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OF MICE AND MEDICINE:  
AN EXAMINATION OF THE ANTI-DEPRESSANT ENTERPRISE

by

James Kenneth Arnette

A Thesis

Submitted in Partial Fulfillment of the  
Requirements for the Degree of  
Master of Arts

Major: Philosophy

The University of Memphis

May 2020

## **Dedication**

I dedicate this thesis to my spiritual master, soulmate, and best friend: Karma. He came to me in 1983 in the form of a humble kitten, full of love and acceptance and loyalty. He died in 2001, and my world fell apart—for he was the one holding it together for me. His mission was to support me because he knew I was in for a very rough life. He came in a form that was ideal for showing me how to live—not with words, of course—but with his actions. He taught me how to live and how to die. He taught me dignity and grace. After he passed, he visited me immediately after I buried his body, showing me his immense power and love. He returned to me again in October, 2019, to rescue me again. Karma spoke to me through the mouth of my dear brother Ben, and again Karma taught me how to rise above everything that was hurting me. I can and do still hurt, and life still contains just as many problems. But now I see what Karma sees in me, and am dedicated to letting that part of myself grow. And he continues to help me through Ben, Chris, Bernardo, Andy, Ed, Ruth, Suzanne, Robert, and all my soul family. My dearest kitty, I live on in an attempt to exemplify what you taught me. May I live up to the standard you have set. Thank you, and I love you.

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## **Abstract**

Anti-depressant (AD) medications appear not to work very well, and present a sequence of puzzling problems: side effects, a long latency period before recovery, an uncertain theoretical foundation for psychopharmacology, the high relative efficacy of placebos, and the generally low efficacy of ADs. Behind these empirical and scientific problems lie a host of ethical issues within drug development: publication bias, conflicts of interest, ghost authorship, and informed consent. I review these issues and find that: (1) there is no reason to believe that ADs should be effective for humans, given their origin in rodent research; (2) the placebo effect rivals the drug effect, showing that ADs are ineffective; (3) drug companies and doctors unethically continue to push the use of ADs; (4) analyses from science and the philosophy of science show that ADs are scientifically unsound; and (5) ethical analyses demonstrate that ADs are ethically intolerable.

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## Chapter One

### Introduction and Background

The diagnosis and treatment of depression in the Western world has a long history, most probably predating the written word and based in shamanistic magic (Hergenhahn, 1986, pp. 315-316). The Greek physician Hippocrates (460-380 B.C.E.) broke with the magical and religious traditions of medicine and attempted to put mental illnesses on an objective basis with his theory of the humors (Hergenhahn, 1986, pp. 317-318): mental health was for him based in a balance of the humors, i.e., bodily fluids. Millennia later, Sigmund Freud proposed a very different theoretical approach that did not involve the body at all: depression was an intrapsychic phenomenon that he characterized as “anger turned inward.” Dissatisfaction with Freud’s psychoanalytic system came from many quarters—based on several objections—but his system persisted in psychiatry for decades. The advent of pharmacotherapy in the mid-twentieth century eventually and finally drove psychoanalysis—and other forms of talk therapy—to the sidelines in psychiatry. The serendipitous discoveries of early anti-depressants (ADs) and early anti-psychotics (Greenberg, 2013a, 2013b) began the *paradigm shift* (Kuhn, 1970) of psychiatry from a focus on a person’s experience to one on a person’s neurochemistry; depression changed from a symptom of negative life events to one of a so-called *chemical imbalance*. Although a *causal* relationship between levels of neurotransmitters—e.g., serotonin—and one’s level of depression has *never* been demonstrated (Breggin, 1991, pp. 141-144), this *serotonin hypothesis* of depression has continued to be influential.

In this thesis, I will defend two highly related hypotheses. First, the psychiatry of depression has followed a developmental path beginning with Freud’s psychoanalytic theory—considered by many to be a *pseudo-science* (not authentic, but appearing to be a science)—and leading to a current emphasis on psychopharmacology that is severely under-supported by the available scientific evidence, thus rendering it a *quasi-science* (resembling, but not the same as, science). I argue that the extra-scientific forces (that is, forces from outside of science) of politics and economics have taken control of this quasi-science and distorted it into a money-making medical machine that has largely failed so far in providing effective treatment but has been very effective in generating corporate profits (Breggin, 1991; Greenberg 2013a, 2013b).

The second hypothesis addressed in this thesis is related to the *ethics* of the entire Anti-depressant Enterprise (AE). I will defend the hypothesis that the psychiatry of depression is, at best, highly questionable from an ethical point of view, and at worst completely unethical. This hypothesis is strongly related to the first. I will cite evidence from many aspects and sources demonstrating that—although psychiatry claims that its approach to anti-depressants is scientific—the psychiatry of depression is in fact very far from science. This in itself constitutes a case of *unethical behavior* since ADs are represented both to and by physicians and to the public at large as scientifically based and proven. Thus, the AE, spanning from development of the drugs to the prescribing thereof, is inherently deceptive, misleading, and filled with disinformation. This is the basis for my view.

I begin with a brief overview of the history of the psychiatry of depression; this is important to review in some detail, as it will provide context for my arguments. This is followed by an explication of the factors that compromise the AE; each factor has dual implications—the enterprise is undermined both scientifically and ethically by each. Since scientific and ethical inadequacies are intimately connected, development of the scientific aspects is quite important.

### **Overview: History and Context**

Although psychology had already begun its separation from philosophy, psychotherapy—in the form of psychoanalysis—began with Sigmund Freud in the late 19<sup>th</sup> century as a verbal enterprise focused on self-revelation and self-understanding. Together, his theory of the mind and therapeutic methodology constituted the psychoanalytic *paradigm* (Kuhn, 1970; Ladyman, 2002). Both the theory and therapy focused on the unconscious mind—where, Freud held, the actual reasons and motivations for our cognitions, emotions, and behavior were found. But this was criticized by many as being pseudo-science—since the main tenets of the Freudian approach were considered to be *unfalsifiable* (Ladyman, 2002; Popper, 2002) and so not scientific.

This led many people to reject psychoanalysis and its offspring, and to search for approaches that were scientific and falsifiable. Thus, new schools of thought and methodology began to arise, such as behaviorism at the turn of the 20<sup>th</sup> century. But these methods were never adopted to any significant degree by psychiatry. Then, in the mid-20<sup>th</sup> century, the serendipitous discovery of anti-psychotic medications, followed shortly by a similarly fortuitous discovery of the first anti-depressants (Greenberg

2013a, 2013b) launched a revolution. These early psychotropic drugs proved to be more effective than psychoanalysis for serious and persistent mental disorders such as psychotic disorders (e.g., schizophrenia).

Accordingly, over time psychiatry began a slow shift from the verbal psychotherapeutic paradigm to a psychopharmacological paradigm (Breggin, 1991); the shift was *not* precipitated by the discovery of *anomalies* (Kuhn, 1970) within the former paradigm, unless one considers the failure of psychoanalysis to cure schizophrenia to be an anomaly. (It is noteworthy here that even Freud did not consider his paradigm appropriate for psychotic disorders.) Even if this was the case, the paradigm shift went well beyond the treatment of schizophrenia and major depression; eventually psychopharmacological treatment broadened into the favored approach for practically all forms of mental disorder (Frances, 2013). The shift was greatly accelerated by extra-scientific forces of several types, to be discussed below.

### **Psychopharmacology in the Treatment of Depression**

With respect to depression, this shift rapidly gained momentum in the 1980's with the invention of the first serotonin-specific reuptake inhibitor (SSRI), Prozac, which was seen as being based in science (Breggin, 1991, 2010), and was accompanied by a theory known as the *serotonin hypothesis*: depression is caused by inadequate levels of the neurotransmitter serotonin in the neurons and intercellular fluid around them in the brain (Stahl, 1996). Earlier ADs, such as tri-cyclic anti-depressants, boosted levels of three neurotransmitters—serotonin, noradrenalin, and dopamine—but the serotonin hypothesis stated that *only* serotonin was relevant to depression, hence the SSRI label. The selectivity of SSRIs was *the* major selling point.

Thus the goal of AD development became the selective targeting of serotonin pathways in the neural system, seeking to block the re-uptake of serotonin molecules into the neuronal cell bodies and so providing a higher concentration of serotonin for longer periods in the intercellular fluid in the synaptic gap (Greenberg, 2013a, 2013b; Stahl, 1996). But more important to the paradigm shift than the *apparent* success of ADs was the fact that drugs were a time-saving (and thus money-saving) method that met the demands of the emerging managed-care industry. Again a proliferation followed, now of drugs targeting mental illness (especially depression), accompanied by a concomitant decline in the use of psychotherapy in psychiatry. The result is that today, psychiatrists are involved mainly in diagnosing

mental illness, and prescribing and managing medications. The Freudian psychoanalytic paradigm is dying out in psychiatry.

However, this paradigm shift, I maintain, has *not* resulted in a science of depression in the field of psychiatry, but in *at best* a quasi-science of depression—and the reasons for this are also highly questionable ethically. The evidence I cite in support of my hypotheses falls into two categories: *scientific/empirical* (showing that the psychiatry of depression is no better than an immature proto-science despite claims to the contrary) and *political/economic* (showing that any evolution towards being a true science has been thwarted by unethical and unscientific practices). Each of these two groups involves several aspects, much of the groundwork for which has been developed above. In what follows, I will briefly describe and develop the major factors under each topic to support my hypothesis. Further exploration occurs in the following chapters.

### **Scientific and Empirical Considerations**

The scientific/empirical evidence category includes the following considerations: (1) uncertainty over the mechanism of anti-depressant action; (2) related to the first point, changes over time in the purported anti-depressant mechanism; (3) the effectiveness of placebos versus anti-depressants in clinical trials; and (4) the side-effects of anti-depressants. First, the serotonin hypothesis is just that: a hypothesis. This hypothesis has never been demonstrated to be true in a causal sense (Breggin, 1991, 2010; Greenberg, 2013a, 2013b; Stahl, 1996). That is, it has not been demonstrated that a dearth of serotonin (a so-called “chemical imbalance”) *causes or initiates* a depressive episode (Frances, 2013). An exhaustive search of the medical literature regarding the serotonin hypothesis reveals that *nowhere* in the literature is the term “chemical imbalance” used. More importantly, there is absolutely no evidence that depression is *preceded* by a lowering of serotonin levels. Rather, only *correlational* evidence exists as a link between serotonin and depression. Yet, the hypothesis has stood for many years without causal evidence; it remains an unproven assertion (Frances, 2013; Greenberg, 2013a, 2013b).

Second, the serotonin hypothesis is further undermined by an important change in the claimed mechanism of AD action (Greenberg, 2013a, 2013b). As new SSRIs flooded the market, it became apparent that they were not always effective and, for many people, were not effective at all. This drove drug companies to attempt new approaches, with an accompanying change in the hypothetical

mechanism. The new class of drugs worked on *both* serotonin *and* noradrenalin re-uptake receptors and thus was labeled serotonin-noradrenalin re-uptake inhibitors (SNRIs). Gone was the “selective” part of the terminology, and back into the picture came noradrenalin, which had previously been eliminated as supposedly unimportant for depression. So, the sands were shifting beneath the feet of psychiatry as it tried to determine which neurotransmitter(s) was or were important for depression, and whether selectivity mattered at all.

Third, and even more threatening to the new psychopharmacological paradigm, were the results of the gold standard of drug studies: double-blind, placebo-controlled drug trials (Breggin, 2010; Frances, 2013; Horgan, 2011; Kirsch, 2010). These trials showed that placebos, inert pills that were given as medication to control groups, were almost as effective as the active drug (usual reported effectiveness rates of roughly 25% and 30% respectively, on average); in some studies, the placebo was actually *more* effective than the real drug. David Healy, a reform psychiatrist, has recently estimated that AD effectiveness is about 10%, while placebo effectiveness is about 40%, an absolutely damning result if accurate (Healey, 2012, p. 83). A more complete discussion of clinical trials and the placebo effect constitutes Chapter 3 below.

These placebo results cast severe doubt not only on the serotonin hypothesis, but on the entire psychopharmacological paradigm by implying that patients’ belief in anti-depressants may be as powerful as the drugs themselves. If placebos work so well, then what role does the active drug play? How could this question be answered in an empirical way? It is possible, in fact, that the active drug plays no role at all other than as a very expensive placebo (Horgan, 2011). Thus, the claimed chemical basis of depression has been called into question by an increasing number of clinical scientists and psychiatrists (Breggin, 2010; Greenberg, 2013a, 2013b; Healy, 2012).

Fourth and finally, many of the *side-effects* of anti-depressants (physical symptoms, mental symptoms, and behavioral issues) are simultaneously *symptoms* of depression (Breggin, 2010; Fournier et al., 2010; Horgan, 2011; Read, Cartwright & Gibson, 2014). For example, one possible symptom of depression is sleep disturbance (either insomnia or hypersomnia), and a common anti-depressant side-effect is insomnia. Another potential symptom is sexual dysfunction, which is also a well-known side-effect of these drugs. Third, suicidal ideation and attempts are strongly associated with depression, yet

one of the warnings regarding anti-depressants is that they can cause suicidal ideation (or worse). ADs can even have the side effect of causing depression itself (Breggin, 1991, pp. 157-158).

A fourth example is aggressive behavior, which paradoxically can be a symptom of depression, and again can be a side-effect of anti-depressants (Breggin, 1991). Overall, it is difficult to fathom how a drug that purports to be a treatment for a condition can actually *cause* symptoms of that same condition (Breggin, 1991, 2010). I suggest that this indicates that there is something fundamentally amiss regarding the nature and direction of the AD enterprise: if anti-depressants can actually cause depression, there is reason to question whether this is an effective treatment for the general population. For this and the other reasons cited above, it is therefore *unethical* to make the claims (for both effectiveness and a scientific basis) that have been made for this class of medications. And of course if one gives a depressed person a medication that increases that depression, this is clearly an ethical violation that can end in suicide.

The four major points above have severe ethical and scientific implications. From the scientific point of view, the very studies meant to support a psychopharmacological interpretation of depression and its treatment directly undermine that paradigm. From the ethical point of view, with the science of anti-depressants thus undermined, it is deceptive (in fact, manipulative and lying) to make claims for the effectiveness of these drugs and for a scientific basis for their mechanism and use. The lack of causal evidence for the serotonin hypothesis, the shifting claims as to the chemical basis of depression and the action of ADs, the obvious power of belief as evidenced by placebo-controlled studies, and the contradictory message suggested by AD side-effects all combine to cast grave doubt on the new psychiatric paradigm. As it currently stands, the psychiatry of depression is *at best* a rudimentary form of science, a proto-science, in its infancy. *At worst*, the psychopharmacological treatment of depression is an expensive, unethical sham—that may well be harming instead of helping people.

### **Political and Economic Considerations**

The *political/economic* evidence category includes the following factors: (1) funding for clinical trials provided by the drug companies themselves; (2) the highly selective reporting and publication of trial results; and (3) the ghost authorship of published trials. First, the federal Food and Drug Administration (FDA) is responsible for overseeing the development of new drugs and determining their safety and effectiveness prior to approval for use with patients in the United States. In order to be effective, such a

process must be independent of the interests of the pharmaceutical companies (i.e., *autonomous*) and be completely oriented towards the interests of potential recipients of new medications (Barker & Kitcher, 2013). This is not the case, however.

In reality, most of the FDA's budget for drug evaluation is provided by the *drug companies themselves* (Anderson et al., 2015; Lexchin, 2013). This does not merely blur the corporate-governmental boundary, but also destroys the FDA's independence and autonomy, and hence its objectivity. Here, there is an inherent, unethical *conflict of interest* since the watchdog is being supported by those being watched; this can lead to premature or inappropriate approval of anti-depressants for market, some of which have later been found to be ineffective or even dangerous, thus subverting a truly scientific approach.

The second important factor in the political/economic category is the nature of studies reported to the FDA (or the corresponding European governmental agencies) and published in medical journals (Anderson et al., 2015; Gøtzsche & Jørgensen, 2011; Lexchin, 2013). It is very well known, first of all, that journals (medical and otherwise) rarely publish studies in which no statistically significant effects are found. In order to get a publication, the author or authors usually must find a positive, statistically valid drug effect. Occasionally, some studies with no significant outcomes do get published—especially if they are attempted replications of previous, supposedly successful trials—but this is the rare case.

More importantly, pharmaceutical companies never even submit most negative studies to the FDA or to journals. Unsuccessful results comprise the great majority of drug studies, and these studies are buried and ignored by the companies—this has been called the “file-drawer effect”—and its meaning is that for every successful study published, there are several other unsuccessful studies of that same drug that never see the light of day. Thus, the published studies are a small fraction of the total number conducted, making them extremely unrepresentative of the complete empirical information gathered. This is not the way of science, nor does it meet even a minimal standard of ethics.

The third factor concerns the nature of the authors of published studies. While studies are rarely published in medical journals without partial or complete authorship by medical doctors, it is nonetheless true that in some or many cases, physicians are not the actual authors. Rather, the articles are written by pharmaceutical company representatives as ghost authors, while doctors agree to have their names

listed in the authors' role (Lexchin, 2013; Stretton, 2014). This ghost authorship allows the companies to use their own statisticians, and to interpret the results as favorable to their drug—regardless of the realities of those results—whenever possible.

