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Something Must Be Done: An Argument for the Partial Deregulation of Research on Bipolar Disorder and the Implementation of Rolling Informed Consent

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SOMETHING MUST BE DONE: AN ARGUMENT FOR THE PARTIAL DEREGULATION OF RESEARCH ON BIPOLAR DISORDER AND THE IMPLEMENTATION OF ROLLING INFORMED CONSENT

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Bipolar disorder (BD) cripples the lives of countless individuals across the globe. The healthcare community has had difficulty securing effective, long-term treatment for this disease. This Note argues that enlarging the pool of possible research subjects through partial deregulation of BD research would facilitate the development of better treatment. This Note further proposes the implementation of a system of rolling informed consent to ensure that actual and full consent is obtained from BD research subjects.

Retaining his original sensibility . . . he gives himself up to all the extravagances of maniacal fury, or sinks inexpressibly miserable into the lowest depths of despondence and melancholy. If the former, he resembles in ferocity the t[i]ger, and meditates destruction and revenge. If the latter, he withdraws from society, shuns the plots and inveiglements which he imagines to surround him, and fancies himself an object of human persecution and treachery, or a victim of divine vengeance and reprobation.

—Philippe Pinel, A Treatise on Insanity (1806)[1]

Winston Churchill. Ernest Hemingway. Abraham Lincoln. Virginia Woolf. Former Chicago Bears first-round draft pick Alonzo Spellman. "Terminator" star Linda Hamilton. These prominent individuals, all considered great successes in their respective fields, had/have one thing in common: they all expressed symptoms of bipolar disorder ("BD").[2] In fact, BD has been recognized as a

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1. PHILIPPE PINEL, A TREATISE ON INSANITY (1806), *quoted in* ROY PORTER, THE FABER BOOK OF MADNESS 12–13 (1991).

2. Parris M. Kidd, *Bipolar Disorder as Cell Membrane Dysfunction: Progress Toward Integrative Management*, 9 ALTERNATIVE MED. REV. 107 (2004); David Haugh, *Bipolar ex-Bear Hoping: Former Defensive Tackle Alonzo Spellman Wants to Make NLF Comeback*, CHI. TRIB., Jan. 25, 2005, at C1; Interview by Larry King with Linda Hamilton, Actress, on *Larry King Live* (CNN television broadcast Oct. 14, 2005).

mental disorder for thousands of years.[3] In all that time, though, humankind has been unable to conquer the illness that has been (and continues to be) mentally crippling to millions of people worldwide.[4]

Something must be done to help those afflicted with this disease that tears apart lives. The medical community has made little significant progress in the search for treatment for this disease since the discovery of lithium as a mood stabilizer over thirty years ago.[5] Current federal regulations inhibit the progress.[6]

The time has come for the partial deregulation of federally-funded research seeking to find a new treatment for BD in adults. Because of the unique nature of BD, it should not be subject to the current *Code of Federal Regulations* (C.F.R.), but rather to a separate set of appropriately tailored rules. Because it is no coincidence that a disproportionately large number of incarcerated individuals experience bipolar symptoms, this Note argues that research should be allowed on prisoners provided that appropriate informed consent is given. The Note further argues that, because of the varying mental states a bipolar patient can endure, informed consent from such research subjects should be obtained on a rolling basis.

To begin, this Note examines some basic facts and figures of BD, including a synopsis of current treatment options. Then it explores why the disease is such a problem in American society, and why something must be done to facilitate successful research. Next, it analyzes current experimentation and the role that the *Declaration of Helsinki* and the C.F.R. play. Once this foundation is established, the Note proposes two reforms to the current legal treatment of bipolar research: (1) § 46.301 of the C.F.R. should not apply to bipolar research, thereby allowing prisoners to participate in experimental studies pertaining to the disease; and (2) there should be implementation of a series of rolling consent confirmations for bipolar subjects to ensure that consent is truly and freely given.

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3. BD has been recognized since the time of Hippocrates in 400 B.C. Kidd, *supra* note 2, at 107.

4. Some experts estimate that 1.3% to 1.6% of the general population will experience BD in a lifetime. Bruno Müller-Oerlinghausen et al., *Bipolar Disorder*, 359 THE LANCET 241 (2002). Others estimate that the percentage is as high as 3.7%. Kidd, *supra* note 2, at 108.

5. *See, e.g.*, Joseph F. Goldberg & Leslie Citrome, *Latest Therapies For Bipolar Disorder. Looking Beyond Lithium.*, POST GRADUATE MED., Feb. 2005, at 25 ("After more than 50 years of use in psychiatric medicine, lithium remains the standard against which the potential mood-stabilizing properties of newer psychotropics are judged.").

6. *See, e.g.*, 45 C.F.R. § 46.306 (2006).

