & Jenni, 2004; O'Reilly, 1995) making treatment of this target behavior especially important. Many of the interventions to increase sleep cycle compliance and decreased latency to fall asleep include self monitoring, stimulus control to the nighttime routine, and use of relaxation techniques (Alperson & Biglan, 1979). Other interventions to increase sleep duration include faded bedtime with response cost (Piazza & Fisher, 1991), antecedent changes such as closing the doors, decreasing caffeine, and contingency contracting.

Other manic symptoms can include delusional statements, verbal disruptions and bizarre speech. Travis and Sturmey (2010) found Differential Reinforcement of Alternative behavior (DRA) and extinction to be effective at decreasing delusional statements when the behaviors were maintained by social attention. Lancaster et al. (2004) found non-contingent reinforcement (NCR) to decrease bizarre speech. Perhaps due to being maintained by a different function, appropriate verbal behavior did not increase through the use of non-contingent reinforcement. Similar to NCR, fixed-time schedules of reinforcement have substantially decreased inappropriate verbal behaviors (Rasmussen & O'Neill, 2006).

Cognitive Behavior Therapy

Cognitive Behavior therapy (CBT) is one of the most prevalent evidence based treatment practices for mental illness. The use of CBT continues to make headway with various mental illnesses to include BD. It can be highly effective to decrease negative statements during depressive states and overly optimistic statements during manic states. It has also proven effective for medication compliance and decreased negative outcomes in other areas (hospitalization, noncompliance, hyper sexual behaviors, etc). CBT decreases stays in the hospital and increases social functioning when used in conjunction with lithium or other prescribed medication regiment (Miklowitz, 2008). Scott et al. (2006), on the other hand, found limitations with the effectiveness of CBT; it appears to be most effective with less severe cases or those with under 12 episodes prior to treatment. Puvulari et al. (2004) has developed a combination of the family focused treatment with CBT (CFF-CBT), which has been effective at decreasing overall severity of symptoms in adolescents with BD.

Dialectical Behavior Therapy

Dialectical Behavior Therapy (DBT), originally designed for borderline personality disorder, reduced suicidal ideation, symptoms of depression and, overall, behavioral incidents (Katz, Cox, Gunasekara, & Miller, 2004; Linehan, 1993, Rathus & Miller, 2002) in treatment of BD. Given that these behaviors are often found in other disorders, investigations into its effectiveness began as part of a treatment package for BD. The findings have been adopted by many practitioners. Most recently, application of DBT to adolescents has been pursued with promising results (Goldstein et al., 2007). Unlike ABA based therapy that typically targets the outward manifestation of a behavior—the objective and measurable topography of the symptom—DBT focuses heavily on emotional regulation. One aspect of this is to teach emotion identification and stress reducing coping strategies, while decreasing behaviors that provide high arousal and increase medication compliance (Marra & Thomas, 2005).

Conclusion

Bipolar disorder is a complex mental illness highlighted by manic and depressive symptoms. Due to the complex nature of the disorder, animal models have failed to produce a completely encompassing model. Even so, behavioral treatment models continue to develop and evolve in an attempt to better serve clients with the disorder. Applied behavior analysis, CBT and /or DBT are adjunctive treatment options to medication compliance to produce the best outcomes possible for decreased severity and duration of symptoms for bipolar disorder.

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