This situation in turn means that the study then becomes an advertisement for the industry and the results are skewed in favor of the drug's effectiveness, thus opposing the spirit and goals of a true science. And ethically, this is tantamount to lying. In recent years, some medical journals have made policy changes to address these concerns (Stretton, 2014). These changes include requiring full disclosure of funding for the studies and banning ghost authorship. Even so, these policies are not consistently present across all medical journals, and are probably insufficient to guarantee a solution to the problems the policies are intended to address. In addition, these policy changes have no impact at all on the file-drawer effect.

These political/economic aspects of anti-depressant development point to a crisis in the development of anti-depressants, and of many other types of medications as well. The FDA funding issues undermine the integrity and autonomy of any ethical and scientific approach to drug development. The file-drawer effect, combined with ghost authorship of articles, means that neither the FDA nor the public are getting the complete and accurate picture in terms of clinical effectiveness, and reduces the status of published studies to that of advertisements rather than science; yet, these studies are portrayed as science, not advertisements. This is not only dishonest and unscientific, but most importantly unsafe for the future users of such drugs. Drugs are often fast-tracked for approval via this process, only later to demonstrate severe side-effects and sometimes lethal effects not seen—or even seen but covered up—during the trial phase. And drugs approved through such a process come with no assurance that they will be effective. All of this is evidence that supports Breggin's (1991, p. 148) statement that "(t)he biology of depression is based less on science than on politics".

### **Implications and Consequences of the Empirical/Scientific and Political/Economic Factors**

In the face of all this evidence, I conclude that a *scientific* psychiatry of depression has been elusive from the outset due to a high level of uncertainty about: (1) the cause or causes of depression; (2) the roles of neurochemistry and of belief in the origin and treatment of depression; and (3) the mechanisms of action of drugs that appear to be effective for only some of those treated with anti-

depressants. The *ethical* implications of these empirical considerations are that: (1) patients, and perhaps many physicians and psychiatrists, have been misled by the pharmaceutical industry and thus hold false beliefs—such as the idea that anti-depressants are sound scientifically; (2) this deception, on such a massive scale, has led depressed people to believe in and rely on drugs that are both expensive and likely ineffective or not sufficiently effective; and (3) the world in general has been denied the totality of available knowledge about anti-depressants, and thereby denied the ability to make informed treatment decisions.

The primary examples of extra-scientific forces at work in the psychiatry of depression are the political/economic ones I have described. These forces encourage the adoption of the neurochemical model of depression, because if psychotherapy could be discouraged as a treatment then anti-depressants would be the only game left in town, so to speak, and lead to much greater corporate profits. Psychotherapists would see shrinking caseloads, and many private practitioners would go out of business. Hour-long verbal psychotherapy sessions over a period of weeks, months, or even years, would be supplanted by brief medication-management sessions with psychiatrists—thus not only lining the pockets of pharmaceutical companies, but also saving psychiatrists' time so that they could see many more patients per day.

Furthermore, insurance companies would save money by limiting, reducing, or even eliminating payment for verbal psychotherapy and paying for psychiatric visits and medications instead. Everyone involved would make more money and thus be better off—except for the depressed patients themselves. These patients would be left in a situation wherein each is an experimental group of one, and the physician or psychiatrist tries various medications until (hopefully) one appears to work. Given that (1) only about a third of patients (at best) respond well to anti-depressants and that (2) the placebo effect may be responsible for the majority or even all of that effectiveness, the system would be doing these patients a great disservice.

I have phrased the consequences given immediately above as possibilities, but in fact each has already become a reality. Over the past 30 years or so, all of these changes have come to pass to one degree or another. The effectiveness of verbal psychotherapy has been questioned and attacked (Breggin, 1991, p. 12), psychiatrists have been pressured to prescribe drugs rather than counsel patients,

and in fact primary care physicians are now the leading prescribers of anti-depressants (Francis, 2013, p. 101). This last single point is unethical in and of itself, since physicians get very little psychiatric training in medical school. Money appears to be well on its way to superseding mental health as the goal of the healthcare system. *This is a supreme ethical violation.* One cannot serve two masters—ethics and science on one hand and money on the other—and it appears that money has the upper hand.

### **Ethics and Anti-Depressants: My View**

In the preceding development, I have noted at numerous points that various empirical issues as well as political and economic influences undermine the ethics of the AE. Here, I summarize my perspective on the issues I have raised. Any and all of the following words or phrases could be used to describe the medical and corporate practices I have reviewed: dishonesty, deceitfulness, deception, misinformation, manipulation, willful withholding of vital information, and lying. The anti-depressant enterprise is not oriented towards understanding the causes, mechanisms, and treatments or cures for depression. I do not wish to be overly cynical, but the possibility exists that the medical-industrial complex favors long-term maintenance of depressed patients over a cure because of the assurance of continued business.

The entire system is money-driven, rather than patient-centered. The welfare of the patient is a secondary consideration, at best, as demonstrated by the great lengths to which pharmaceutical companies go to hide negative results; trumpet positive ones; make unproven, science-like claims; and try to eliminate psychotherapy as an affordable treatment option. Insurance companies are major players in this last effort. The psychiatry of depression is actually a huge experiment, given the uncertainties and dishonesty, and patients are unwitting participants in this experiment. In fact, as I hinted above, each doctor-patient interaction is a mini-experiment, as doctors have no way of knowing whether any anti-depressant—or which one—will be effective for any given patient. Thus, it is typical that the doctor and patient go through numerous “clinical trials” of various ADs, trying to find the one that works.

### **Overview of the Thesis**

In this Introduction, I have described ethical issues in the anti-depressant enterprise that are intimately intertwined with scientific issues. I have divided the issues into the categories of scientific/empirical and political/economic. For each of the issues under these two headings, I have

outlined the individual issues and given some detail. All of this is meant to give a broad view of the ethical and scientific landscape that I will explore in the chapters to come. In Chapter Two, I begin where drug development starts: in laboratories where rodents are used as test subjects for anti-depressant candidate drugs. Here, I examine standard techniques in AD development and point out the severe inadequacies of the methodology employed in this setting.

Chapter Three describes the standard clinical trial process, through which candidate drugs must be evaluated. This process nearly always involves an inert placebo given to a control group, and the results of these placebo trials spell trouble for the validity of ADs. I explore this problem in depth. In Chapter Four, I examine the AE from the perspective of the philosophy of science and identify problems from this standpoint. It will be clear that AD development methodology is both unscientific and violates tenets established by philosophers Karl Popper and Thomas Kuhn.

Chapter Five presents ethical analyses of the AE from the ethics of German Idealism, specifically Immanuel Kant and G. F. W. Hegel. Kant addresses a more individual form of ethics, while Hegel takes a more societal and historical approach. Both analyses result in negative evaluations of the AE. Finally, Chapter Six summarizes my findings in the preceding chapters. From this summary, I make my final conclusions. I close with a view to the future of the AE, pointing out some emerging trends that are troublesome in the context I have developed.

## Chapter Two

### The Invention of Anti-Depressants in the Laboratory

Unfortunately, for many patients, treatment is difficult since their depression is not alleviated by conventional anti-depressants, whose therapeutic efficacy is often limited due to side effects and delays in treatment effectiveness.... For these reasons, the elucidation of the etiology of depression, as well as the search for novel anti-depressants, are two of the foremost challenges in mental health research today. (Morales-Medina, Iannittib, Freemanc, & Caldwell, 2017, p. 563).

Clinicians and nonclinical neuroscientists need to become more involved in the collaborative development of both laboratory experiments and clinical research programs. Very few clinicians work on animal models of psychiatric disorder. Similarly, few basic scientists contribute to clinical research programs. Matthews et al. (2005) mention that a former leading researcher in animal models of depression confessed that despite having written about the topic for over 15 years, he had never actually met or spoken to someone with depression. (Czéh, Fuchs, Wiborg, & Simon, 2016, p. 304).

The first of these quotations points to something of a triple crisis in the Anti-depressant Enterprise: (1) the ineffectiveness of anti-depressants for many people, for whom the number of options is dwindling; (2) the lack of understanding of the etiology of depression—despite repeated revisions of theories, and the concomitant development of drugs based on them over the past four decades; and (3) the upcoming or previous expiration of very profitable patents for anti-depressants, with very few good new prospects on the immediate horizon.

The second quotation highlights the wall of separation between the clinical and scientific sides of psychopathology research and drug development. Clinical and scientific researchers fail to communicate with each other, when it would seem obvious that the findings and observations of one group would be vital to the other. The situation should be analogous to the interaction between theoretical and experimental branches in the physical sciences, which depend upon each other for both ideas and grounding of the research. The scientific process in the physical sciences would either grind to a halt or

seriously deviate from progress if the two sides did not communicate. It appears that the field of AD research began and remains at that stage.

The result of all the factors above is that drug companies are struggling to come up with new AD candidates; Czéh et al. (2016, p. 304; see also Song & Leonard, 2005, p. 628) say further: “(f)or commercial reasons, drug companies need valid models for the development of new therapies.” Recently this has been difficult because “of the lack of success in developing truly new compounds.” This has led companies to withdraw somewhat from the development of new anti-depressant medications, with the view of mental disorders “as a challenge that is ‘too difficult’ to attract major investment”. Nonetheless, basic research continues to be performed in laboratories worldwide, in the study of new candidate compounds based on a wide variety of theories about the etiology of depression and using as a “model”—an animal used in studies as a stand-in for human beings—the seemingly odd choice of the humble rodent, i.e. mice and rats.

This chapter argues that the choice of a rodent model—and specifically a mouse model— for human psychopathology, and Major Depressive Disorder (MDD) in particular, is not just odd but in fact wholly inappropriate on both the scientific and (especially) the philosophical levels of analysis and is probably the source of many highly problematic issues in the use of anti-depressants in humans, which I have discussed previously. I begin by describing the use of rodent models for human depression with an overview; I then discuss briefly a specific example using mice. I will thereafter describe the actual experience of MDD from my perspective as both a clinician and a sufferer of the disorder. This is in response, partially, to the comment by Czéh et al. (2016, p. 304) quoted at the beginning of this chapter.

I will then: examine the clinical picture of depression, comparing this with the actual experience thereof; address the question of whether depression is inherently embodied; survey proposed etiologies of depression in humans and give an analysis of the applicability of rodent models to these ideas; conclude that the projection of rodent psychiatric research results onto humans is invalid, and explain the reasons for this; and provide some remarks on the effects that the rodent model approach has on the lives of humans. I close with some brief reflections on the cost of corporate profits in terms of human suffering. A full ethical analysis awaits Chapter Five.

## The Rodent Model for Human Depression

Clinical researchers in search of new AD medications have major problems at the outset. To quote Czéh et al. (2016, p. 293): “(d)espite extensive investigations, the exact neurobiological processes that lead to depression are not fully understood.” This is something of a monumental understatement. One need not work with very many depressed clients to observe that the description of the disorder—officially Major Depressive Disorder (MDD)—varies with the individual, and that the conditions precipitating MDD are almost as varied. Czéh et al. (2016, p. 295) admit as much: “(d)epression is a symptomatic heterogeneous disease, and its clinical symptom profile varies among patients.” Thus, with a variable symptom profile and a very uncertain theoretical etiology, researchers believe that the problem is best approached initially by use of an animal model of the disease. For many decades, rodents have been the test subjects for the great majority of drug development, and it is no different in the present age of psychotropic drugs: “(r)odents are frequently used to model human mental illness” (Czéh et al., 2016, p. 299).

Yet, how does one connect the mental states of less-complex creatures like rodents with the mental states of depressed humans? Studies of anatomy, physiology and development of drugs for *physical* medical conditions could be more transferable. *Depression in humans*, however, is typically *diagnosed* by clinical interviews and/or psychometric testing—neither of which can be done with a non-human animal, obviously—as is also true with the *assessment* of a drug’s therapeutic *effects*. The only choice, then, is to use the *behavior* of an animal model to assess the effectiveness of drug candidates. In this kind of experiment, an MDD-like state is first induced in the animal, which is then treated with the experimental drug. Czéh et al. (2016) review many approaches typically used to produce depression in experimental animals. Here I focus on one very popular approach: the olfactory bulbectomy (OBX) model of depression.

Morales-Medina et al. (2017) review the use of this technique with rats. The authors describe the rationale for the OBX technique. Since “the olfactory system is an evolutionarily ancient sensory modality, it relays information into more primitive parts of the brain, specifically, the limbic system” (Morales-Medina et al., 2017, p. 563). In the mammalian brain, the limbic system has many functions, one of which is the processing of emotions. Therefore, the authors claim, it is not a surprise that “deficits in olfaction are

observed in patients that have compromised emotional processing, such as those diagnosed with depression” (Morales-Medina et al., 2017, p. 563). This correlation is therefore the basis of the OBX model in rodents, “used as a model of depression-like behavior” (Morales-Medina et al., 2017, p. 563). One might legitimately question whether this correlation is sufficient to make inferences about humans based on rodent studies. Morales-Medina et al. claim that the answer to this question is “yes” because the OBX model “has face, predictive, and perhaps construct validity for human depression” (Morales-Medina et al., 2017, p. 563). What does this mean, and is it true? (I address these questions presently, but first I note that the reasoning given in this paragraph is extremely invalid; I will wait until after the coming development before addressing this fundamental, fatal flaw.)

The review by Czéh et al. (2016) is useful here, for these authors delineate and explain the various kinds of validity that are possible and necessary in this type of experimentation, in order that the transfer of results between species is most likely to be valid overall. The authors briefly summarize the history of the types and definitions of validity over the past several decades, and state that the currently accepted types of validity are (Czéh et al., 2016, p. 295): (1) *face* validity: “similarity between the behavioral phenotype and the clinical-symptom profile”, that is, similarity between the behavior of the animal model and depression symptoms in humans; (2) *predictive* validity: “amelioration or attenuation by clinical effective anti-depressant treatments and conversely, absence of changes by clinically ineffective treatment of the human disorder”; (3) *etiological* validity: “triggering by events that are known to be important for eliciting the human disorder”; and (4) *construct* validity: “similar neurological underpinnings.”

Thus, Morales-Medina et al. are promising us only two, maybe three, of the four types of validity currently recognized as important. I might add here that from a philosophical point of view, I would cast the first form of validity as *phenomenological* validity, because in an accurate animal model the depressed agent—human or non-human animal— should experience very similar phenomena. This has broad and deep implications, which I will explore in various ways through the remainder of this chapter. I also note that face validity, as defined here, is distinctly behavioral in nature—as it necessarily must be—and thus is open to all the criticisms of behaviorism. But here it is much worse, for the scientists are imputing mental states in the rodents via their behavior, and this identification seems clearly

anthropomorphic in nature; this is a great violation of the original vision of behaviorism. I will further comment on this below.

Morales-Medina et al. (2016) go on to say that effects such as depression from OBX are reversed by anti-depressant treatment, but that how depression originally results from OBX is still a mystery. What is not a mystery is the extensive brain damage that the procedure causes in the rodent—by design, after all. OBX “results in long-lasting irreversible atrophy, volume loss, degeneration and sclerosis of glomerular and tufted cells...” (Morales-Medina et al., 2016, p. 565). In addition, researchers found that OBX caused the death of 55,000 neurons in the PirC (“olfactory”) cortex, an area of the brain crucial to the rodent’s connection with the outside world (Morales-Medina et al., 2016, p. 565). Further, changes in the hippocampus (shrinkage) have been observed following OBX (Morales-Medina et al., 2016, p. 565). In other words, the brain damage is massive, extensive, and located in critical regions of the cortex and below.

Morales-Medina et al. (2016) discuss observational methods used to infer psychological states in rats. For depression, they state that the Tail Suspension Test (TST) is often used. This is based on “the association between adult neurogenesis and immobility” (Morales-Medina et al., 2016, p. 568), but the authors immediately admit that any such corresponding associations in humans “are yet to be established” (Morales-Medina et al., 2016, p. 568). There is much more discussion and many other issues, aspects, and problems, but nonetheless the authors conclude that “the OBX model provides a relevant, and important, tool to evaluate possible anti-depressants using the plethora of behavioral paradigms that measure different traits of depression” (Morales-Medina et al., 2016, p. 571). The apparent suggestion here is that we can use different paradigms on rodents to isolate and study different aspects of depressive symptomology, from a behavioral perspective, and assemble the different results to complete the puzzle and identify possible treatment for MDD in humans. This seems far-fetched.