I. BIPOLAR DISORDER TODAY

In 2000, more than 2.3 million American adults had BD.[7] This disease that "too often erodes the desire and will to live"[8] results from abnormalities in brain biochemistry and in circuit structures.[9] BD is characterized by extreme mood shifts from intense manic highs to deep depression.[10] It is associated with a high rate of morbidity as well as mortality.[11]

A. Types of Bipolar Disorder

In all forms of BD, individuals suffer from periods of mania and depression that can often incapacitate them.[12] The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* defines manic episodes as including three or more of the following symptoms: inflated self-esteem or sense of grandiosity, decreased need for sleep, unusual talkativeness or pressure to keep talking, racing thoughts, distractibility, and/or excessive involvement in pleasurable activities with a high potential for painful consequences such as spending sprees, and casual or unsafe sex.[13] A major depressive episode lasts at least two weeks and is characterized by "either depressed mood or the loss of interest or pleasure in nearly all activities" and at least four of the following symptoms: "changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficultly thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts."[14] The

7. NAT'L INST. OF MENTAL HEALTH, DEP'T OF HEALTH & HUMAN SERVS., BIPOLAR DISORDER RESEARCH AT THE NATIONAL INSTITUTE OF MENTAL HEALTH 1 (2000), *available at* http://www.nimh.nih.gov/publicat/bipolarresfact.cfm.

8. *Id.* (quoting KAY REDFIELD JAMISON, AN UNQUIET MIND 6 (Vintage Books 1996) (1995)).

9. *Id.*

10. *Id.*

11. Lori Altshuler, *Prescribing Antidepressants for Depression in Bipolar Disorder-Point/Counterpoint*, PSYCHIATRIC TIMES, Aug. 2004, at 88.

12. NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 1.

13. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 332 (4th ed. 1994); Kathryn Wilkins, *Bipolar I Disorder; Social Support and Work*, *in* HEALTH STATISTICS DIV., STATISTICS CANADA, 2004 ANNUAL REPORT: HOW HEALTHY ARE CANADIANS? 21, 23 (2004), *available at* http://www.statcan.ca/english/freepub/82-003-SIE/free.htm (click "Annual Report 2004" PDF hyperlink).

14. AM. PSYCHIATRIC ASS'N, *supra* note 13, at 320.

average depressive episode experienced by BD individuals lasts six months.[15] Individuals who have experienced at least one episode of severe mania are said to have bipolar I disorder.[16] Individuals with bipolar II disorder have experienced at least one hypomanic episode.[17] A hypomanic episode differs from a full-blown manic episode because it is characterized by increased energy, euphoria, irritability, and intrusiveness to a milder extent than in a manic episode.[18] Hypomanic episodes may not prevent a bipolar individual from participating in everyday life but are noticeable to others.[19] Cyclothymic disorder is the mildest form of BD and is diagnosed in individuals who experience periods of mania and depression that are not intense enough to meet the criteria for either Type I or Type II BD.[20]

B. Current Treatment Options: Drugs and Psychotherapy

Treatment for BD can vary greatly from patient to patient and can include medication, therapy, and other treatments. For some individuals, medication can help and typically includes a combination of mood-stabilizing medication, anti-mania drugs, and antidepressants.[21] Lithium and valproate are the most commonly used mood stabilizing drugs today.[22] Lithium has been approved by the Food and Drug Administration as a mood-stabilizer since 1970.[23] Lithium is particularly beneficial for BD patients because it is proven to reduce suicidal behaviors.[24] Some patients do not respond well to lithium, however, and others cannot tolerate the drug's side effects.[25] These side effects can include weight gain, tremor, memory loss, reduced sensitivity to light, and long-term effects on the kidneys and thyroid.[26] The drug also has other nega-

15. ROGER GRANET & ELIZABETH FERBER, WHY AM I UP, WHY AM I DOWN? UNDERSTANDING BIPOLAR DISORDER 84 (1999).
16. NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 3.
17. *Id.*
18. *Id.*
19. *Id.*
20. *Id.*
21. *Id.* at 6.
22. *Id.*
23. Goldberg & Citrome, *supra* note 5, at 30.
24. *Id.* at 25.
25. NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 6.
26. GRANET & FERBER, *supra* note 15, at 152–53; Goldberg & Citrome, *supra* note 5, at 25; NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 6.

tive aspects, such as its narrow therapeutic range.[27] Additionally, when taken in large amounts, lithium is toxic.[28] Divalproex (Depakote) is an anticonvulsant that is often used to treat acute mania.[29] The FDA requires labels warning of hyperglycemia and diabetes on second-generation antipsychotics.[30]

Treatment via medication often becomes less effective over time.[31] Despite medication and psychotherapy, a high rate of relapse into depression continues in BD patients.[32] Over a period of five years, 85% of those with BD will have a relapse after one affective episode.[33] Thus, BD continues to take a high toll on the individuals who suffer from the disease as well as on society as a whole. Only 15% of those with BD will consider treatment effective and describe themselves as being able to function well.[34]

II. IMPACT ON THE INDIVIDUAL AND ON SOCIETY

BD often has a crippling effect on the lives of those who suffer from it. Some patients are incapable of having meaningful emotional relations, holding jobs, and functioning in society.[35] Some require hospitalization in periods of intense depression and/or mania.[36] People with BD are much more likely than the general population to be obese, afflicted with asthma, suffer from migraine headaches, and experience panic.[37] They are 4.4 times more likely than those without BD to have had sexually transmitted diseases because of hypersexuality that may occur during periods of hypomania or mania.[38]

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27. Kidd, *supra* note 2, at 115.

28. Harold Hopkins, *Calming the Roller Coaster Ride of Mood Swings*, FDA CONSUMER, Nov. 1988, at 20, 23.

29. Goldberg & Citrome, *supra* note 5, at 26.

30. *Id.* at 28.

31. Kidd, *supra* note 2, at 116.

32. *See* NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 1.

33. Don St. John, *Bipolar Affective Disorder: Diagnosis and Current Treatments*, 15 CLINICIAN REVS. 6, 44 (2005), *available at* http://www.clinicianreviews.com/print.asp?page=courses/105041/lesson.htm.

34. GRANET & FERBER, *supra* note 15, at 79.

35. *See* St. John, *supra* note 33, at 44 ("with two thirds of patients experiencing functional and occupational impairment and strained social relationships").

36. *See* GRANET & FERBER, *supra* note 15, at 125.

37. Wilkins, *supra* note 13, at 24–25.

38. E. FULLER TORREY & MICHAEL B. KNABLE, SURVIVING MANIC DEPRESSION 258 (2002).

Perhaps the most impacting effect associated with BD is the relationship between the disease and suicide. According to one study, BD is the leading cause of suicide in the United States.[39] More than half of those inflicted with BD have outwardly expressed suicidal thoughts.[40] Twenty-five to 33% of patients with BD attempt suicide.[41] About 15% of all individuals who suffer from the illness will eventually complete suicide.[42] Accidental death is also frequent, particularly when a BD patient is experiencing a manic episode, because "[g]randiosity and delusions may lead the person to drive 100 miles an hour, challenge a police officer holding a gun, or try to leap between the rooftops of buildings, often with fatal consequences."[43] The current mortality rate for BD individuals is 2.3 times the mortality rate of the general population.[44]

People with BD are more likely to become involved with substance abuse, particularly in the United States.[45] Some estimates indicate that nearly 50% of those with BD have such dependencies.[46]

For individuals with BD who are capable of functioning in the workplace, barriers other than death or injury can keep them out. The Americans with Disabilities Act of 1990[47] cast a broad net of anti-discrimination protections for people with disabilities.[48] For those with BD, however, the net was not cast wide enough.

The ADA protects many individuals, but courts have been reluctant to use the Act to help those with BD. Many courts accept that

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39. GRANET & FERBER, *supra* note 15, at 2.

40. Ian Daly, *Mania*, 349 THE LANCET 1157, 1158 (1997).

41. St. John, *supra* note 33, at 43; Müller-Oerlinghausen et al., *supra* note 4, at 241.

42. St. John, *supra* note 33, at 43.

43. TORREY & KNABLE, *supra* note 38, at 105.

44. *Id.* at 104. The mortality rate is much worse in men than in women. The life expectancy of a man with a serious mental illness is 14.1 years shorter than that of a healthy man. *Id.* That of a woman with a serious mental illness is reduced by 5.7 years. *Id.*

45. Müller-Oerlinghausen et al., *supra* note 4, at 221.

46. *Substance Abuse and Mental Health Servs. Admin.: Hearing Before the Subcomm. on Labor, Health and Human Servs.*, 109th Cong. 6 (2005) [hereinafter *Hearings*] (statement of Charles G. Curie, Administrator, Substance Abuse and Mental Health Services Administration, U.S. Dept. of Health and Human Services).

47. Americans With Disabilities Act of 1990, Pub. L. No. 101-336, 104 Stat. 327 (codified as amended in scattered sections of 42 U.S.C.). Title I of the Act prohibits employment discrimination and Title II of the Act addresses discrimination in the context of public services, programs, and benefits. A disability, for the purposes of these two Titles, means: (1) a physical or mental impairment that substantially limits one or more of the major life activities of an individual; (2) a record of such an impairment; or (3) regarded as having such an impairment. 29 C.F.R. § 1630.2 (2006); 28 C.F.R. § 35.104(4) (2006).

48. Yuri N. Walker, *Protecting the Public, The Impact of the Americans with Disabilities Act on Licensure Considerations Involving Mentally Impaired Medical and Legal Professions*, 25 J. LEGAL MED. 441, 448–49 (2004).

BD counts as a mental impairment under the ADA, but refuse to accept that the disease substantially limits a major life activity.[49] Whether a disease substantially limits a major life activity is determined on a case-by-case basis.[50]

Courts that are willing to accept BD as a disability for the purposes of the Act often refuse to extend the Act's protection to disability-caused misconduct.[51] The majority of the circuits believe that "Congress, in enacting the ADA, intended to prohibit unfair stereotypes about the disabled but not to shield the disabled from the consequences of misconduct."[52]

Because the ADA typically withholds protection from individuals with BD, otherwise capable individuals are often denied professional opportunities. This permissible discrimination is prevalent in several professional fields, but particularly in those of medicine and law. Though requirements vary state-by-state, many boards of bar examiners (and boards of medical reviewers) inquire into applicants' mental history, including BD.[53] The existence of BD is thought to be related to an applicant's moral character and present fitness to practice law or medicine.[54] When applicants challenge these refusals under the ADA, the state boards' actions are almost always upheld.[55] If there were an effective treatment for BD, professional review boards might be more willing to consider BD a non-debilitating condition that does not prevent otherwise able doctors and lawyers from becoming licensed.