Yet, this sentiment was also expressed a decade earlier in a review by Song and Leonard (2005), who reviewed the OBX rat depression model as it was at that point. A comparison with the more recent review of Czéh et al. (2016) discussed above is instructive. Song and Leonard cite a less refined and extensive list of types of validity that the scientist should seek; this list does *not* include *etiological* validity. Thus the indication is that over a decade, notions of validity have become more expansive. Further, they

admit problems with their line of research that Czéh et al. neglect to mention, to wit: “the core symptoms of major depression...may ultimately depend on the complexity of the brain” (Song & Leonard, 2005, p. 628). This would seem to be a fatal flaw, but the authors rescue their enterprise with the claim that despite the imperfections, OBX can still provide pieces of the depression puzzle, similar to the claim of Czéh et al. And as with these latter authors, Song and Leonard claim that the OBX method has face and possibly construct validity. Their overall conclusion is also the same: the method has significant merits.

An *example* of the use of this overall methodology with mice—aiming at the specific case of mild traumatic brain injury (mTBI) in humans—is provided by a group of researchers at the University of Tennessee Health Science Center (Heldt et al., 2014; Liu et al., 2017), and elsewhere. In the earlier paper, the researchers establish that their method of inducing mTBI in mice is effective for their purposes: “(w)e have developed a mouse model of closed-head primary blast injury using high-pressure air blast delivered to...the left side of the head. This model simulates the temporal and physical dynamics of the forces causing shock wave mediated mild TBI, such as would occur from an explosion or a blow to the head” (Heldt et al., 2014, 1-2). Such an injury, the authors state, results in “minimal brain damage” but also “persistent psychologically debilitating symptoms that can include irritability, anxiety, fearfulness, and depression” (Heldt et al., 2014, p. 1) in humans and—the authors hold—in mice. Thus, while this paper’s focus is not directly on depression, it includes depression as a condition of interest.

As the assessment technique for depression, this study uses the Tail Suspension Test (TST) mentioned earlier. The authors describe this methodology: “mice suspended by their tails eventually stop attempting to escape and become immobile, with a depressive-like state indicated by a short latency to immobility and longer duration of immobility over the test period” (Heldt et al., 2014, p. 4), which was five minutes. The measurements were made using an automated digital camera interfaced with a computer. Therefore, the measurement of depression is entirely behavioral, and accomplished with a single assessment method, with a major inference made from the mouse’s behavior to the mouse’s mental state. And the state inferred is very complex.

With their methodology—along with the claim of induced depression—established in the earlier paper, this research group then applied their method to the elucidation of the effects of a novel AD compound, labeled SMM-189 (Liu et al., 2017). In these experiments, the TST was *not* employed; rather,

induction of depression in the mouse model was *assumed* and the experimental method focused on electrophysiological measurements. The authors found that SMM-189 effected “(t)he rescue of these electrophysiological abnormalities [caused by the air blast]...which has been shown in previous studies to rescue mTBI behavioral deficits” (Liu et al., 2017, p. 9). Similar claims are made in studies employing the OBX method.

Before moving on, I comment as promised earlier on the basic logic at work here. The logic is irretrievably wrong from the very beginning. I earlier described the logic used by Morales-Medina et al. (2017) in justifying the OBX method of mouse depression induction, and I did not comment at the time. Here, after the discussion, I highlight the reasoning that generated the OBX method. The claim is that (1) since depression in humans results in decreased olfactory sensitivity, (2) removing the olfactory bulb of a mouse will cause depression in the mouse. Note the *lack* of logic here. The two parts of the argument are contradictory. First, the *arrow of causality* has been reversed: decreased olfactory sensitivity in humans is the *result* of depression, *not the cause*. The OBX procedure is invalid due to this alone. Second, there is an unwarranted and unsupported *interspecies leap of faith* involved: what depresses or cures the mouse also depresses or cures the human. Well, part (1) of the argument being incorrectly applied to mice means that part (2), even if it were true, would be inapplicable in this case.

### **Major Depressive Episode: Human Phenomenology**

The clear suggestion made by the research reviewed above is that procedures that, *according to the claim*, induce psychopathology in rodents—and especially depression in mice—can be negated by AD medications, and that therefore these compounds are potentially useful in the treatment of human depression. In fact, the research described constitutes the *first step* in the development of ADs for humans, due to the claims of the various types of validity being satisfied. But before examining these ideas, it is important to establish exactly what we are dealing with here: the full-blown, multi-symptom, devastating disease of MDD in humans. This is what we seek both to understand and to treat successfully. Given that researchers are usually unfamiliar with the condition they are researching, we have from a philosophical perspective the duty to define *what it is like to be depressed*. In no other way can we make informed judgments about any question regarding the etiology and treatment of depression.

Only by understanding the *phenomenology* of depression can we begin to understand the nature of the task before us in this chapter, the exploration of the possible validity of the OBX method's results for human depression. Ataria (2014, p. 4) appears to understand the importance of phenomenology:

the phenomenological method...seeks to describe the lived, bodily experience.... Phenomenology focuses on the study of experience from the individual's perspective: usual assumptions and manners of perception are "bracketed out"...thus forcing us to suspend judgment about the "natural world" and return to things themselves.... Essentially, since pure phenomenological research seeks to describe rather than explain its methods are particularly effective at drawing out the experiences and perceptions of individuals from their own perspectives.... we follow the principle that one must stop asking "why" and start asking "how".... We are not looking for the "truth" but rather the authentic experience.

It is this authentic experience that provides both the data of what it is like to be depressed and data on the effectiveness of any treatment. While there are certainly *behavioral* (or *objective*) components in both cases, a major difference between mental and physical disorders (other than, e.g., pain) is that mental disorders also have a *subjective* component. One can have a mental disorder—e.g. MDD—and be able to mask it from others. This is key in my analysis to come.

So what is depression like, from a first-person, human perspective? *What is it like to be depressed?* Consider the following.<sup>1</sup> Sarah is in the midst of an intense MDE. She could feel it coming on days ago, beginning with a sensation in her abdomen, a bit like nausea but more like an ache. With each day, she felt physically worse, but mentally was plunging even faster. Everything seemed to be getting darker. Very unpleasant thoughts began to come. Now, in the throes of her depression, Sarah is deeply mired in self-hatred. She examines her life and wonders why it ever occurred, marveling at what a waste it is. She desperately wants to die. She is in great mental pain—emotionally she is sad, has no joy in life, feels less than worthless; cognitively, she constantly questions her future, and whether she even has one, as well as constantly berating herself and labeling herself with the most angry, insulting terms. Sometimes she gets angry with others, but can't express it because she feels she has no right. She gets restless and nervous, wants to get up and do something, but has nothing to do—at least nothing appealing.

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<sup>1</sup> In what follows, I integrate my clinical training, my experience as a therapist with depressed clients, and my personal experience with lifelong depression. This description, then, is not mainly my own experience, but is thereby augmented and informed. MDE stands for Major Depressive Episode; see next section for definition.

The worst part, though, is the fundamental self-rejection that is at the heart of both the cognitive and emotional symptoms. She feels rejected by the world; she feels that her very existence is invalid. The thought of death is simultaneously seductive and repellant. She thinks the world and herself would be better off parted, but then reminds herself that she could die and no one would know for months—so, her life is superfluous and the world would not notice her death. She has no basis for a claim to a valid, useful life, no justification for her existence—which consists mostly of pain—and wonders why she continues to exist. Is it so as not to offend the few people who know her? Would they really care for very long if she were gone? Is it valid to live in agony so that others are spared some temporary discomfort? If this is a living hell, then what is the point of living? And when this lets up, it's only going to return with a vengeance.

### **Major Depressive Disorder: Clinical Definition**

Clinically, MDD is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition, by the American Psychiatric Association (DSM-V; APA, 2013). This is the standard for definitions of psychiatric and psychological disorders used by all mental health professions in the United States, and thus has an incredible amount of power and influence in the field. Some psychiatrists have objected to and criticized the new (and previous editions of the) DSM (see e.g., Francis, 2013; Greenberg, 2013b). We must, however, deal with it as it is. While a variety of mental disorders have depression as a *symptom*, the central disorder of MDD *is* depression.

MDD is a heterogeneous disorder—i.e., it is a collection of symptoms that may or may not spring from the same etiology; each symptom may or may not be present in any individual case. The diagnostic criteria are listed in Table One (below). Criteria A through C must be met for a Major Depressive Episode (MDE) diagnosis, and all the criteria must be met for a diagnosis of MDD. Criterion A includes the specific symptoms of Major Depression—five of the nine symptoms must be present, and one or both of the first two symptoms is required. Note that both symptoms (1) and (2) can be reported by others—implying that behavioral manifestations are possible—or can be self-reported. The next four symptoms are traditionally referred to as “vegetative” or bodily, and the first three can go in either direction from a person’s normal state.

**Table One**  
**DSM-V Criteria for Major Depressive Disorder (MDD)<sup>2</sup>**

Criterion/ Symptom <sup>3</sup>	Description
A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:
<u>(1)</u> <sup>4</sup>	depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful);
<u>(2)</u>	markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others);
<b>(3)</b> <sup>5</sup>	significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day;
<b>(4)</b>	insomnia or hypersomnia nearly every day;
<b>(5)</b>	psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down);
<b>(6)</b>	fatigue or loss of energy nearly every day;
(7)	feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick);
(8)	diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others);
(9)	recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	The episode is not attributable to the physiological effects of a substance or to another medical condition.
D.	The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E.	There has never been a manic episode or a hypomanic episode.

<sup>2</sup> Adapted from the DSM-V criteria for Major Depressive Disorder (APA, 2013, pp. 160-161)

<sup>3</sup> Criteria A through C serve as the definition of a Major Depressive Episode (MDE).

<sup>4</sup> One or both of the underlined symptoms are required for the diagnosis.

<sup>5</sup> Symptoms in **bold** have traditionally been considered “vegetative” (bodily) symptoms. See text for a discussion of this aspect of MDD.

The final three symptoms are traditionally considered to be “cognitive” or “mental” symptoms. These may or may not be evident to others, because they are defined according to the patient’s *subjective* experience. While symptoms (1) and (2) are also subjective, they are more potentially observable to others than symptoms (7) through (9), especially if the person never speaks about such symptoms to others. Since only five symptoms are required, a person can have MDD unknown to others by having and suppressing symptoms (1), (2), (7), (8) and (9).

### **Major Depression: Inherently Embodied?**

The scenario given just prior to Table One presents us with the possibility that MDD can be present in a person, yet be *undetectable behaviorally*. This means—first and foremost for the argument of this chapter—that MDD need not be *observable* in order to occur. Such is well-known to clinicians: clients often present symptoms that are only knowable through self-report. Furthermore, it is quite unusual for a therapist to have input from others about a client’s behavior unless, for example, the therapy is court-ordered. So in the great majority of cases, the therapist proceeds on the basis of the client’s self-report, the therapist’s observations in-session, and possibly psychometric testing. Almost none of this is available with an animal model, as we have seen. I discuss the grave implications of this for the animal-model research paradigm below.

In addition to the observability (or lack thereof) of MDD, a second question arises in view of the clinical definition of MDD: is MDD inherently an embodied disorder? This is a tricky question, the answer to which depends on whether one considers symptoms (1) and/or (2) to involve the body, not just the brain. Are depressed mood and/or anhedonia mental or bodily? In view of the example presented earlier, I would have to respond with “yes” to that question. This is not to say, however, that every person with MDD would agree—thus, again, MDD is heterogeneous in its individual expression. But in general, given the possible symptom profile, it is hard not to believe that most cases of MDD involve the body explicitly to some degree. Nonetheless, it may be behaviorally undetectable. This matters with regard to mice.

### **Major Depression: Etiology**

As previously mentioned, depression has been recognized as a human problem since ancient times. While in prehistoric times a shaman may have been enlisted to deal with a depressed member of his tribe by divination and the invocation of spirits, early Greek culture played a pivotal role in Western

thought concerning disease by turning away from religious or spiritual explanations and treatments and towards more proximate possibilities. In this section, I trace a few of the major historical ideas regarding the etiology of depression, in preparation for my analysis of the viability of the OBX approach to understanding and treating MDD in humans.

*Hippocrates and Galen: imbalance of humors.* The Greek physician Hippocrates is considered the “father of medicine” (Hergenhahn, 1986, p. 31) in the Western world. He rejected the idea of disease as possession by spirits, instead proposing natural causes for illnesses. He invoked the concept of bodily *humors*, one corresponding to each of the four elements. He defined disease as imbalance in the humors (Hergenhahn, 1986, pp. 317-318). About 500 years later, Galen extended Hippocrates’ theory, equating depression (melancholia) with an *imbalance* involving “black bile” (Hergenhahn, 1986, pp. 317-318). This represented the first attempt to define depression biologically.

*Freud: anger turned inward.* In modern times, Sigmund Freud, with his system of psychoanalysis, represents a distinct turning point in our understanding of depression. Going beyond ancient spiritual ideas and theories of humors, Freud’s view of depression is completely intrapsychic. It is not *biological* but *psychological*—and not in *isolation* from experience, but rather as a *result* of it. Consider Freud’s (1965, p. 169) words on the origin of depression:

(i)f one listens patiently to the many and various self-accusations of the melancholiac, one cannot in the end avoid the impression that often the most violent of them are hardly at all applicable to the patient himself, but that with insignificant modifications they do fit someone else, some person whom he loves, has loved or ought to love.... So we get the key to the clinical picture—by perceiving that the self-reproaches are reproaches against a loved object which have been shifted on to the patient’s own ego.

This is the source of the common phrase used to describe Freud’s definition of depression: *anger turned inward*. Such anger can arise from many sources, and at any time in life. In the psychoanalytic system, the person is unaware of the origin of the anger but aware only of the anger itself and directs it towards the self. The identity of the legitimate target of the anger lies in the unconscious mind, and the person thus has no legitimate, *conscious* target—other than self.

*Ellis and Beck: disorder of thought.* In the 1950's, Albert Ellis invented a new theory and method of therapy, called cognitive therapy (CT; Varga, 2013). In this framework, *cognition* is primary and emotion is derivative of it. Thus, psychopathology consists of a flawed thought process that can be drawn out, examined, and corrected via the therapeutic process: "(a) central claim is that depression is characterized by inaccuracies in information processing that therapy aims to correct" (Varga, 2013, p. 3). The manifestation of the flawed cognitive process is called *automatic thoughts* (Varga, 2013, p. 5): negative self-talk that is reflexively triggered by certain experiences or stressors. The client is trained to identify and nullify these.

*Yalom: a crisis of meaning and activist treatment.* Much more recently, psychiatrist and existentialist Irvin Yalom (1980)—originally trained as a psychoanalyst—has integrated philosophical existentialism with psychopathology and psychotherapy and thereby has become a major founder of existential psychotherapy, "a dynamic approach to therapy which focuses on concerns that are rooted in the individual's existence" (Yalom, 1980, p. 5). Yalom examines the psychoanalytic model of psychopathology and finds it lacking by virtue of its characterization of the etiology of psychopathology. In the Freudian scheme, the origin of psychopathology is *intrapsychic conflict*, due to id-based irrational drives that cause anxiety—leading to defense mechanisms that constitute psychopathology, including depression (Yalom, 1980, pp. 10-11).

The existential model replaces intrapsychic conflict with "awareness of ultimate concern" (Yalom, 1980, pp. 10-11); Yalom identifies four existential, Ultimate Concerns for humans: (1) death, (2) isolation, (3) freedom, and (4) meaninglessness. While any of the four can cause psychopathology, Yalom identifies meaninglessness as the primary cause of depression (Yalom, 1980, pp. 419-483). He refers to depression as a "crisis of meaning" (Yalom, 1980, p. 454). Of further interest is Yalom's basic therapeutic approach in cases such as this. He recommends what we could call an *activist approach* to treatment. By this, I mean that Yalom prescribes for the client a *re-engagement in life* through *activities* that, while not pointed directly at generating meaning, do so as a result of *active engagement* in life. Meaning is a side effect of activity and engagement in life. Verbal psychotherapy is important, but the client still must act in the world.

*Neuroscience: imbalance of neurotransmitters.* Shortly after the publication of Yalom's book, the

psychiatry of depression changed radically and rapidly due to the discovery, introduction, and vigorous marketing of Prozac, the first AD of the SSRI class. In a sense, this brings medicine back full circle, because the neurotransmitter theory involves an *imbalance* of neurotransmitters (rather than humors). While this is much more sophisticated of course than ancient theories, it represents the same spirit of biological causation due to changes in internal components of the body. Prozac was seen as being based in science (Breggin, 2010), and was accompanied by the *serotonin hypothesis* (Stahl, 1996).

But major problems have arisen with this theory (Breggin, 2010; Fournier et al., 2010; Healey, 2012; Horgan, 2011; Read, Cartwright, & Gibson, 2014). Czéh et al. (2016, p. 294) point to several limitations to the theory's explanatory power, as well as its power to generate new drug candidates. This has led to a slow abandonment of the older neurotransmitter models and driven the development of new theories and thus new drug candidates (Czéh et al., 2016, p. 294). Still, the biological model generally stands as the dominant framework in the field, and animal (rodent) research continues to be the first step in anti-depressant development.