BD also presents a significant drain on fiscal resources. In the United States, people with serious mental illness represent the single largest diagnostic group of those receiving Social Security.[56] This is compounded by additional costs by way of foregone earnings attributable to lower productivity and decreased

49. *See, e.g.*, Taylor v. Phoenixville Sch. Dist., No. 98-1273, 1999 U.S. App. LEXIS 19572, at *17–18 (3d Cir. Aug. 18, 1999); *see also* McConnell v. Pioneer Hi-Bred Int'l., Inc., No. CIV. 98-4060-KES, 2000 U.S. Dist. LEXIS 3335 (S.D.S.D. Jan. 25, 2000) (granting summary judgment against an employee who was terminated after twenty-five years of service when diagnosed with BD that resulted in total or partial disability five months per year).

50. Albertson's, Inc. v. Kirkingburg, 527 U.S. 555, 566 (1999).

51. *See, e.g.*, Valentine v. Standard & Poor's, 50 F. Supp. 2d 262 (S.D.N.Y. 1999); Den Hartog v. Wasatch Acad., 909 F. Supp. 1393 (C.D. Utah 1995).

52. *Den Hartog*, 909 F. Supp. at 1401.

53. Allison Wielobob, *Bar Application Mental Health Inquiries: Unwise and Unlawful*, A.B.A. J. HUM. RTS., Winter 1997, at 16, *available at* http://www.abanet.org/irr/hr/welobob.html.

54. Applicants v. Tex. State Bd. of Law Exam'rs, No. A93CA740SS, 1994 U.S. Dist. LEXIS 21290, at *3 (W.D. Tex. Oct. 11, 1994).

55. *See, e.g.*, Johnson v. Kan. Sup. Ct., 888 F. Supp. 1073 (D. Kan. 1995); *Tex. State Bd. Of Law Exam'rs*, 1994 U.S. Dist. LEXIS 21290; Walker, *supra* note 48, at 441, 448–49.

56. *Hearings*, *supra* note 46, at 6.

employment.[57] In 1991, the cost-of-illness of BD was an estimated $45 billion.[58] The great cost of this illness on American society is recognized in the President's 2006 budget proposal for the Substance Abuse and Mental Health Service Administration.[59] During the proposal, bipolar patients were referred to in terms of the "public health burden" they created.[60]

About 1% of Americans suffer from BD.[61] This figure is comparable to the other populations, such as Ireland,[62] but surprisingly lower than the number of those afflicted in other countries. In Hungary, for example, three percent of the population has BD and in Canada, the number is 2.4 percent.[63] If the cost to society is so great in the US, one can only imagine how great it is where BD is three times as prevalent.

III. REGULATION AND CURRENT EXPERIMENTATION

Current research in the field of BD is inadequate. There is a greater need for research subjects to combat limited test sample sizes.

A. Regulation

Human experimentation is governed by international doctrine as well as by domestic regulation. The *Declaration of Helsinki*[64] and the *Nuremburg Code*[65] are the two most prominent sources of international guidelines for research and experimentation involving humans as subjects. Further research into BD would require research and experimentation on human subjects. The *Nuremburg*

57. Wilkins, *supra* note 13, at 22.

58. Müller-Oerlinghausen et al., *supra* note 4, at 241.

59. *See Hearings*, *supra* note 46, at 2.

60. *Id.* at 6.

61. Altshuler, *supra* note 11, at 88.

62. *See* Daly, *supra* note 40, at 1157.

63. Wilkins, *supra* note 13, at 23.

64. WORLD MED. ASS'N, WORLD MED. ASS'N DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964), *available at* http://www.wma.net/e/policy/pdf/17c.pdf [hereinafter *Helsinki Declaration*].

65. THE NUREMBERG CODE, *in* 2 TRIALS OF THE WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, 181–82 (Government Printing Office, 1949), *available at* http://www.hhs.gov/ohrp/references/nurcode.htm.

Code, developed after the trials of Nazi doctors at Nuremburg after World War II, states that voluntary consent of human subjects is absolutely essential.[66] It also requires that experimentation avoid all unnecessary physical and mental suffering and injury to the subjects, and that the risk involved in the experiment never exceeds its humanitarian importance.[67]

The *Declaration of Helsinki* was promulgated by the World Medical Association, of which the United States is a member.[68] The introduction to the *Declaration* quotes the *International Code of Medical Ethics* and declares the norm applicable to all medicine, experimental or otherwise: "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."[69] The *Declaration* espouses various principles, like respecting the privacy of the subject,[70] evaluation of costs/risks and benefits,[71] and the right of test subjects to abstain from participation or to withdraw consent at any time during the experiment.[72] It also leaves much to the discretion of individual member states, like determining what is a "reasonable likelihood that the populations in which the research is carried out stand to benefit,"[73] or "if the importance of the objective outweighs the inherent risks and burdens to the subject."[74] In the United States, these determinations are made through Institutional Review Boards (IRB) whose roles are codified in the C.F.R.[75]

The United States implements essential principles of the *Declaration of Helsinki* and the *Nuremburg Code* in the common rule elements of the C.F.R.[76] The common rule applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency that takes

66. *Id.*
67. *Id.*
68. *Helsinki Declaration*, *supra* note 64.
69. *Id.* at A(3).
70. *Id.* at B(21).
71. *Id.* at B(17)–(19).
72. *Id.* at B(22).
73. *Id.* at B(19).
74. *Id.* at B(18).
75. *See, e.g.*, 34 C.F.R. § 97.111 (2006) (describing criteria for Institutional Review Boards' approval of research); 40 C.F.R. § 26.102(g) (2006) (stating that Institutional Review Boards must be established for review of human research subject to the Common Rule); 40 C.F.R. § 26.109(a) (2006) (stating that Institutional Review Boards are required to review and have the authority to approve, require modifications in, or disapprove all research activities covered by the Common Rule).
76. *See generally* 40 C.F.R. §§ 26.100–26.111 (2006).

appropriate administrative action to make the policy applicable to such research.[77] 40 C.F.R. § 26.111(a)(1)–(a)(7) list the criteria for IRB approval of research, which reiterate the basic requirements under the *Declaration of Helsinki* (minimized and reasonable risk to subjects, equitable selection of subjects, informed consent of subjects, protection of the privacy of subjects, and ensuring the safety of subjects).[78]

B. Current Experimentation

Working within the current C.F.R., researchers have made limited progress. Presently, experimentation is proceeding on four main fronts: (1) Pharmacotherapy research, (2) psychiatric treatment, (3) genetic exploration, and (4) alternative possibilities.

1. Pharmacotherapy Research—There is little empirical evidence about new drugs for BD because there is a lack of double-blind, placebo-controlled trials that compare the efficacy of different treatments.[79] Current research in this area has changed from lithium's therapeutic focus to anticonvulsant drugs and second-generation antipsychotics.[80] Of the eleven FDA-approved drugs for BD treatment, the FDA has approved eight of them only within the past five years.[81] Despite the recent onslaught of drugs, there has been limited noticeable impact on the disease. Most drugs are as effective as lithium but have more tolerable side effects.[82] Many BD patients take a combination of these drugs to ward off symptoms.[83] Finding an effective combination formula is an experiment unique to each patient.

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77. *Id.* at § 26.101(a).

78. *Id.* at § 26.111(a).

79. Altshuler, *supra* note 11, at 88. The World Medical Association recently clarified that the *Declaration of Helsinki* states that placebos should "only be used in the absence of existing proven therapy . . . [or] [w]here for compelling and scientifically sound methodological reasons its use is necessary . . . [or] [w]here a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition." *Helsinki Declaration*, *supra* note 64, at n.1.

80. Goldberg & Citrome, *supra* note 5, at 25.

81. Chlorpromazine HCl was approved before 1970; lithium was approved in 1970; Divalproex sodium was approved in 1995; Olanzapine was approved in 2000; Olanzapine and fluoxetine HCl capsules as well as Lamotrgine were approved in 2003. *Id.* at 30–31. In 2004, the FDA approved Carbamazepine, Risperidone, Quetiapine fumarate, Ziprasidone, and Ariprazole. *Id.*

82. Goldberg & Citrome, *supra* note 5, at 30–31.

83. *Id.*

Some pharmacotherapy researchers are seeking agents that activate gamma-aminobutyric acid (GABA) receptors in the brain.[84] The effect of the agents is a reduced level of GABA in the cortex, nucleus accumbens, and brain stem in depressed subjects, yielding an antidepressant effect.[85] Benzodiazepines, such as Alprazolam (Xanax), increase GABAergic neurotransmission by increasing GABA reception.[86] Mood stabilizers (lithium) tend to increase brain GABA.[87] Limited data is available about the effects of some FDA approved drugs on GABA.[88] Further research is needed into the area of GABA to utilize it to its full potential for BD patients.

2. Psychiatric Treatment—Psychiatric treatment is another area where experimentation is ongoing (but producing few substantial results). Typical sessions of psychiatric treatment have long been prescribed for BD patients, but recently the focus has shifted (especially for young BD patients) to family-based treatment.[89] "Engaging parents in the treatment process and reducing the toxicity of a negative family environment can contribute to better treatment engagement, retention, compliance, effectiveness, and maintenance of gains."[90] Family psychiatric treatments can be effective as an augmentation to other treatments,[91] but no psychotherapy is "of much value unless the person is also taking medication."[92] Further research must be done to consider precise methods for administration of such treatment.

Cognitive therapy is another psychiatric frontier. It is similar to typical psychoanalytic psychotherapy but differs in that cognitive therapy assumes that the patient's conscious thoughts are important determinants of behavior (whereas psychoanalytic psychotherapy focuses on unconscious thoughts).[93] This form of therapy has been used in the past for treatment of depression and anxiety for years, but only recently has been used to treat BD and is still considered experimental.[94]

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84. Wang & Ketter, *The Emerging Role of GABAergic Mechanisms in Mood Disorders*, PSYCHIATRIC TIMES, Sept. 2005, at 89, *available at* http://www.psychiatrictimes.com/showArticle.jhtml?articleId=171201536.

85. *Id.*

86. *Id.*

87. *Id.*

88. *Id.*

89. *See* Guy Diamond & Allan Josephson, *Family-Based Treatment Research: A 10-Year Update*, 44 J. AM. ACAD. OF CHILD & ADOLESCENT PSYCHIATRY 872, 875–76 (2005).