#### **Inside the Rodent Mind?**

Simply looking at the nine symptoms listed for MDD in Table One, one is forced to wonder: are all, or any, of these phenomena likely—or even *possible*—in the lived experience of a rodent? Can a rodent have depressed mood—that is, feel sad? Can a rodent experience anhedonia? We are probably on fairly safe ground to claim that symptoms (3) through (6), the vegetative symptoms (Kaplan & Sadock, 2000), can be observed behaviorally in rodents because of their bodily, measurable nature. Czéh et al. (2016, p. 304), agreeing with my assessment of the bodily symptoms, also claim that symptoms (1) and (2) have measurable behavioral analogues.

In fact, much of their article chronicles the ways in which MDD symptoms can be induced in rodents, separately and one at a time using a different technique for each symptom. This is in line with the general approach of the field: to take depression apart, one symptom at a time, so that rodents can be bred, modified surgically, or trained through exposure to exhibit behaviorally the target symptom, which is then treated with an anti-depressant candidate. This is the *ultimate in reductionism*—to decompose a complex, heterogeneous, highly individualized human disorder into various samples of altered or trained *rodents*, “solve” each of the symptoms separately, then put everything back together and claim to have a

cure for the *human* disorder. But this reductionism destroys the very entity it claims to explain, by denying its unitary nature.

### **Depressed Mouse vs. Depressed Person**

Thus, the phenomenology of human depression—*what it is like to be depressed*—belies this experimental approach. Humans do not experience depression as symptoms that occur in an isolated way, independent of other symptoms, wherein (theoretically) a person could take a medication for each symptom and be cured of MDD. Instead, human depression is an integrated experience that consumes and dominates the entire person in a variety of ways all at the same time. There is no dismemberment of depression into particulates that can be dispensed with individually. And depression, while having for the great majority of people a strong *bodily* component, is also at its core a *mental* phenomenon, as indicated by symptoms (7) through (9) in Table One. It is, at least in my own estimation, *impossible* for a mouse to have feelings of worthlessness or guilt; to have problems with thinking, concentration, or making decisions (at least in the truly human sense of these terms); or have recurrent thoughts of death, contemplate suicide, attempt suicide, or even have a concept of death at all. These mental aspects of MDD are at the core of its power to destroy a life—even literally—and it would not seem possible for them to have a rodent analogue. Even Czéh et al. (2016, p. 304) agree with this; in fact, they state that the TST was never designed to assess mouse depression and that this and related tests “are not appropriate for animal models of depression” (Czéh et al., 2016, p. 304). Recall the point, quoted earlier, by Song and Leonard (2005, p. 628): “the core symptoms of major depression...may ultimately depend on the complexity of the brain.” Indeed, the rodent brain is too simple to contemplate death.

Czéh et al. (2016, p. 304) admit as much, implicitly, when they say creating an animal that will commit suicide is impossible. Some may go so far as to say that a rodent is incapable of committing suicide, even if it can conceive of suicide. But this is false. A rodent can kill itself merely by refusing food or drink for a little as a week. A deeply depressed mouse that no longer wanted to live could go to the corner of its cage, become immobile, and remain there until death. That no such occurrences have ever been observed casts severe doubt on the *face* (or what I call *phenomenological*) *validity* of the animal model, independently of any other consideration. When all the considerations are included, the use of this model for these purposes seems absurd.

Thus, some important validity claims by the animal model community meet their demise. The claim of *face validity* falls flat, due directly to the considerations immediately above. Can the symptoms of rodent depression have phenomenological (or might I even say *existential*?) validity when a core part of human depression—and a crucially important one in terms of *saving lives*—is not even observable in humans (until after the fact), much less in rodents, who most likely lack such capacities in any event? Can a mouse really feel worthless and wallow in self-loathing? Can a mouse feel anger turned inward? Can a mouse have Ultimate Concerns? Can isolation, freedom, or the foreseeing of death cause psychopathology in a mouse? Can a mouse experience a crisis of meaning? Can a mouse have any concept of meaning, purpose, value, or even death? Can a mouse have a disordered thought process resulting in depressing automatic thoughts? Is the immense complexity of the human brain and psyche moot in terms of the lived experience of mice versus humans? And could anyone plausibly answer “yes” to *any* the above? No.

Next crumbles *etiological validity*, at least in most cases. This type of validity requires that an MDE be triggered by an event known to be important for instigating human depression. (I note the bald-faced irony here that depression is induced by experience, yet is an inherently chemical disorder according to the theory.) It is, I think, obvious that no case of MDD in humans is the result of an OBX. In fact, the vast majority of cases of depression in humans are not caused by any kind of physical brain trauma, while in the OBX method, this *is* the etiology of claimed MDD-like states. Thus, there is no match, or even similarity, in the etiologies of depression in the two species. And consequently any claim of etiological validity is absurd.

This same logic also condemns any claim of *construct validity*, that the neurological basis of MDD is similar in humans and rodents. Clearly, after the OBX, the rodent’s brain is even less like a human one than it was at the start. Thus, the neurology—including, e.g., perception, cognitive processing, structural connections among different brain regions, and so on—cannot be similar and there can be no construct validity. All that remains is *predictive validity*, which is an empirical question; at least in the example I provided above (Liu et al. 2017), this criterion *was* satisfied. But one out of four is not good, to understate the situation. Overall, validity of all the kinds I have listed, defined, or re-defined—face/phenomenological/existential, etiological, construct, and predictive—is missing save for the last. For

these reasons, then, I find that the application of drugs developed in this manner is *inappropriate for use in a human population*. I will now make this conclusion even more clear, using this last example.

### Discussion

Let us take a closer look at the example provided by Liu et al. (2017). The methodology involves electrophysiological (EP) measurements to determine the effects of the candidate drug. There follows a chain of inference: (1) the EP results are correlated with the TST, so depression and its resolution are inferred from this correlation; but (2) the TST is assumed to be valid because it correlates with the Forced Swimming Test (FST), which had previously been the assessment of choice—so the EP results are used to infer TST results that imply the results of the FST (while neither the TST nor the FST are actually used); thus (3) The EP results are used to attribute an MDD-like state in mice that is assumed to adequately resemble human MDD; and (4) success of the compound SMM-189 in reversing MDD in mice is inferred, from EP results, to have the same effect in humans. Each step of this process is highly questionable, even before it reaches the stage of application to humans. But it is step (4) that is the most speculative by far, has the least theoretical and empirical support, and is probably the locus of AD issues.

To spell this out even more starkly, consider these inferences from a statistical point of view. (1) The EP results correlate with the TST, which (2) correlates with the FST, which is (3) taken to be correlated with depression in mice; then, (4) depression in mice is correlated (or perhaps another word) with depression in humans. These are empirical claims with statistical meanings. To say that EP is correlated with TST is to say that a statistical analysis of appropriate data yields a correlation coefficient  $r$ , where  $-1 \leq r \leq +1$ . This value squared,  $r^2$ , is called the variance, representing the amount of shared variability between EP and TST. If the two are completely and positively correlated, then both  $r$  and  $r^2$  will equal 1.0; if, however, the correlation is not perfect, then  $r^2$  will be smaller than  $r$ .

Thus, since correlation coefficients are almost always far from 1.0, the shared variance will be small for each step in the chain of inference. By the time we reach the third step, the shared variance between EP and mouse depression (with no TST or FST results) will be quite small, such that making the EP-mouse depression relationship claim is highly questionable. And this is even before the giant interspecies leap. If the claim is then that mouse and human depressions are correlated, not only must one surely question this proposition with a highly critical view, but even if the correlation is there, the

coefficient must surely be very small—then the mouse EP-human depression correlation will be exceedingly weak and useless for practical purposes. And indeed, this is how I see it.

It is then perhaps no surprise, given the development presented in this chapter, that the drug industry faces the triple crisis identified at the chapter outset and that there are considerable problems with currently used anti-depressants in humans. Overall, then, the Anti-depressant Enterprise appears to be resting on a very shaky foundation, one capable of collapsing at any moment, depending on research advances. The chain of inference leading from rodent research to human clinical trials, then to approval and marketing of anti-depressants, appears highly questionable on its face and at each step; and when closely examined, is filled with logical, empirical, and interpretive problems. The drugs yielded by this process thus also inherit the uncertainty arising from the development process. The flaws in the developmental methodology may lie behind the obvious flaws in the drugs themselves. Since we are marketing anti-depressants to *humans*, the presumed efficacy of a drug candidate in a presumably depressed *mouse* is an inadequate basis. The rodent model of human depression, for all its convenience, is quite simply *too simple* to accurately mirror the human condition.

### **Conclusion**

From a philosophical perspective, the application of rodent research to the complex, mysteriously multifaceted human condition of MDD is indefensible. From the perspectives of phenomenology, existentialism, and philosophy of science, the Anti-depressant Enterprise—given that this kind of research is its origination point—is tainted beyond rescue by the very limited human-mouse resemblance, the illogic in the chain of inference used in conjunction with this research, and the falsity of the premises. Further, the poor results for ADs in humans indicate deep, fundamental problems with the way this enterprise is conceived and conducted.

This is unfortunate from many perspectives, but especially from that of the depressed person. She takes her ADs, assured by her doctor that they will work in a few weeks, and while she complies with treatment, spends her money, and waits, the chances are good that nothing—other than side effects—is going to happen. If she does see some relief, that may come purely by placebo and thus not be lasting. In the meantime, she suffers, mostly silently, because others do not understand her condition and are likely

to *blame her* for it—she is weak, has poor character, is a whiner, or just needs to “suck it up” and get on with life, like everyone else.

While she waits and suffers, every other part of the system is thriving (Breggin, 1991, p. 140). The drug companies make gigantic profits—the “crisis” they are facing is the looming end of this very longstanding and highly lucrative windfall. Advertisers continue to make money, as demonstrated by the endless series of television commercials touting their products for the cure of depression. Doctors fill their offices with patients seeking diagnoses for their afflictions, refills of their drugs—or a prescription for another drug, since all up to now have failed. Basic scientists continue to generate publications, grants, tenure and promotion, and Ph.D. graduates. Of course, insurance companies also are very big winners in this scenario, for they have benefitted greatly from the proliferation of anti-depressants. It would appear that everyone benefits from the current system, save one group: *the patients*—for whom this entire enterprise was supposedly undertaken—their welfare lost in the green forest of money and profits.

## Chapter Three

### Clinical Trials and the Problematic Placebo Effect

The accumulating evidence points to unethical behavior at all stages of clinical trials from their design, to whether or not ethical approval is obtained, the way that the trials are conducted, the use of ghost writers to write up the results, the withholding of data and finally the use of Phase IV trials as marketing tools. Even more importantly, is the violation of multiple articles about the ethical conduct of clinical trials that are enunciated in the Declaration of Helsinki. (Lexchin, 2013, p. 11).

The first two chapters have shown that there are enormous scientific and ethical problems with anti-depressants, and with the initial step in AD development. The scientific and ethical problems are divided into two categories: empirical/scientific and economic/political, with several issues under each heading. Examination of the first step in drug development, laboratory studies with rodent models, reveals that there is an unquestionably flawed series of logical steps at work behind this research. This begins with the first claim: depression in humans reduces their olfactory sensitivity; thus, removing the olfactory bulb of the mouse will produce a depressed mouse. The arrow of causality is so clearly reversed here—along with an interspecies leap of faith—that it is stunning to realize that the OBX method relies completely on these absurdly wrong assumptions. Of course, the rest of the logical chain is at best tenuous—so the problems only *begin* here. And at the end of the chain is another interspecies leap of faith, this time from rodents back to humans. So already we have reason to suspect that ADs developed in this way lack validity when applied to human beings.

In the present chapter, I address the next steps in AD development. This is the multi-phase clinical trial process, overseen by the federal Food and Drug Administration, that each candidate drug—for any condition—must pass before being approved for public use. The opening quotation above indicates ethical problems with this process, and mentions many of the overall issues I have raised. And there are certainly problems with this process; I have outlined the major problems in Chapter One. Here, I will give a brief summary of the overall process; then discuss the ethical issues I have previously raised within this context; and finally address the placebo effect for ADs revealed by this process and examine

the meaning of the placebo effect for the Anti-depressant Enterprise. The following discussion is general in nature; when I am addressing ADs specifically, I will indicate this.

## **The Clinical Trial Process**

### **The Phases of Clinical Trials**

A candidate AD drug shown to be effective with rodents in laboratory settings is then forwarded to the institutional apparatus that tests the drug on humans. This testing consists of several phases; each phase is designed to serve a certain purpose, beginning with safety issues and ending with efficacy. There are four officially designated stages for a clinical trial, but the divisions among the stages and the goals of each stage can be somewhat porous; thus, the divisions are somewhat arbitrary. I will therefore present the stages in their simplest forms without the complexities—which are not very relevant to the subject at hand.

“In the past several decades, the randomized clinical trial has emerged as the preferred method in the evaluation of medical interventions” (Friedman et al., 2015, p. 1). The randomized clinical trial (RCT) process has been refined over that time, such that there is now general agreement, and enforceable federal regulations, regarding the RCT process. A clinical trial is defined as: “a *prospective study comparing the effects and value of intervention(s) against a control in human beings*” (Friedman et al., 2015, p. 2). A clinical trial must involve: one or more methods of intervention; one or more control groups, which may involve a placebo and/or a current standard therapy; adequate similarity among the participants of all groups before the intervention(s) are invoked; and standardized procedures that apply to all groups. “(T)he ideal clinical trial is one that is randomized and double-blind” (Friedman et al., 2015, p. 4). I would also add that the trial should include a placebo control group; the importance of this will be demonstrated. Friedman et al. (2015, pp. 31-32) support this idea: “(o)ften, a blinded placebo control provides the most complete information about risks and benefits of a new therapy as an inert placebo is the best approximation of a neutral control.” Highly relevant to MDD, the authors add: “(a) placebo control is particularly important when studying conditions with a variable course and/or frequent spontaneous remissions, when existing therapies are inconsistently effective or have serious side effects...” (Friedman et al., 2015, p. 33). Depression meets *all* these criteria. Almost all of the studies to which I will refer in this thesis are placebo-controlled, double-blind RCTs.

Phase I generally begins with a small number of healthy volunteers. The purpose of this trial is not the efficacy of the drug, but its toxicity and tolerability. The general goals are to: “examine drug tolerance, metabolism, and interactions, and describe pharmacokinetics and pharmacodynamics” (Friedman et al., 2015, p. 5). Additionally, Phase I studies “focus on questions such as bioavailability and body compartment distribution of the drug and metabolites. They also provide preliminary assessment of drug activity” (Friedman et al., 2015, p. 6). In most cases, the initial step is to determine the maximum tolerable dose. This process begins with a very low dose and a group of participants as small as three members (Friedman et al., 2015, p. 6). If the drug is found to be tolerable and not toxic at reasonable doses, it moves to Phase II.

The second phase is designed to determine the drug’s biological activity or effect. This is measured against one or more control groups that can include such things as historical controls. A study in this phase may serve to help determine dosages, so there may be different groups with different dosages. The participants in this phase “are usually carefully selected, with narrow inclusion criteria” (Friedman et al., 2015, p. 7). While Phase I studies use very small groups, Phase II studies use larger groups, on the order of tens of people.

Information from Phases I and II are used to design Phase III studies, which assess the efficacy of the candidate drug for the condition targeted; these studies also assess harm in a limited way. These studies have a short follow-up period, shorter than the typical period of drug use in clinical practice. Thus, Phase IV trials address this aspect of development. In Phase III, the number of participants is limited to several hundred or thousand participants. So, Phase III trials assess a drug’s effects for too short a follow-up time and for far fewer people than the number who eventually will take the drug (Friedman et al., 2015, p. 9). These are glaring problems for Phase III, and particularly for depression—a long-term condition, affecting millions of people. FDA approval to proceed to Phase IV “depends greatly on at least one well-designed clinical trial plus supporting evidence (often, another clinical trial)” (Friedman et al., 2015, p. 10). Healy (2012, p. 77) had previously written: “only two trials with statistically significant positive results are needed to let a pharmaceutical company put a drug on the market, even though there might be up to ninety-eight negative studies.” This runs directly against scientific reasoning.

If the drug candidate passes Phase III, then the drug is approved for prescription by doctors for the targeted condition. The results obtained from the general population (market) constitute Phase IV. That is, the final phase of testing is conducted on the general population, where people use the drug for longer periods than tested in Phase III and far more people use the drug than were involved in the prior three phases (Friedman et al., 2015, p. 9). This phase is intended to determine long-term (1) safety and (2) effectiveness. It is noteworthy for the purposes of this thesis that these two highly important factors are not completely determined until *after* the drug is made available for public use, and patients are unaware of this.

Essentially, everyone using a newly available AD is a test subject who is involved in Phase IV, but such information is not provided to the patients who take these drugs: “sometimes the balance between benefit and harm becomes clear only when larger phase IV studies are done, or when there is greater clinical experience” (Friedman et al., 2015, p. 9). Thus, it is almost as though clinical trials for ADs never actually end. This is relevant to *informed consent*, which I will address below. I note that: “(w)ell run clinical trials of adequate magnitude are costly, and therefore almost always require *sponsors* willing to pay for them” (Friedman et al., 2015, p. 14; emphasis added). This issue will be addressed in more detail below.

### **Ethical Issues in Clinical Trials**

In Chapter One, I provided an overview of scientific and ethical concerns connected with clinical trials. Here, I expand on the ethical issues—and these are prominent during the drug trial process. I previously identified the major political/economic issues as: (1) drug companies sponsoring studies of their own drugs, causing a *conflict of interest*; (2) *publication bias*, including the file-drawer effect, that limits the amount of information available for a drug; and (3) published studies with *ghost authorship*, obscuring the true identities of the researchers. In light of the discussion immediately above, I can add: (4) the incomplete information given MDD patients about ADs, making truly *informed consent* impossible.

Before addressing these four topics, I describe recent attempts to address some of the ethical problems arising from clinical trials. To help guard against publication bias, there has been an effort to legislate transparency of the clinical trial process. The result has been the establishment of several drug trial registries, all listed in the WHO International Clinical Trials Registry Platform (Friedman et al., 2015,

p. 16). These include ClinicalTrials.gov, a primary resource. Many journals and sponsors now require this registration. Such journals will not publish unregistered studies. But there remains much resistance and continuing violation of these regulations. I examine this issue below.

**Conflict of Interest.** First, I consider the *conflict of interest* generated by companies funding RCTs of their own drugs. Since “(p)harmaceutical companies fund the vast majority of clinical trials” (Lexchin, 2013, p. 11), these companies have a vested interest in the studies’ outcomes. Lexchin (2013, p. 11) puts it bluntly: “companies need trials with positive results in order to get their drugs on the market and drive sales. Negative trials can have significant adverse effects on sales.” Furthermore, this motivation can lead to malintent: “there is a strong temptation to deviate from the ideal for economic reasons. The result is trials that are unethical in some manner” (Lexchin, 2013, p. 11). This behavior is believed to be common. Lexchin cites two cases relevant to these points. He concludes that “(i)n both cases, positive trials were much more likely to be published and trials that had *negative* results when they were reviewed by the FDA had *positive* results in journal publications” (Lexchin, 2013, p.11; emphasis added). This illustrates what a combination of greed and opacity in the process can do to thwart efforts to make the RCT process more honest, open, fair, and ethical.

Friedman et al. (2015, p. 33) state that conflict of interest can result in biased “design, conduct, data analysis, interpretation, and reporting of findings.” In other words, this practice violates scientific principles as well as ethical ones, and generates unreliable results. But the very strong influence of money—to fund research and to give companies profitable drugs—makes it nearly impossible to avoid conflicts of interest. “Therefore, most clinical trials find it more realistic to manage conflicts of interest rather than to avoid them completely” (Friedman et al., 2015, p. 33). The influence of money in RCTs is inescapable.

To make things worse, the rate of compliance with registration and publication laws is unbelievably low. Anderson et al. (2015) have made an assessment of the compliance rate for drug testing regulations, and have found that this rate is alarmingly inadequate. They describe the history of regulatory attempts and the successes and failures of these attempts. The most applicable law is the FDA Amendments Act (FDAAA) of 2007, which requires “sponsors of applicable clinical trials to register and report basic summary results at ClinicalTrials.gov” (Anderson et al., 2015, p. 1031). Also required is that

trial results be reported by the sponsoring entity within a year following the completion of data collection (Anderson et al., 2015, p. 1031). The authors (Anderson et al., 2015, p. 1031) comment that “(s)tudies have shown that compliance with the FDAAA provisions is generally poor, despite a growing consensus favoring transparent, public reporting of human trials—an enterprise whose ethical justification rests on the creation of generalizable scientific knowledge.” So, drug companies are knowingly violating the law; this suggests awareness of guilt on their part.

Anderson et al. (2015) describe their meta-analysis of more than 13,000 trials. Among other results, they find that industry is the major funding source (65.6%), followed by the National Institutes of Health (NIH; 14.2%), and other academic or governmental entities (20.2%). They also state the rates of compliance with the FDAAA at one and five years following initial data collection: industry (17.0% and 41.5%, respectively); NIH (8.1% and 38.9%), and other (5.7% and 27.7%). It is striking how low the compliance rate is, even after five years, regarding data that should be reported within the first year. Regarding summary data, the authors conclude that these data are unavailable to the public for the majority of studies required to be reported. The authors conclude that “industry, the NIH, and other government and academic institutions all performed poorly with respect to ethical obligations for transparency” (Anderson et al., 2015, p.1039).

What, then, is to be done if even federal regulations are not enough to solve this problem? Friedman et al. (2015, p. 33) state: “(m)ost late phase clinical trials are sponsored by industry, and although the investigators enrolling and following participants may not stand to gain financially from the results of the trial, the sponsors clearly do. Therefore, analysis should be conducted, or at least validated, by groups independent of the industry sponsor.” While this comment seems to me to go in the right direction, it is a relatively weak solution. Lexchin (2013, p. 11) is more to the point: “(t)he solution is simple in concept but politically very unappealing to those with the power to implement it—a separation between the funding of clinical trials and their conduct, analysis, and write up.” This seems entirely correct—and, unfortunately, almost literally impossible. A veritable sea change in our culture, politics, and government would be required to transform the AE into an honest endeavor. Currently, there is little chance for this.

**Publication Bias.** Closely related to the problem of conflict of interest is the issue of publication bias: the selective publication of RCT results such that a false impression of efficacy is portrayed in the

literature. This is clearly a gigantic problem from the perspectives of both science and ethics. I quoted Lexchin earlier regarding *conflict of interest*; here I repeat the quote to emphasize the fact that *publication bias* is also involved. Lexchin (2013, p. 11; emphasis added) describes two groups that examined RCTs submitted to the FDA: “(i)n both cases, *positive* trials were *much more likely to be published* and trials that had negative results when they were reviewed by the FDA had positive results in journal publications.”

Friedman et al. (2015, p. 34) agree with Lexchin: “(f)inancial conflicts may also contribute to the problem of ‘negative’ trials being less likely to be published or having their publication delayed.... Trials with positive results are published more often....” They later say: “it is well known that publication bias exists. Positive or exciting findings are more likely to be published than null results” (Friedman et al., 2015, p. 42). Highly related to this point is another made by Lexchin (2015, p. 11): “(t)here are a number of instances where companies have been guilty of withholding data from investigators and from those conducting systematic reviews.” Gøtzsche and Jørgensen (2011), describing a very similar situation with the European Medicines Agency (EMA), agree—adding that “(s)elective reporting can have disastrous consequences”, especially for people with MDD. It seems that money has a deleterious effect at each and every point in the AE process.

“Doctors cannot choose the best treatments for their patients despite the existence of hundreds of thousands of randomized trials. The main reason is that research results are being reported selectively” (Gøtzsche & Jørgensen, 2011). This is the practical and functional consequence of the process I have described. It has severe implications for patient care, especially in the case of MDD—a life-threatening condition. These authors also say: “(c)omparisons of published drug trials with unpublished data available at drug regulatory agencies have shown that the benefits of drugs have been much over-rated and the harms under-rated” (Gøtzsche & Jørgensen, 2011). To support this statement, the authors cite a study of ADs by Turner et al. (2008) that is consistent with the description immediately above.

Turner et al. (2008) performed a meta-analysis involving 74 trials of ADs. Of these, 38 were considered to have positive results, and all but one of these were published. Of the remaining 36 studies—which were considered to have negative results—22 were unpublished. The remaining eleven studies showed no favorable results, but this was obscured in the published versions. Thus, there is a clear and large disparity between favorable and unfavorable studies in terms of publication, clearly

displaying the results of publication bias. The authors state: “(a)ccording to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall” (Turner et al., 2008, p. 252). Blatant dishonesty and misrepresentation of the data can make a failed study publishable, but most negative studies go unpublished. This deception can lead to the approval of drugs that range from ineffective to deadly. I must emphasize that the target population is people whose understanding and judgement may be impaired by their depressed condition—and so are in a poor position to determine whether they want to try the drug. Instead, they trust their doctor.

Anderson et al. (2015, p. 1038) make this point: “(t)he reporting requirements of the FDAAA reflect the ethical obligation of researchers and sponsors to respect human trial participants through fidelity to commitments made explicit in informed consent: namely, to make results of trials available to contribute to generalizable knowledge.” So, the unethical practices examined so far—and those to come—defeat the goals of generating reliable scientific knowledge and treating participants ethically. Gøtzsche and Jørgensen (2011) say: “(t)he EMA put protecting the profits of the drug companies ahead of protecting the lives and welfare of patients.” Again, it is clear that scientific validity and ethics are intimately intertwined and are being flouted in the name of profits.

**Ghost Authorship.** The case for dishonesty in the development and testing of AD candidate drugs is already strong, but there is much more to come. Within the topic of RCTs, there is yet another aspect of publication that is problematic: the listed authors of many publications are not actually connected with the study. This is known as *ghost authorship*. And as with the topics discussed so far, the same critics identify and examine this problem. As Friedman et al. (2015, p. 43) state: “the papers are written by employees of the sponsors, who are not listed as authors, and the academic-based investigators, who may have had little or no role in drafting the manuscript, are given authorship credit. We deplore this practice.”

Indeed, this practice is deplorable and abusive: there is the opportunity for great deception and dishonesty in the process of data collection and analysis, the interpretation of results, and the manner in which the manuscript is written: “the message in the article is one that has been developed by the

company to further its commercial interests” (Lexchin, 2013, p. 11). Lexchin (2013, p. 11) finds that ghost authorship ranges from 12% to 75% in trials funded by industry, which of course are the majority of trials.

Stretton (2014) distinguishes between ghost authorship and ghostwriting, which she defines as: “paid or unpaid writing contributions to a manuscript that do not meet authorship criteria [and] are not disclosed in the acknowledgments.” This distinction is not made in other literature on this topic. Ghost authorship would appear to be a larger threat than ghostwriting, but one cannot be sure in any given case which may be happening—and both may be happening. Stretton stresses that the distinction between these two phenomena is not clear to all researchers, and some researchers do not make a distinction. Most of her article regards ghostwriting, but Stretton (2014) does report four cross-sectional studies of ghost authorship: “(t)he prevalence of ghost authoring reported in these cross-sectional surveys varied from 0.7% to 70% of publications or authors” (Stretton, 2014). Efforts to reduce ghost authoring have met with very limited success. There is no question that such a practice occurs and is a major problem.

**Informed Consent.** Various aspects of informed consent (or the lack of it) have been mentioned as I reviewed the evidence for other categories of economic/political influence in AD development. Here, I address this issue directly but briefly, as I have already laid the groundwork. Friedman et al. (2015, p. 35) give a table containing the elements of informed consent. There are many considerations involved; the table provided concerns informed consent in RCTs. My main concern is somewhat different—informed consent in the doctor’s office, involving the conversation between the doctor and patient *before* ADs are prescribed. In this regard, I have already pointed out that Phase IV of RCTs occurs *after* drug approval and marketing to doctors and patients. It appears that informed consent in the doctor’s office does not typically include notification of the patient as to the status of the drug—e.g., that a newly released AD is still in the testing phase, and the patient is actually a participant in a very large experiment (Breggin, 1991, p. 161). This alone is ethically intolerable.

But further, truly informed consent would include a full discussion of the drug’s effects, side effects, the degree of placebo response to the drug in studies, the time needed until the drug begins to be effective, and how the drug prescribed compares to other medications available for the condition in question. “To be able to make such decisions, or at least to be involved in the discussion, people need to know the truth about their disease, its possible outcomes, and the full range of medical options available”

(Brody, 2000, p. 30). Surely, some of these aspects are at least briefly discussed, but it is very doubtful that the placebo effect is mentioned; it is also probably rare that a doctor admits that the prescription is an experiment and the doctor has no idea of the probable outcome. It is not conceivable that a doctor would tell a depressed patient the absolute truth about an AD—first, because of all the detail and science involved; second, because doctors themselves do not always have such information; and third, because the doctor wants to enhance the placebo effect in all ways possible, which means restricting information and professing confidence in the AD.

### **The Problematic Placebo Effect**

So, why would a doctor avoid a discussion of the placebo effect in the office with a depressed patient? The answer is that this would undermine the effect of the drug. This statement may seem outlandish—why should a person’s knowledge about the placebo effect (or about anything else) affect the action of a drug in the body? The answer is unclear. Nevertheless, in RCTs, a placebo effect (PE) can be measured for almost all drugs, and even for procedures such as acupuncture or the installation of a medical device. In all these cases, a placebo is a sham treatment: an inert pill portrayed as actual medicine; a sham operation; or a dummy procedure that looks like the real thing. What is very odd and not understood is how such phony treatments can have positive effects. But we understand that this does happen, and quite frequently.

Howard Brody (2000, p. 7) states that:

(t)he placebo response seems to be the body’s reaction to some healing signal in the environment, which acts through the mind.... Consider the general concept of a *symbol*.... We usually call something a symbol when it stands for or invokes something much more powerful or vast than the thing itself.... If the traditional placebo seems to be “inert” all by itself, and yet somehow has the capacity to unleash very powerful responses, we can understand this by viewing the placebo *as a symbol*.”

Further, he holds that the symbol’s effect can be conscious or unconscious. He adds (Brody, 2000, p. 8): “symbols might help explain why the most powerful placebo responses are in one way or another often embedded in important human relationships.” An example of one such relationship is the doctor-patient relationship.

Brody goes on to give his full definition of the placebo response (effect): “(a) change in the body (or the body-mind unit) that occurs as the result of the symbolic significance which one attributes to an event or object in the healing environment” (Brody, 2000, p. 9). Brody stresses the importance of the healing context. Such a context is a powerful representation in the patient’s mind, and generates potentially great expectations. Such a healing environment can include the doctor’s office. Brody goes on to clarify that a placebo effect is distinct from the natural course of a disease, i.e., spontaneous healing. He then makes a crucial point that is essential to understanding MDD: “(t)he normal course of most illnesses is to get better even without any healing intervention, whether from a healer or from oneself” (Brody, 2000, p. 10). On this point, Breggin (1991, p. 158) says: “(s)pontaneous improvement of depression...takes place in at least one-quarter of patients within the first month or so of becoming depressed and in one-half or more over a few months.... Since it takes most antidepressants a month or more to have their presumed beneficial effect, it easily overlaps with spontaneous recovery.” This is a crucial point regarding the latency period for ADs, as we will see. Further, Breggin (1991, p. 171) says: “the vast majority of people overcome depression without resort to any mental health services.”

Making use of the concept of the symbol—but somewhat indirectly—Brody (2000, p. 62) says that most studies comparing ADs with *inert* placebos show ADs to be superior, but *active* placebos (that mimic the AD’s side effects but not the therapeutic effect) are equal to ADs in effectiveness. This suggests that the side effects are the key to the effectiveness of an AD: side effects act as a symbol or signal that healing is occurring, leading to the patient’s expectancy of improvement. Thus, side effects may be key to understanding the placebo effect. Below, I will discuss a major research project that strongly bolsters this idea. I also note here that, given the natural course of MDD, the best RCTs of ADs should include not only a placebo control group, but a no-treatment group as well—in order to estimate the effects of the natural disease course.

The frequency and intensity of the PE with ADs are striking, and appear to be greater than for many other therapies. This is demonstrated by RCTs that include a placebo control group in the design. But one must be careful in evaluating the PE in the context of an RCT. Hróbjartsson and Gøtzsche (2001, p. 1594). state, regarding placebos in general:

The vast majority of reports on placebos...have estimated the effect of placebo as the difference from base line in the condition of patients in the placebo group of a randomized trial after treatment. With this approach, the effect of placebo cannot be distinguished from the natural course of the disease, regression to the mean, and the effects of other factors. The reported large effects of placebo could therefore, at least in part, be artifacts of inadequate research methods. In fact, the claimed large effects of ADs themselves are vulnerable to the exact same critique. These are general concerns for all RCTs, and for ADs this point may be crucial in explaining not only side effects, but also the unusually long time required for ADs to be apparently effective (latency period), and—as promised above—the placebo effect as well. I will address this last issue presently, and the other two issues afterwards, in the Discussion and Conclusion.

In their meta-analysis of placebos for a wide variety of conditions, Hróbjartsson and Gøtzsche (2001; p. 1599) conclude that “we found little evidence that placebos in general have powerful clinical effects. Placebos had no significant pooled effect on subjective or objective binary or continuous objective outcomes.” Their pool of studies, however, included only three AD studies involving a total of 152 participants; they comment: “(p)lacebo had no significant effect on these outcomes, but the confidence intervals were wide.” There is no mention here of side effects—which, as we saw above, are a key aspect. Additionally, studies to be described below have much more statistical power than this, and do show significant PEs for ADs.