90. *Id.* at 872.

91. *Id.* at 873.

92. TORREY & KNABLE, *supra* note 38, at 207.

93. *Id.* at 208.

94. *See id.* at 209.

Some patients also experiment with other types of psychiatric treatment, including Interpersonal and Social Rhythm Therapy (IPSRT) and Group Therapy.[95]

3. Genetic Exploration[96]—The possibility is great that BD is hereditary.[97] This possibility leads scientists to believe that BD has a genetic component, and much research is underway to isolate the responsible gene or genes.[98] One candidate gene is the brain-derived neutrophic factor (BDNF) gene on chromosome 11.[99] Another possible gene is the variable number tandem repeat (VNTR) polymorphism in intron 2 of the serotonin transporter gene (5-HTT).[100] Still other scientists suspect the culprit(s) resides on chromosomes 18 and/or 21.[101]

Some researchers who believe that BD is genetic think that genomic imprinting and mitochondrial inheritance also play a role in the hereditary nature of BD.[102] Further and more expansive research must be done in this area. By identifying the genes that make patients susceptible to BD (and the brain proteins these genes code for), the medical community will be better able to develop more effective treatments, and possibly even preventive measures.[103]

4. Alternative Possibilities—Some BD research today is centered on treatment that considers alternatives to pharmacotherapy and gene therapy. One type of alternative research focuses on nutritional supplements, calling upon the healing powers of different combinations of vitamins, minerals, orthomolecules, herbs, and

95. *Id.* at 209–11.

96. The reader need not comprehend the scientific details of this section. The author describes genetic exploration simply to illustrate another frontier to which BD research has spread.

97. Yvette P. Conley et al., *Genetic Susceptibility to Psychiatric Disorders*, 13 MEDSURG NURSING 319, 320 (2004) ("Estimates of heritability for BP [Bipolar Disorder] are in the range of 60%.").

98. *See, e.g.*, NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 1 (describing the National Institute of Mental Health Bipolar Disorder Genetics Initiative).

99. Conley, *supra* note 97, at 320. This gene is linked with stress and antidepressant responses. *Id.* at 321.

100. Natasha Coyle et al., *Variation at the Serotonin Transporter Gene Influences Susceptibility to Bipolar Affective Puerperal Psychosis*, 356 THE LANCET 1490, 1490 (2000) (describing a study of ninety-seven United Kingdom-born white females with BD who experienced an episode of severe psychiatric disturbance soon after giving birth). Other possible gene loci include 18p11, 18q22, 4p16, 21q21, and Xq26. Müller-Oerlinghausen et al., *supra* note 4, at 243.

101. GRANET & FERBER, *supra* note 15, at 63.

102. Müller-Oerlinghausen et al., *supra* note 4, at 241.

103. NAT'L INST. OF MENTAL HEALTH, *supra* note 7, at 3.

omega-3 fatty acids.[104] Another area of research postures that infectious agents contribute to BD.[105]

An alternative therapy that has been gaining momentum is electroconvulsive therapy (ECT) and its more subtle sister, transcranial magnetic stimulation (TMS).[106] ECT has been studied since the 1940s and involves the use of electrical stimulation to generate generalized tonic-clonic seizures.[107] Despite its negative pubic reputation,[108] electroconvulsive therapy has been effective in treating both depression and mania,[109] but causes amnesia in half of its patients.[110] This memory loss is usually only temporary.[111]

TMS was introduced to the scientific community in 1985[112] and has been conducted under codified safety regulations since 1993.[113] TMS utilizes alternating magnetic fields to induce electrical currents in the brain.[114] It is "a relatively simple, noninvasive, and usually painless" procedure[115] and, when used repetitively over the course of two weeks, has been proven to result in significant, though clinically modest, reductions of depressive symptoms.[116]

For patients who fail to respond to traditional therapy, alternative therapies can be wonderful, but much more research must be done to determine what non-pharmaceutical therapies are effective and

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104. Kidd, *supra* note 2, at 107.

105. *See* Kevin Wack, *Deep Pockets Fuel Brain Researcher's Quest: A Wealthy Benefactor Allows Dr. E. Fuller Torrey to Start a Brain Bank and Search for Causes of Schizophrenia*, PORTLAND PRESS HERALD (Maine), Oct. 17, 2004, at A14.

106. Kidd, *supra* note 2, at 117.

107. Andrew D. Krystal et al., *EEG Effects of ECT: Implications for rTMS*, 12 DEPRESSION & ANXIETY 157, 157 (2000).

108. GRANET & FERBER, *supra* note 15, at 5.

109. Hopkins, *supra* note 28, at 23.

110. Kidd, *supra* note 2, at 117.

111. GRANET & FERBER, *supra* note 15, at 179 ("Studies show that the patient's capacity to retain, learn, and recall new information is undisturbed six to nine months after treatment.").

112. Leon Grunhaus et al., *Repetitive Transcranial Magnetic Stimulation Is as Effective as Electroconvulsive Therapy in the Treatment of Nondelusional Major Depressive Disorder: An Open Study*, 47 BIOLOGICAL PSYCHIATRY 314, 314 (2000).

113. Michael Henry et al., *Electromagnetic Stimulation Shows Promise for Treatment-Resistant Depression*, HEALTHYPLACE.COM, http://www.healthyplace.com/Communities/Depression/treatment/tms/index.asp (last visited Feb. 2, 2006).

114. Kidd, *supra* note 2, at 117.

115. John Travis, *Snap, Crackle, and Feel Good? Magnetic Fields That Map the Brain May Also Treat Its Disorders*, SCIENCE NEWS, Sept. 23, 2000, at 204.

116. Robert M. Berman et al., *A Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depression*, 47 BIOLOGICAL PSYCHIATRY 332, 332 (2000).

safe. Private research facilities, funded by private individuals, conduct many alternative therapies.[117]

IV. SUGGESTED REFORMS

A. Permit Experimentation on Volunteering Prisoners

An incredibly prohibitive limitation on the success of bipolar research is the small sample size of participants in studies.[118] Increasing the pool of possible subjects would partially alleviate this problem. One way to increase the pool is to seek possible participants among bipolar individuals in state penitentiaries or other correctional facilities. By relaxing the C.F.R. to allow experimentation upon consenting bipolar prisoners, the medical community could make great strides through the use of increased (adequate) sample sizes.[119]

Estimates indicate that 40% of bipolar individuals have been arrested at sometime in their lifetime.[120] Upon entering prison, people with BD remain there about three times longer than prisoners who are not mentally ill.[121] BD rates in prisons are up to five times greater than in the general population.[122] Current figures estimate that at least one in six prisoners in the United States has a mental illness.[123]

The C.F.R. greatly limits the accessibility of inmates to serve as subjects in medical research experiments.[124] This limitation is due,

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117. *See, e.g.*, Wack, *supra* note 105, at A14 (describing the donation of hundreds of millions of dollars from a man whose son has BD).

118. *See, e.g.*, Robert L. Findling et al., *Double-Blind 18-Month Trial of Lithium Versus Divalproex Maintenance Treatment in Pediatric Bipolar Disorder*, 44 J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY 409, 409–14 (2005).

119. The author would like to stress that only consenting prisoners should be permitted to participate in experiments. Informed consent requirements should be the same for prisoners as for non-incarcerated BD patients. Informed consent from bipolar patients should be procured on a rolling basis, discussed in detail below.

120. TORREY & KNABLE, *supra* note 38, at 251.

121. *Id.*

122. Cynthia L. Blitz et al., *Gender-Specific Behavioral Health and Community Release Patterns Among New Jersey Prison Inmates: Implications for Treatment and Community Reentry*, 95 AM. J. PUB. HEALTH 1741, 1741 (2005); Cynthia Golembeski & Robert Fullilove, *Criminal (In)Justice in the City and Its Associated Health Consequences*, 95 AM. J. PUB. HEALTH 1701, 1701 (2005).

123. Golembeski & Fullilove, *supra* note 122, at 1701. In one Massachusetts prison, more than 60% of the inmates suffered from some form of mental illness. Peter Reuell, *Mental Illness Rampant Inside Women's Prison*, BOSTON HERALD, Aug. 14, 2005, News, at 6.

124. *See generally* 45 C.F.R. § 46.306 (2006).

in part, to the historical significance that experimentation has played in prisons.[125] Correctional facilities offered an ideal test environment because they harbored stable study groups with many possible (and often very willing) subjects.[126] Prisoners would often "volunteer" hoping to be rewarded for their bravery.[127]

Naturally, this situation raises ethical concerns. In 1976, all medical research on federal prisoners was outlawed and research in state penitentiaries was quick to follow.[128] All of the concerns that lead to this prohibition could be alleviated by treating prisoner subjects like non-prisoner subjects. Compensation should be equal and the prisoners should be given no hope of early parole as consideration for participation. Additionally, actual consent must be validly obtained.

Today, prisoners may usually only participate in research directly related to incarceration.[129] Inmates may participate in medical research not directly related to incarceration if it has the intent to improve the health of the subject *and* consists of the use of accepted practices.[130] Many BD prisoners are so situated because accepted practices do not help them with their illness. This situation makes it impossible to meet both of these conditions. Therefore, experimentation on most BD prisoners is illegal.

Many individuals with BD who are in prison are typically there because they do not respond to traditional treatment, and instead self-medicate through the use of drugs and alcohol.[131] These are the individuals who need help the most. They need progress in the treatment of this disease. Some even die because of the prison system's inability to administer proper treatment.[132] In many states, all

125. *See generally* ALLEN M. HORNBLUM, ACRES OF SKIN; HUMAN EXPERIMENTS AT HOLMESBURG PRISON 76–115 (1999).

126. *Id.* at 112–13.

127. *Id.* at 82–83 (describing malaria experiments at Statesville prison where "test participants were 'all sure that some means would be found to give [them] consideration,' " resulting in the "commutations of sentence or paroles to 317 of the 432 convicts who participated in the malaria tests including 24 murderers and 1 rapist").

128. *Id.* at 113–14.

129. 45 C.F.R. § 46.306 (2006).

130. 46 C.F.R. § 46.306(2) (2006).