I have summarized some of the results regarding placebo effects for ADs that were obtained in the 1990's and early in the 2000's, when much of the data regarding SSRIs and other new antidepressants had not yet been obtained. Later studies, and meta-analyses of studies, cast much more doubt and uncertainty on AD effectiveness and demonstrated placebo effects larger than previously recognized. To illustrate this, I review the work of two more-recent authors, David Healy and Irving Kirsch, who unveiled the truth regarding ADs and their putative anti-depressant effects. I begin with the simpler case made by Healy (2012, p. 83) regarding ADs:

How minimal are the treatment effects? In 2006 the FDA asked companies making [ADs] to submit all placebo-controlled trials to the agency. Just as some people recover from infections without treatment, based on 100,000 patients who had been entered into these [AD] trials, the

data showed that four out of ten people improve within a few weeks whether treated with a drug or not. This may in part be due to the natural history of depressions in which 40 percent recover within a few months whether treated or not.... On the active drugs, five out of ten apparently responded. But what comparing an active drug to a placebo shows us is that of these five, four (80 percent) of apparent responders to an [AD] would have improved had they received the placebo. In other words, only one in every ten patients responds specifically to the [AD], whereas four in every ten treated with a placebo show a response.

Thus, the conclusion from a sample of 100,000 patients is that ADs are 10% effective, while placebos are 40% effective. This is a stunning result that belies the claims of the scientific and corporate interests held by drug companies. What Healy reports is fatal to the myth that ADs are scientific and effective. It seems that the human mind is much more effective than drugs.

In addition to the study reported by Healy involving data from 2006, there was another study that essentially closes the case on ADs and their ineffectiveness. This study was carried out by Kirsch and associates (2010), who performed a meta-analysis on a large group of AD studies. Kirsch began his work in 1995, out of a general interest in placebos, then devoted himself to the PE for ADs because the PE here is so pronounced. Over time, he collected published and unpublished data (from suppressed studies) that allowed an assessment of AD efficacy with more representative data than only published studies could offer.

Kirsch and his coworkers went to great lengths to obtain all available relevant data. Beyond published and suppressed studies that employed placebo-control, they obtained data from no-treatment groups from studies of the effectiveness of psychotherapy for depression (Kirsch, 2010, p. 7) to assess the disease's natural course. This research group explored so many possibilities and potential factors in the AD picture that the publication of their full results did not occur until 2006, eleven years after they began the project. In the end, 38 clinical trials were included in the meta-analysis, involving over 3000 depressed patients (Kirsch, 2010, p. 9).

The results of this analysis were presented as a bar graph plotting group (drug, placebo, psychotherapy, and no treatment) versus effectiveness. The graph shows that there is a large amount of improvement in the placebo group compared with the no-treatment group. Second, psychotherapy is the

most effective treatment, barely beating out the drug effect. But third and most importantly, the difference between the placebo and drug groups is small; most of the drug effect is actually placebo effect. Finally, the effect of simply letting time pass was relatively small. This allowed Kirsch to make a series of conclusions, some of which lie in the mere description of the results above.

Perhaps the most important results were that “only 25 percent of the benefit of antidepressant treatment was really due to the chemical effect of the drug. It also means that 50 percent of the improvement was a placebo effect. In other words, the placebo effect was twice as large as the drug effect” (Kirsch, 2010, p. 11). Reflecting on the surprisingly low drug effect, the researchers noted that their analysis involved a variety of drugs used as ADs, and there was a question as to whether some of the drugs tested were better than others. Examination and further analysis of the data, however, demonstrated that “the diversity of drugs had not affected the outcome of our analysis” (Kirsch, 2010, p. 12).

But beyond this result, they discovered that some of the drugs tested as ADs were decidedly *not* ADs. Such drugs included: a barbiturate, a benzodiazepine, a synthetic thyroid hormone, stimulants, and opioids (Kirsch, 2010, p. 13). Even though these were not ADs, they showed the same AD effect in clinical trials. But another drug, based on a different hypothesized mechanism, showed itself to be *ineffective* as an AD. This drug differed from the others in that it displayed an *absence of side effects*. Kirsch says (2010, p. 14): “(c)linical trials show that whereas the therapeutic benefits of antidepressants are relatively small when compared to placebos, the difference in side effects is substantial.”

Thus, typical placebos have a lower level of side effects than active drugs. Kirsch (2010, p. 17) realized that “side effects have been associated with figuring out whether one has been given an active drug or a placebo in a clinical trial” and that if a participant in an AD trial experienced strong enough side effects, the participant could figure out that the drug was not a placebo. Thus, the blinding condition of the experiment had been broken, and the results were affected. Kirsch concluded that the drug effect was actually an enhanced placebo effect, and this led him to search further. He noted that there is a high correlation between improvement and side effects in the use of SSRIs, supporting the emerging hypothesis that improvement with ADs was due to the placebo effect, the natural disease course, and the presence of side effects; that is, *there is no actual drug effect at all*.

Given this possibility, it stands to reason that if one statistically accounts for side effects, any remaining effect would be the *true* effect of the drug. Kirsch and his team performed this analysis, and found that “once you adjust for drug-placebo differences in side effects, differences in rates of improvement are no longer statistically significant” (Kirsch, 2010, p. 19; see also Breggin, 2008, p. 32). This is sufficient to judge ADs to be ineffective as true ADs, and it also suggests that if one were to use an *active placebo*—one that has no AD effect but does have significant side effects—then one should find no difference between the actual drug treatment and active placebo treatment. Kirsch’s group found nine studies that compared ADs with active placebos, and “a significant difference between drug and placebo was found in only two” (Kirsch, 2010, p. 20). With this, the hypothesis entertained by Kirsch is completely supported. In his book, Kirsch explains other aspects of the results that needed to be examined, but in the end there is no evidence to contradict his conclusion. ADs appear to work, but the effect is a combination of the three factors I identified above. In other words, anti-depressants are a hoax.

### **Discussion and Conclusion**

As a result of Kirsch’s work and the supporting work of others, I am now in a position to examine the three phenomena I identified earlier: side effects, the long induction time for ADs, and the placebo effect. Using Kirsch’s findings as well as the earlier ones I described that involved the role of side effects, I suggest that the following scenario is at work behind the scenes: ADs have no legitimate drug effect. Instead, they induce side effects. The psychological result of the side effects is a *symbol* to the depressed person that healing has begun. This interpretation on the part of the patient induces the placebo effect. The PE is added to the natural course of depression, and initial ingestion of the drug is merely a marker in time. Thus, if a person’s course is heading downward at treatment initiation, the continuing symptoms will be wrongly interpreted as side effects of the drug—since the assumption is that the drug is working—and if the person’s course is upward at initiation, the subsequent improvement will be wrongly credited to the drug. In other words, the drug is assumed to be effective; therefore, all changes following treatment initiation are attributed to the drug. And this is wrong.

Further, the time between initiation and any improvement is incorrectly attributed to a latency period for the drug; in fact, this is the natural course of the disease. This means that the various tortured explanations for the latency period are completely wrong—there is no latency period, because the drug is

not effective—and delayed spontaneous recovery is mistaken as the latent drug effect. Seen in this way, ADs are “just placebos with side effects” (Horgan, 2011). There is an additional issue here. “Side effects” of ADs can include suicidal ideation and suicide attempts. But if ADs are ineffective, then suicidality after treatment initiation is just the continuation of the downward course—not an effect of the drug.

Such suicidality has previously been explained as a heterogeneous effect of ADs: the claim is that early in treatment, the patient’s vegetative (bodily; see Table One) symptoms—including energy—improve, while the cognitive symptoms improve later. This supposedly leaves a window of time during which the depressed person still has suicidal ideation, but now has the energy to carry out suicide. But we have seen that this is incorrect. So, in this scenario, suicidality is not the result of drug *action*, but rather the result of drug *inaction*. This type of case illustrates the danger in believing the AD propaganda and depending on an AD to preserve a life. The prescription and use of ADs instead preserve a *lie*. And this lie, in some cases, can lead to death. This explains why, occasionally, a person who has completed suicide is found on autopsy to have been taking ADs.

Thus are illustrated the folly and danger of believing the neurotransmitter theory of depression. Depending on ADs to reverse one’s depression is an exercise in faith with no basis. Taking pills—instead of taking time to examine one’s life and self, discover problems and issues, and come face to face with life and its problems—is actually taking a detour from reality and one’s place in it. In view of the development in this thesis so far, true informed consent in the doctor’s office would look very different. Instead of saying something like “this drug has been shown in clinical trials to be effective for your depression,” the doctor could—if being honest—only say “this drug makes brain-damaged mice wiggle when suspended by their tails.” The honest doctor should also add: “this drug is relatively new, so you are a participant in the clinical trial of this drug.” This would understandably not reassure the patient that help is within reach. Even a severely depressed patient would still have enough cognitive capacity to object to a drug promoted on this rodential and trial basis. Thus the key to the overall financial success of ADs has been the keeping of this tremendous secret from those who need to hear it: patients and their doctors. The secret resides openly in the medical literature, but drug companies count on this knowledge remaining outside the mainstream. And until now, this strategy has worked—to the detriment of people in very vulnerable positions.

## Chapter Four

### Science and Philosophy of Science in the Anti-Depressant Enterprise

At the beginning of this examination of the Anti-depressant Enterprise, we saw that there are a host of ethical and scientific problems in this area; I summarized the many issues under the headings of empirical/scientific and economic/political. We then closely examined the first developmental stage of ADs, testing in rodents. This revealed that the animal research is founded on contradictory logical grounds and that there is no reason to consider drugs developed in this manner as effective for humans. Then we turned to the clinical trial process for approving or rejecting new ADs and found that, indeed, the suspicion that animal testing was improper and inadequate for human use is upheld by the uselessness of ADs as unveiled by this process.

I now turn to a closer examination of the science-related issues in the AE and views from the philosophy of science. Since logic is one place where science and philosophy intersect, I begin with a logical analysis of our results thus far, then identify the scientific conclusions of that analysis. I then apply the views of two major philosophers of science, Karl Popper and Thomas Kuhn, to the scientific problems that ADs present. Finally, I apply the more recent work of Barker and Kitcher to this area. I close this chapter with reflections on how the scientific process has gone so wrong in the psychiatry of depression and the AE.

### Science and the Anti-Depressant Enterprise

I begin with a close logical analysis of the overall concept behind ADs, what I will call the Neurotransmitter (NT) Theory of Depression (NTD). The general claims of the NTD are that people with depression have insufficient levels of one or more NTs available in neuronal synapses, and that by readjusting the supply of NTs one can reverse the effects of depression. But do such claims make sense on their faces, even without the damning analyses in the first three chapters of this thesis? The truth is that there are only guesses going on here. First, there is no known standard as to what the synaptic level of NTs *should be* for a normal person, much less for a depressed person; similarly, patients prescribed ADs never have the NT levels in their synapses checked before diagnosis. The result from any such test would be clinically useless. So we must ask: the depressed person's NT levels are too low *compared to what?* There is no answer to this question. Second, the initial choice of AD is a completely unguided

exercise; the clinician is guessing, based on her clinical experience, as to what AD she *thinks* will work. And third, when the first AD fails, the process then consists of further guesses by the doctor until a successful drug is found, or not.

Such a process is no surprise, given the results from the first part of this thesis. And if we now consider those results, the exercise of putting patients through unguided clinical trials with an *n* of one is truly absurd, since in general they do not work except by the placebo effect. So the search for an effective AD may reduce to the search for convincing side effects. Another theoretical problem with the NTD is the fact that the origin of the so-called NT deficiency is rarely discussed and certainly not understood. Genetics has been suggested as the initial culprit, but this idea is never supported with any further reasoning, such as: is a person born with the deficiency, or does it develop? If one is born with it, is one depressed from birth? If one develops it, what triggers this development, and how does it work?

Beyond these theoretical considerations lie deeper ones. What of life experiences and their effect on self-image, self-esteem, and mood? Even the biological literature occasionally mentions life events that can bring on MDD. In fact, most cases of depression—that do not originate as a symptom of another disease process—appear to spring from experiences. How can NTD cope with this? How can NTD cope with spontaneous recovery? Or with recovery achieved with psychotherapy alone? However depression has its onset, there lies a mechanistic problem to be solved if the NTD is to be invoked as an explanation.

To look more deeply into these issues, I summarize a view on ADs that entertains three types of depression: reactive, biological, and reactive-biological. Preston, O’Neal, and Talaga (1994) wrote their book at a time when ADs were unquestioned by the vast majority of doctors and patients alike—this was before the problems we have seen were generally recognized. Thus, these authors are fully on board with the NTD, but at the time it was still acceptable to recognize the role of life events in MDD. Therefore, they present a model that includes both biological and experiential aspects of MDD. They begin with reactive depression: “(t)hese disorders occur in response to identifiable psychosocial stressors. These stressors may be acute and intense...insidious...or in the distant past” (Preston, O’Neal, and Talaga, 1994, p. 61).

The authors state that reactive depression in its “pure form” leaves the bodily aspects of functioning relatively unaffected, but has deleterious effects on one’s psychology. On the other hand, biological depression—again in its pure form—is *not* seen as a reaction to stressors, and manifests

mainly as physiological symptoms. Instead of a reaction to stressors, biological depression appears apparently spontaneously in a person by virtue of (1) medical illness; (2) fluctuations in female hormone levels; (3) medications and illegal drugs or alcohol; or (4) “endogenous biological depressions” (Preston, O’Neal, and Talaga, 1994, p. 63). This last category would probably describe the majority of so-called biological cases of depression, but there is an innate problem with this suggestion: the authors claim that no stressors are involved, but instead a genetic predisposition exists and that this leads to MDEs.

The problem with the reasoning just above is that it is a partial statement of the diathesis-stress model from psychology, invoked to explain how genetic predispositions (or diatheses) can be triggered by life events (stressors) and thereby be expressed. Thus, even the biological model requires negative life events to trigger the gene expression. It appears that—whether genetically predisposed or not—depression is intimately related to what happens in our lives and the meaning those events have for us. This brings us to the third type of depression these authors identify as the *predominant* type: reactive-biological depression. This type begins as a reaction to life stressors, but over time evolves into the biological type. The result is that the person has both types of depression: psychological and physiological—what the authors term “mixed depression” (Preston, O’Neal, and Talaga, 1994, p. 64).

Such a model might be invoked by the doctor who claims that depression resulting from life events *still* needs NT treatment because of the evolution into biological depression. Such a doctor might well claim that, while the origin of the depression was experiential, it has turned biochemical and thus medication is indicated. This doctor might claim further that it is the biological nature (NTD) that is now maintaining the depression, well beyond the time a reactive depression should have ended. In light of the results in this thesis so far, this reasoning is rejected based on the demonstrated ineffectiveness of ADs.

But further, the medical reasoning traced above is vulnerable to basic logic. If NT imbalances do not *cause* depression, then neither will they *maintain* depression. The putative NT imbalance would be a *symptom* of MDD, not the *cause*. This is a crucial point. Rarely if ever does treating the symptoms of a disease actually cure the underlying disease. For example, if one has a cold and takes medication to reduce coughing, sneezing, etc., then one may have fewer symptoms but the cold is still there. Similarly, in the treatment of Alzheimer’s Disease, medications exist that can provide NT support for memory, but this does not affect the disease process and the person will eventually die despite this treatment. Then,

by analogy, treating an NT imbalance is as effective against MDD as Nyquil is in killing the common cold virus.

A second way to logically view the problem is via statistical reasoning. When a claim of statistical significance is made, this suggests that “ $p \leq .05$ ” or often a more strict criterion. The value of  $p$  is the probability that the obtained result will *not* be reproduced upon further experimentation (5 or fewer times out of 100 attempts in this example), assuming the same methodology, etc. Thus, a study revealing a statistically significant effect should be reproducible upon attempted replication. Now, in light of this meaning, let us again examine Healy’s comment quoted in Chapter Three: “only two trials with statistically significant positive results are needed to let a pharmaceutical company put a drug on the market, even though there might be up to ninety-eight negative studies” (Healy, 2012, p. 77). Negative studies do not count.

In this barely hypothetical example, one hundred performances of the experiment would reveal only two successful attempts. The probability of obtaining a positive result is only two out of 100. This means, statistically, that  $p = .98$ ; that is, the probability of obtaining *negative* results is very large—so large in fact that the reverse hypothesis (the ineffectiveness of ADs) is statistically *proven* to be true. That is, the example illustrates that the outcome can be expected to be positive two or fewer times per 100 attempts. Healy’s example shows that the *opposite* of scientific reasoning holds sway at the FDA. The apparatus of the AE holds fundamentally an *anti-science* point of view. This illustrates how ineffective ADs nonetheless reach the market.

Finally, I address the above from a foundational concept in experimental science: reproducibility. This involves concepts we have already seen. An experimental result in science is only valuable if it is shown that the result can be obtained in any laboratory by any researcher who uses the proper methodology correctly. Generally, this means that anyone qualified should be able to get the same result as in the previous attempt or the same result obtained in another lab. But in Healy’s example, which does not deviate very far from actual examples, we see another kind of reproducibility: *the replication of failure*. Far from proving the effectiveness of the drug, what the AE has demonstrated is that the *failure* of ADs is the *reproducible* result. Yet, it is upon this basis that the drug is approved for marketing. Thus, the entire AE is undermined.