131. *See, e.g.*, Patrick Orr, *Experts Give Testimony in Scalping Case*, IDAHO STATESMAN, Sept. 10, 2005, at 1 (telling of a BD woman on trial for scalping). Sometimes BD patients who are on medication commit crime during prescription-drug induced mania. *See, e.g.*, John Alan Cohan, *Psychiatric Ethics and Emerging Issues of Psychopharmacology in the Treatment of Depression*, 20 J. CONTEMP. HEALTH L. & POL'Y 115, 146–47 (2003) (discussing the "Prozac Defense" in criminal law).

132. *See, e.g.*, Rick Brundrett, *Richland Inmate's Widow Sues Jail's Mental Health Provider Blamed for Suicide*, THE STATE (Columbia S.C.), Aug. 31, 2005, at B1 (telling of an inmate

medications are cut off immediately upon incarceration to allow the prison's health services department an opportunity to evaluate the prisoner.[133] Once prison doctors re-diagnose the prisoner as having BD (which can take days, weeks, or more), an inmate can begin his or her medicine again.[134] It does not help matters that these medications are often rather expensive for the prisons, giving doctors an incentive to deny the diagnosis.[135] Even BD prisoners who receive medication may have inconsistent access to prescriptions and/or therapy.[136]

BD-induced suicide is all too present in correctional facilities.[137] Amending the C.F.R. to allow consenting prisoners to participate in BD research would increase the quantity of possible subjects for experimentation. It would also increase the quality of subjects because many prisoners are patients for whom traditional treatment has not been effective. BD inmates represent BD at its most destructive. If something is to be done, it must be done to help these people. Who better to help than the prisoners themselves?

B. Implementation of a Rolling Consent Requirement

Human participation in research experimentation is subject to the informed consent requirements of the C.F.R.[138] Regulations require the investigator to obtain the "legally effective informed consent of the subject or the subject's legally authorized representative."[139] The basic elements of informed consent require that the investigator explain to the subject a number of items, including any possible benefits of the experiment, any foreseeable risks, confidentiality concerns, and more.[140]

For BD research subjects, the informed consent requirements outlined in the C.F.R. are not enough to solicit actual consent.

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who "was found hanging in his cell .... In a letter to his wife the day before, [the inmate] complained he had not received his medications for seven days").

133. *See, e.g.*, Mary McLachlin & John Pacenti, *Bipolar Inmate Rediagnosed, Denied Medicine*, PALM BEACH POST, Apr. 5, 2004, at 1A.

134. *Id.*

135. *Id.*

136. *See* Kate Coscarelli, *Former Inmates to Tell Hearing About Horrors Behind Bars: National Panel Holding Newark Session on Corrections Problems*, THE STAR-LEDGER (Newark, N.J.), July 19, 2005, at 13.

137. Brundrett, *supra* note 132.

138. *See generally* 34 C.F.R. § 97.116 (2006).

139. *Id.*

140. *Id.* at § 97.116(a).

During a period of depression or during a manic episode, individuals with BD may be more inclined to agree to things that they would not normally agree. A depressed patient may consent to an incredibly risky experiment in an attempt to facilitate suicide. A manic person, soaring on feelings of invincibility, may engage in a similar experiment believing that she can "beat the odds" of possible harm. For this reason, a rolling consent system should be implemented when BD individuals are serving as test subjects in experiments with therapeutic, non-therapeutic, and mixed elements.

There is no way to ensure that a consenting BD subject is ever really outside of mania and depression, but by requiring a series of informed consent solicitations, the risk of "false positive" consents will be greatly diminished. Investigators should be required to obtain written consent from the BD subject three times, each time at least forty-eight hours apart from each other, before beginning any experimentation. Then, once experimentation has begun, signed affirmative informed consent to continue the experiment must again be obtained weekly from each subject.[141] This procedure will reduce the risk that the subject is simply agreeing to the experiment in a manic or depressive state, or similarly, neglecting to withdraw though he or she may wish to withdraw from participation.

Many BD patients have difficulty committing, whether it be to relationships, jobs, or medical treatments.[142] If rolling consent is given, then there is an increased possibility that the consenting BD individual truly is committed to the experiment and will be more likely to continue with the program. This procedure, in turn, will hopefully result in fewer subjects dropping out of experiments before completion. With more subjects "sticking it out," investigators will have more findings with which to proceed for further research. With fewer subjects dropping out of experiments, results will be more complete.

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141. *Id.* at § 97.116(a)(8) (requiring that investigators provide a subject with a statement that the subject "may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."). This requirement is not enough for BD patients. They must be informed of this right each week, and affirmative consent must be obtained rather than relying on an omission of an expressed desire to withdraw from experimentation.

142. *See, e.g.*, TORREY & KNABLE, *supra* note 38, at 240 (describing reasons for medication noncompliance).

V. CONCLUSIONS

BD is a destructive disease capable of crippling those inflicted with it as well as devastating society. Current research is progressing very slowly. To facilitate the search for effective treatment, the C.F.R. should be modified to allow consenting prisoners to serve as research subjects. Additionally, to both yield more complete results and to protect BD individuals from giving "false positive" informed consent, a system of rolling consent should be implemented for all research involving BD subjects. Something must be done to help those with BD. With these suggested reforms, there is hope that something can be done.