## Views from the Philosophy of Science

### Karl Popper and Falsifiability

The issues of replication and reproducibility lead the discussion directly into the territory of philosophy of science, and to the work of Karl Popper in particular. Popper (2002), working in the early 20<sup>th</sup> century, paid close attention to the demarcation problem in the philosophy of science, the role of theory in science, and the *falsifiability* of theories. I will explain this last term as I summarize Popper's position. Early in his book, Popper gives an overview and summary of his views concerning theory, experimentation, and related issues (Popper, 2002, p. 10):

certain singular statements— which we may call 'predictions'—are deduced from the [new] theory; especially predictions that are easily testable or applicable. From among these statements, those are selected which are not derivable from the current theory, and more especially those which the current theory contradicts. Next we seek a decision as regards these (and other) derived statements by comparing them with the results of practical applications and experiments. If...the singular conclusions turn out to be acceptable, or verified, then the [new] theory has, for the time being, passed its test: we have found no reason to discard it. But if...the conclusions have been falsified, then their falsification also falsifies the [new] theory from which they were logically deduced. It should be noticed that a positive decision can only temporarily support the theory, for subsequent negative decisions may always overthrow it. So long as theory withstands detailed and severe tests and is not superseded by another theory in the course of scientific progress, we may say that it has 'proved its mettle' or that it is 'corroborated' by past experience.

Thus, a theory yields *testable* predictions, which—if upheld by experimentation—allow a theory to stand until contradictory evidence or a superior theory supplants the previous theory. Note that the key term here is "testable," which Popper uses interchangeably with "falsifiable." The only legitimate scientific theories are the ones open to this concept (Popper, 2002, p. 17):

all the statements of empirical science (or all 'meaningful' statements) must be capable of being finally decided, with respect to their truth and falsity; we shall say that they must be 'conclusively decidable'. This means that their form must be such that to verify them and to falsify them must

both be logically possible. Thus Schlick says: ‘. . . a genuine statement must be capable of conclusive verification’; and Waismann says still more clearly: ‘If there is no possible way to determine whether a statement is true then that statement has no meaning whatsoever. For the meaning of a statement is the method of its verification.’

Therefore, the falsifiability criterion is crucial to Popper’s view of what science is and how it *should* work. And falsifiability and testability are, in contemporary science, indisputably at the core of how the process *does* work.

These terms are nearly identical in meaning to reproducibility and replicability, which I discussed above. But Popper is extremely careful in how he defines his terms, and how they fit into his perspective (Popper, 2002, p. 18):

These considerations suggest that not the verifiability but the falsifiability of a system is to be taken as a criterion of demarcation. In other words: I shall not require of a scientific system that it shall be capable of being singled out, once and for all, in a positive sense; but I shall require that its logical form shall be such that it can be singled out, by means of empirical tests, in a negative sense: it must be possible for an empirical scientific system to be refuted by experience.

This can partially be rephrased as: a scientific system (theory) can survive any number of tests with positive outcomes for the theory, but this does not verify the theory—which can never be fully and finally verified; the true test of a theory is its ability to generate hypotheses that can be empirically tested, and have a chance to fail those tests.

Hypotheses and the testing thereof serve the purpose of pitting one theory against another so that competing theories can be supported or falsified (Popper, 2002, p. 20):

what characterizes the empirical method is its manner of exposing to falsification, in every conceivable way, the system to be tested. Its aim is not to save the lives of untenable systems but, on the contrary, to select the one which is by comparison the fittest, by exposing them all to the fiercest struggle for survival.

And again, even the surviving theory in this battle must be able to provide consistent accuracy upon attempted falsification (Popper, 2002, p. 23):

Only when certain events recur in accordance with rules or regularities, as is the case with repeatable experiments, can our observations be tested—in principle—by anyone.... Only by such repetitions can we convince ourselves that we are not dealing with a mere isolated 'coincidence', but with events which, on account of their regularity and reproducibility, are in principle inter-subjectively testable.

This connects directly with my discussion of statistical reasoning early in the present chapter. Using Healy's example once again, wherein only 2 of 100 AD trials give positive results, we see that in Popper's language, these rare occurrences would be considered coincidences, and in statistical language would be considered statistical flukes. There is no scientific sense in which such results could be seen as supporting the efficacy of the AD candidate drug. So by Popper's reasoning—as well as my own—the AE has not yielded a valid scientific theory. The NTD has been *falsified* by the overwhelming statistical evidence against it. And here, additional commentary regarding falsification is called for from Popper (2002, p. 66):

We must clearly distinguish between falsifiability and falsification. We have introduced falsifiability solely as a criterion for the empirical character of a system of statements. As to falsification, special rules must be introduced which will determine under what conditions a system is to be regarded as falsified. We say that a theory is falsified only if we have accepted basic statements which contradict it.... We shall take it as falsified only if we discover a reproducible effect which refutes the theory.

Thus, this thesis has demonstrated that what is reproducible is the *failure* of ADs to positively affect MDD. Two basic and highly reproducible statements—that (1) when adjusted for side effects, ADs perform no better than inert placebos and that (2) there is no statistical difference in efficacy between ADs and active placebos—act in combination to refute the NTD. Under Popper's definition, the NTD had a falsifiable nature, as any scientific theory should, but upon rigorous testing has been falsified. A final comment from Popper (2002, p. 91) is appropriate here: "(a) theory is a tool which we test by applying it, and which we judge as to its fitness by the results of its applications." The NTD has been tested by applying it to MDD via ADs, and has failed that test.

## Thomas Kuhn and Scientific Revolutions

At its heart, since it is constructed and conducted by human beings, science is an innately social enterprise. Thus, science is influenced by the culture within which it resides, and is vulnerable to human foibles—including such things as inherent biases or sheer error. Science is limited by our human limitations. It is therefore important to understand how science functions in a social context and what kinds of social phenomena inhibit or promote major changes in science; that is, how do scientific revolutions occur? This is the topic of a landmark work in the philosophy of science, that provided by Thomas Kuhn (1970).

Kuhn was a physicist by training, but developed an interest in the sociology of science, whence came his interest in the nature and structure of scientific revolutions. His book introduces several terms, the explication of which will serve to summarize Kuhn's perspective. But first, regarding Kuhn's recognition of the social aspects of science, he states (Kuhn, 1970, p. 4): "(a)n apparently arbitrary element, compounded of personal and historical accident, is always a formative ingredient of the beliefs espoused by a given scientific community at a given time." He then asserts that the great majority of science falls into the class of *normal science*, which Kuhn defines as (Kuhn, 1970, p. 5): "predicated on the assumption that the scientific community knows what the world is like.... Normal science...often suppresses fundamental novelties because they are necessarily subversive of its basic commitments."

Normal science defends its established turf by ignoring contrary data and phenomena for as long as it can. The novelties to which Kuhn refers he then immediately identifies as *anomalies*, results that "cannot, despite repeated effort, be aligned with professional expectation" (Kuhn, 1970, p. 6). When anomalies accumulate so as to be unignorable, "then begin the extraordinary investigations that lead the profession at last to a new set of commitments, a new basis for the practice of science" (Kuhn, 1970, p. 6). For Kuhn, this process constitutes a *scientific revolution*. It is a revolution because the assimilation of the new theory (Kuhn, 1970, p. 6) "requires the reconstruction of prior theory and the re-evaluation of prior fact, an intrinsically revolutionary process that is seldom completed by a single man and never overnight."

This reconstruction process results in a change of *paradigms*. Paradigms are (Kuhn, 1970, p. 10) "accepted examples of actual scientific practice" that "provide models from which spring particular

coherent traditions of scientific research.” So the assimilation of a new theory provides a new model, or pathways to a new model, that can serve to guide this new, revised science. The road to paradigm shifts is paved with anomalies. And the road leads to a new way of thinking that explains the new knowledge, re-explains the old knowledge, and offers ideas and questions for further research, from a new perspective: “the successive transition from one paradigm to another via revolution is the usual developmental pattern of mature science” (Kuhn, 1970, p. 12).

Normal science, then, is not concerned with developing new theories (Kuhn, 1970, pp. 24, 35); rather, it is busy fleshing out the current paradigm, exploring its inner structure, its predictions, and any parts that have been left incomplete. But this process is not necessarily smooth, and certain controversies arise during its course. Prior to the adoption of a new paradigm, there are “deep debates over legitimate methods, problems, and standards of solution” (Kuhn, 1970, p. 48). Furthermore, these debates “recur regularly just before and during scientific revolutions” (Kuhn, 1970, p. 48). Anomalies introduce an element of chaos to the scientific system, chaos that only a new paradigm can resolve. Kuhn (1970, pp. 64-65) says:

In science...novelty emerges only with difficulty, manifested by resistance, against a background provided by expectation.... Anomaly appears only against the background provided by the paradigm. The more precise and far-reaching that paradigm is, the more sensitive an indicator it provides of anomaly and hence of an occasion for paradigm change.

Turning now to the present issue of the NTD, and applying Kuhn’s model of scientific revolutions, I re-evaluate the history of the Anti-depressant Enterprise. Before the introduction of psychoactive drugs in psychiatry, the dominant paradigm was psychotherapy, and usually psychoanalysis. This was the standard treatment for MDD, and its invention is credited to Sigmund Freud. But with the accidental discovery of ADs and anti-psychotic drugs, treatment began a slow paradigm shift—away from verbal therapy and towards drug therapy. It is very noteworthy that this shift began *without any instigating anomalies*. That is, while there were certainly cases in which psychotherapy was ineffective, there was no detection of anomalies that led to the shift.

Instead, it appears that the paradigm shift to drug therapy was motivated by an old and familiar friend, money. As I discussed in Chapter One, using drugs instead of psychotherapy has many

advantages, as long as the drugs actually work—or if the system does not truly care for its patients. Compared with psychotherapy, drugs save time for psychiatrists and money for insurance companies. If one believes the propaganda, then ADs also save time and money for the patients. However, as we have seen, this last benefit is unnecessary for the AE to continue unabated. And this last benefit is provided by the patients themselves, in the form of the placebo effect. But any benefit from the placebo effect has no effect on the underlying causes of a patient's depression, and if the patient's life is headed in a destructive direction, pills will ultimately fail to prevent that destruction. I remind the reader of a quote from Kuhn earlier in this chapter: "the successive transition from one paradigm to another via revolution is the usual developmental pattern of mature science" (Kuhn, 1970, p. 12). Such appears *not* to be the case in the AE. There were no anomalies leading to the shift to drug therapy, so in Kuhn's system, there was no pressing need or cause for a new paradigm.

Rather, the paradigm shift was born of opportunism provided by the supposed discovery of ADs. The opportunity here was not clinical, but financial. Thus, forces from outside science—the familiar forces of economics and politics—were responsible for the shift. Economics and politics, being unscientific, have no natural role to play in the scientific process as mapped by Kuhn. They are instead intrusive, and interfere with the normal scientific process. This disconnects science from its goal—here, the improvement of people's lives. Rather, the goal of science becomes the generation of profits. And with that loss is also lost the potential that science has to do its original job. Science has been diverted from its true and necessary path, hijacked by sophists and profiteers.

Thus, I have demonstrated that anomalies are not the only path to paradigm shifts. The political and economic realms are also capable of creating a shift, even in the absence of anomalies. Economic and corporate forces alone were enough to cause a very important shift from the psychoanalytic to the psychopharmacological paradigm in the psychiatry of depression. This reinforces, in a somewhat different way than Kuhn envisioned, the Kuhnian idea that science is fundamentally a social enterprise that does not reflect our idealized image of science as a noble and independent endeavor, the goal of which is to seek truth.

## **Barker and Kitcher on the Effects of Society**

If the psychiatry of depression ever had a chance of being a legitimate science, that chance is vanishing with the intervention of the political/economic forces described above. The intervention of these forces contributes strongly to the lack of *autonomy* of a science of mental illness. Barker and Kitcher (2013) discuss the central role of autonomy in basic science. They point out that applied science “can succeed only against a background of basic research directed by scientists in a fully autonomous way” (Barker & Kitcher, 2013, p. 143). Here, the authors are speaking mainly about autonomy from the research interests of governments. The authors say that “political authorities...can put pressure on scientists to draw (or at least publish) only conclusions consonant with the views or outcomes that they prefer” (Barker & Kitcher, 2013, p. 145). As my development in this thesis shows, however, such undue influences on the way in which science is carried out are not limited to governments—corporations can play the exact same role, with even more effectiveness.

This possibility is also, if somewhat indirectly, addressed by Barker and Kitcher. They propose that if governments cannot be relied upon to direct science in a way that is beneficial to all of society, then “perhaps the invisible hand of the market can do the job” (Barker & Kitcher, 2013, p. 148). They ask (Barker & Kitcher, 2013, p. 148): “(m)arkets can function as a democratizing mechanism.... Can they work this way for science?” They identify several factors as interferences in a free-flowing corporate scientific enterprise: patents, focus on profits, and targeting of product development towards the wealthy and the military. The authors address pharmaceutical research briefly, saying that “privately funded medical researchers focus their efforts on proprietary pharmaceutical treatments—although these may be costly to the public and have undesirable side effects—and they may overlook equally effective ‘lifestyle’ interventions” (Barker & Kitcher, 2013, p. 149). Barker and Kitcher remark that the situations described above are “a serious failure of autonomy” (Barker & Kitcher, 2013, p. 149) and conclude that “(t)oday’s science is far from autonomous” (Barker & Kitcher, 2013, p. 150). At least in the case of a scientific psychiatry of depression, the concept of “market-driven science” (Barker & Kitcher, 2013, p. 148) is shown by my development to yield something that is not yet truly science, despite the potential to be such. The so-called free market is *too* free, in the sense that it corrupts science with the power of corporations and their money.

## Discussion and Conclusion

This chapter has focused on the perspectives that science and the philosophy of science have to offer on the AE. First, we saw that the application of simple logic to the NTD and the empirical results thereof led to the rejection of the NTD on those grounds alone. Second, we used statistical reasoning to again reject the NTD. Third, we viewed the AE through the lens of Popper's approach, with its emphasis on falsifiability. Again, and very forcefully, the argument developed led the NTD to its grave. Fourth, Kuhn's vision of how science operates and how it is periodically revolutionized by the discovery and accumulation of anomalies—if this is to be taken as an accurate model—is completely violated by the history of AD development and the extra-scientific forces that led to the demise of psychotherapy in psychiatry and the current dominance of drug therapy.

The results of this chapter's analysis are complementary to those described in the previous two chapters, and go a very long way towards explaining the problems that were first identified and briefly described in Chapter One. In Chapter Two, the sheer folly of the first step in AD development was exposed as the logical and empirical travesty that it is. This examination showed that the animal testing model is fatally flawed from its very conception, not to mention the illogic that followed and amplified that fatal flaw. The conclusion was that psychiatric drugs—specifically ADs—that are developed using rodent models of depression are invalid for use in humans, and that one should expect such drugs to be ineffective.

Chapter Three is a testament and monument to the colossal ineffectiveness of ADs—confirming the suspicions previously identified. Further, Chapter Three unveiled the placebo effect. Understanding the placebo effect, side effects, the disease course, and the typical outcomes of AD usage revealed that ADs are simply active placebos that work by inducing the placebo effect, rather than through direct drug action. Effects either blamed on the drug or credited to the drug are in fact the combination of the disease course and the placebo effect. The claims for the ADs are false. Thus, the four chapters to this point tell a consistent story that explains the complexities and mysteries behind ADs from the perspective of their *ineffectiveness* and this shift of perspective quickly resolves many of the questions and paradoxes of ADs. It is also clear from these four chapters that the AE is an unethical venture from several points of view. In the next chapter, two analyses drive home the point that the AE is innately unethical.

## Chapter Five

### Ethical Analyses from German Idealism

Throughout this thesis, I have labeled as unethical a very large number of aspects composing the AE, and even the AE itself; many of the authors I have quoted have reached the same conclusion. Yet, neither myself nor those I cited gave any fundamental rationale for the claims of unethical behavior. That is, none of us have provided a systematic rationale for why these practices are unethical. For my part, and I suspect for others too, I have relied on what Shafer-Landau (2015, p. 7) points out regarding morality: “(a)ny morality worth the name will place *some* importance on justice, fairness, kindness, and reasonableness”; that is, the great majority of us have an innate understanding of morality and ethics that includes the factors identified by Shafer-Landau. So, to this point, I have relied on this common-sense ethical view.

But the conclusions of this thesis are on much firmer ground if I evaluate them within an accepted system of ethics. In the field of biomedical ethics, this system is very often that of Kant, both because Kant’s system is secular—as opposed to, e.g., the Golden Rule—and because Kant is considered one of the greatest philosophers and ethicists (Shafer-Landau, 2015, p. 159). His system is often used in textbooks on biomedical ethics (see, e.g., Munson, 2000). Therefore, this chapter contains two formal ethical analyses: first from Kant’s system and second from Hegel’s system. I choose Hegel to complement the Kantian analysis because Hegel gives an ethical view from the standpoint of society, while Kant’s is predominantly from an individual perspective. In this way, I give a more complete analysis—on both the personal and societal levels.

I first evaluate the ethical implications of the issues raised in this thesis from the perspective of Immanuel Kant’s ethical system (deontology), as set out in his works *Groundwork of the Metaphysics of Morals* (primary source) and *The Metaphysics of Morals* (secondary source). In these works, Kant posits a number of principles that are clearly violated by the anti-depressant enterprise, and I will detail these as my development proceeds. But the major Kantian theoretical umbrella under which these principles can be subsumed is that of the *autonomy* of individuals. In the second part of this chapter, I will defend the idea that Hegel’s ethical system, as presented in his *Elements of the Philosophy of Right*, is relevant today and in the realm of AD use. I will argue that this is due to the fact that Hegel took ethics to a new

level—for his place in history—in terms of addressing the role of the nation-state in the lives of its citizens, including its regulatory agencies as well as the workings of the putative free market in capitalistic societies. Hegel provides us with a path for looking at the ways in which government has duties to its citizens—duties that may or may not be fulfilled—as well as ways in which the free market can either promote or thwart effective treatments for depression. I will argue—from a Hegelian perspective—that both the government and the free market have failed us in this effort. As I review the evidence, I point out general ethical concerns—then later apply Hegel's perspective.

### **An Analysis from Kantian Deontology**

#### **The Kantian Ethical View: General Considerations**

It is no exaggeration to say that the AE process described in this thesis to some degree reduces the patient's status to one not too far above an experimental laboratory animal, albeit one who can talk, give feedback, and drop out of the experiment at any time (unless institutionalized). Thus the medical-industrial complex, in the case of the psychiatry of depression, almost appears to be designed to use people as means to its *own* end, *not* to treat people as ends in themselves. Even if not *designed* in this manner, the system certainly seems to *function* this way. And in this phrasing of my view, I have firmly in mind the thought of Kant.

One of Kant's major ethical principles is that people should not be treated merely as a means to another's purposes, but as ends in themselves; this is one of the formulations of the Categorical Imperative (CI). This is but one of several important and interrelated concepts, some of which are: (other formulations of) the CI, truth-telling, rationality, internal causality (freedom of the will), dignity, duty, and beneficence. All of these concepts can be subsumed under, and logically derived from, the single concept of *autonomy*. This is meant here in the individual sense, not the same as the autonomy of science I cited in Chapter Four. So we begin with Kant's notion of individual autonomy.

In the *Groundwork* (Kant, 1996a), Kant searches for a single, supreme principle of morality. He seeks a principle that is not influenced by circumstances, situational variables, or a person's *inclinations* (i.e., motives born of interests other than rationality or moral law). That is, he wants an absolute principle that stands and guides us in all situations. He says: "I will therefore call this basic principle the principle of the **autonomy** of the will in contrast with every other, which I accordingly count as **heteronomy**" (Kant,

1996a, 4:433). Having previously derived three forms of the CI, Kant continues his exposition of autonomy by relating it to one of those forms: “(t)he concept of every rational being as one who must regard himself as giving universal law through all maxims of his will [the CI], so as to appraise himself and his actions from this point of view, leads to a very fruitful concept dependent upon it, namely that of a *kingdom of ends*” (Kant, 1996a, 4:433).

In Kant’s kingdom of ends, an admittedly idealized world, all rational beings are autonomous, yet follow laws they have in common. This world consists of “a whole of all ends in systematic connection (a whole both of rational beings as ends in themselves and of the ends of his own that each may set himself)” (Kant, 1996a, 4:433). The CI is seen again in this statement. Kant continues to strongly emphasize the CI, following the previous statement with: “all rational beings stand under a law that each of them is to treat himself and all others *never merely as means* but always *at the same time as ends in themselves*” (Kant, 1996a, 4:433). Only under these conditions is a kingdom of ends possible. Kant adds: “(a) rational being belongs as a member to the kingdom of ends when he gives universal laws in it but is also himself subject to these laws” (Kant, 1996a, 4:433).

Thus, the concept of *rationality* is clearly displayed in these quotes, and just as clearly plays a crucial role in Kant’s system. Only rational beings are capable of being moral. In fact, Kant hints that the CI—the supreme moral principle—and rationality are intertwined: “(t)he ground of this principle is: *rational nature exists as an end in itself*” (Kant, 1996a, 4:428-429). But further, rationality is only useful in this sense if one has *freedom of the will*: (internal) causality that enters the world of appearances [“the world of sense” (Kant, 1996a, 4:451)], where determinism holds, from the world of things-in-themselves [“the world of understanding” (Kant, 1996a, 4:451)], where the will is free. I note here that mere freedom of the will is not sufficient—the will must be a *good will*. Kant believes the good will to be a necessary condition for a person to even be worthy of being happy (Kant, 1996a, 4:393). He considers the good will to be good in itself, but holds that it must also lead to action (Kant, 1996a, 4:394). So the concepts or principles of people as ends in themselves, the CI in its various forms, the freedom of the will, the necessity of a good will, and rationality all work together under the canopy of *autonomy* of the will to make morality possible.

Kant relates intimately the principles above with the concepts of duty and dignity. Regarding *duty* and its relationship to the supreme moral principle, he says:

“(t)he practical necessity of acting in accordance with this principle, that is, duty, does not rest at all on feelings, impulses, and inclinations but merely on the relation of rational beings to one another, in which the will of a rational being must always be regarded as at the same time *lawgiving* since otherwise it could not be thought of as an *end in itself*” (Kant, 1996a, 4:434).

This quote is one of the more clear passages in which Kant links together some of the various concepts crucial to his ethical system. Kant makes further comments about duty; for example, the discussion of the good will leads directly into an exposition of duty and its relationship to the good will: duties are the obligations dictated by a good will. From this idea, Kant draws three propositions (Kant, 1996a, 4:398-401) that are strongly interrelated and appear to be variations on a theme: the moral worth of an action is determined not by its consequences but by its maxim—that is, perhaps to oversimplify, intention is what is to be judged, not outcomes. And moral actions are *only* those performed out of *duty alone* (Kant, 1996a, 4:401).

Regarding dignity, Kant depicts it in various ways. He says that reason invokes the universal law (CI) in every maxim “from the idea of the dignity of a rational being, who obeys no law other than that which he himself at the same time gives” (Kant, 1996a, 4:434); that is, dignity and autonomy are in a close, reciprocal relationship. Shortly thereafter, he says that “morality, and humanity insofar as it is capable of morality, is that which alone has dignity” and defines the dignity of a human being as one’s “inner worth” (Kant, 1996a, 4:435). A short while later, Kant makes the direct connection between dignity and autonomy: “(a)utonomy is therefore the ground of dignity in human nature and of every rational nature” (Kant, 1996a, 4:436).

Generally, to explicitly connect three important concepts (morality, autonomy, and the CI), Kant says: “(m)orality is thus the relation of actions to the autonomy of the will, that is, to a possible giving of universal law through its maxims [a version of the CI]” (Kant, 1996a, 4:439). In addition, “(a)utonomy of the will is the property of the will by which it is a law to itself (independently of any property of the objects of volition)...the above principle of autonomy is the sole principle of morals...its principle must be a categorical imperative, while this commands neither more nor less than just this autonomy” (Kant, 1996a,

4:440). Concerning the relationship between autonomy and free will, Kant says: “what, then, can freedom of the will be other than autonomy, that is, the will’s property of being a law to itself?” (Kant, 1996a, 4:447); and further, “freedom and the will’s own lawgiving are both autonomy and hence reciprocal concepts” (Kant, 1996a, 4:450). These quotes are about as clear an expression of the interrelation of concepts that Kant offers us in the *Groundwork*.

As the title of the *Groundwork* suggests, Kant does the great majority of his conceptual construction in that work. For the purposes of this thesis, the *Groundwork* provides sufficient development for the application to come. But before moving on to that application, I note that in *The Metaphysics of Morals* (Kant, 1996b), Kant’s view of dignity shifts somewhat. He identifies it (Kant, 1996b, 6:420) as “inner freedom, the innate dignity of a human being....” This is somewhat different from the views put forth in the *Groundwork*. Further on (Kant, 1996b, 6:435), Kant reiterates the definition (from the *Groundwork*) of dignity as “an absolute inner worth”, but shortly thereafter refers to one’s “dignity as a *rational human being*”, implying that our dignity lies in our rationality, rather than our inner freedom or inner worth. The net suggestion then in *The Metaphysics of Morals* is that dignity is all the following: inner freedom, inner worth, and rationality. Given Kant’s extreme emphasis on rationality, these three views might be compatibilized: rationality is the source of both our inner freedom and our inner worth.

### **The Kantian Ethical View: Application to the Anti-Depressant Enterprise**

I have to this point in the thesis built a foundation for the application of Kant’s thought to the Anti-depressant Enterprise that includes such factors as: (1) the history of the development of these drugs; (2) the empirical, political, and economic factors that render the enterprise unscientific and unethical; (3) my own views of *why* all this constitutes unethical behavior; and (4) a summary of theoretical concepts from Kant that bear on this issue. I believe it is relatively straightforward to see how the enterprise violates Kant’s system; my goal now is to make this violation as explicit as possible. Kant conveniently provides four examples of behavior in the *Groundwork*, two of which bear directly on the present problem. I will address in depth these two examples, as well as some very closely related issues.

In the *first* relevant example, Kant presents the case of a man who needs to borrow money, but lacks the ability to repay the loan. Kant implicitly asks whether it is unethical to make a *lying promise* in this case, given the individual’s dire needs and lack of resources. This person’s maxim would be: “when I

believe myself to be in need of money I shall borrow money and promise to repay it, even though I know that this will never happen” (Kant, 1996a, 4:422). Is such a maxim *universalizable*, according to one version of the CI, without invoking self-contradiction? No: the universalization of this maxim *must* lead to a societal breakdown in which no one could believe a promise. Following the introduction of another form of the CI, Kant readdresses the example from his view of one’s *duty to others*. Does the above maxim treat others as ends in themselves? No: a person using this maxim “wants to make use of another human being *merely as a means*, without the other at the same time containing in himself the end” (Kant, 1996a, 4:429).

Here, Kant is addressing truth-telling versus lying, deception, etc. There is an obvious connection between Kant’s hypothetical liar and the institution called Big Pharma, the conductor of the Anti-depressant Enterprise. One might suggest that there is some difficulty in applying ideas and examples that reference individuals to a corporation or even an entire industry. I maintain that even though the responsibility for unethical behavior is diffuse in the corporate and industry cases, the ethical principles still apply. I believe that Kant would support this position. In his idyllic kingdom of ends, individuals and corporations would have the same maxims, necessarily; so there would be no problem with the generalization I propose. I will thus proceed to treat the industry as an individual (as some political figures currently claim to be the case).

We are accustomed to using each other as means in our industrialized, capitalist society. This is justified, even for Kant, by the idea that the buyer and seller are doing this reciprocally in any transaction, and that each deals fairly with the other, such that each is treating the other as both a means *and* an end simultaneously. Kant allows for this. But what if the seller knows that (1) the product is highly suspect; (2) was developed, approved, and marketed under false pretenses; (3) was the subject of false claims; and (4) was likely to not work—but that (5) the buyer’s *belief* in the product could give it the *appearance* of effectiveness (at least for some fraction of his buyers)? This seller is selling deception, and if the product “works”, it is likely due *only* to this deception. This is the seller using the buyer *only* as an end, and this is expressly forbidden by Kant. Also, this situation is sufficiently similar to Kant’s concept of a lying promise that I can safely conclude that Kant, as I do, would condemn the enterprise as unethical.

Of course I intend the above as an analogy with the Anti-depressant Enterprise, wherein the seller is Big Pharma and the patient is the buyer—to oversimplify vastly; in reality, the situation is far more complex and worse in other ways than this lone analogy suggests. For as I proposed earlier, the doctor-patient relationship has nearly been reduced to that of a scientist and her experimental animal. *This represents a severe breach in the patient's autonomy*, in a variety of ways, since—as we have seen—autonomy underlies several other concepts. First, it is obvious that the patient has inadequate, biased, and probably *false* information about the prescribed drug. The doctor may also be in this state, which would be itself unethical; or may not be in this state, which makes the physician or psychiatrist complicit in the *lying promise*, of which the patient is the victim. Second, under such conditions, it is impossible for the patient to legitimately give *informed consent* (Munson, 2000, p. 393) to treatment with anti-depressants, since the patient can hardly be truly informed in this situation—thus having to make decisions based on trust and belief in an otherwise nearly fact-free zone. Autonomy and informed consent go hand-in-hand (Munson, 2000, pp. 389-394).

Third, the entire enterprise is an insult to the *dignity* of the patient individually, and to patients and people generally; people would be highly offended if they understood the facts of the situation. To be treated as a laboratory animal is certainly beneath the dignity of a human being, and possibly to that of the actual animal as well. Recall that Kant says: “(a)utonomy is therefore the ground of dignity in human nature and of every rational nature” (Kant, 1996a, 4:436). Fourth, the anti-depressant enterprise violates the duties to others to be *beneficent* and to promote their *happiness* (appropriately, since the issue is depression).

This last point is well-illustrated by Kant's *second* relevant example in the *Groundwork*: he presents the case of a person who is doing well, and recognizes that it is possible thereby to benefit another. But this person's maxim is: “I shall take nothing from him nor even envy him; only I do not care to contribute anything to his welfare or to his assistance in need!” (Kant, 1996a, 4:423). Is such a maxim universalizable? No: “a will that decided this would conflict with itself, since many cases could occur in which one would need the love and sympathy of others and in which, by such a law of nature arisen from his own will, he would rob himself of all hope of the assistance he wishes for himself” (Kant, 1996a, 4:423). Does the above maxim treat others as ends in themselves? No: it is impossible to treat “*humanity*

as an end in itself unless everyone tries, as far as he can, to further the ends of others” (Kant, 1996a, 4:430). Kant calls this a “meritorious duty to others” and the “principle of humanity” (Kant, 1996a, 4:430). This is our duty of beneficence; this is our duty to make others happy.

Given the facts regarding the anti-depressant enterprise, I hold it impossible for the industry to claim any form of beneficence. The deceit, trickery, and withholding of vital information belie any such claim. And, as I have already established, the industry is certainly not treating the public as ends in themselves. This is very, very far from a kingdom of ends. Instead, it is predation—with the wolves hiding in the clothing of industry executives, clinical scientists, advertising firms, and even physicians and psychiatrists in some or many cases. It is difficult to doubt that Kant would find the entire situation irredeemably unethical, as do I.

Further reinforcement of my point can be found in *The Metaphysics of Morals*, wherein Kant is less concerned with deriving a foundational theory and more concerned, in some ways, with fleshing out his theory and including some specific issues and situations. *The Metaphysics of Morals* contains a veritable plethora of relevant quotes, although not many are needed in the face of the development that the *Groundwork* provides. Nonetheless, I cite here some of Kant’s words in *The Metaphysics of Morals* that add shades of meaning to what has already been developed. First, regarding *lying*, Kant says: “(t)he greatest violation of a human being’s duty to himself regarded merely as a moral being...is the contrary of truthfulness, *lying*” (Kant, 1996b, 6:429). In addition, “(b)y a lie, a human being throws away and, as it were, *annihilates his dignity as a human being*....such a speaker [liar] is a mere deceptive appearance of a human being, not a human being himself” (Kant, 1996b, 6:429; emphasis added). Kant notes that lying need not be harmful to be unethical, for truthfulness is a duty to oneself, not to others (Kant, 1996b, 6:430). Of course, I have argued that Big Pharma’s lies do indeed cause harm, thus multiplying the ethical violation.

Second, regarding *beneficence*, Kant holds that it is our duty to love others, a “principle of mutual love” that must be balanced with respect for others (Kant, 1996b, 6:449). This love, however, is of a certain kind: “the maxim of *benevolence* (practical love), which results in *beneficence*” (Kant, 1996b, 6:449). Further, this duty to love others “can, accordingly, also be expressed as the duty to make others’ ends my own (provided only that these are not immoral)” (Kant, 1996b, 6:450). A perfect realization of this

duty would result in the kingdom of ends. But as we have seen, the practices of the AE lie very far from this. Here, Kant insists, as elsewhere, that benevolence must be reflected in one's actions: "it must be taken as active benevolence, and so as having to do with the maxim of actions" (Kant, 1996b, 6:450). One's actions reflect and spring from one's maxims. Regarding the medical-industrial complex and its various entities, through their acts we shall know them for what they are. And what they are is unethical.

### **Implications**

The unethical Anti-depressant Enterprise exposes the inherent danger in a capitalist economic system. Entire industries can be based on deception and yet succeed, at least in generating profits. This willful disregard for the ends of others violates Kantian deontology to its core, despite the appearance of governmental regulation and oversight. There is no beneficence to be found in this enterprise, and its inherent deception is an insult to the dignity of people. The enterprise and industry of anti-depressants fails its duty to itself by lying; it fails its duty to others by treating people merely as ends.

As a *very* incomplete way of reducing the unethical nature of ADs, I envision a scenario in which physicians and psychiatrists are fully informed as to the ethical and scientific problems with these drugs, and discuss these issues honestly and completely with their patients. At the very least, patients would then be as fully informed as possible—and thus empowered to give or deny *truly* informed consent. In such a situation, I can imagine that many patients would decline the drugs; at the very least, they would be wary for signs that the drugs are not working or are causing other problems. I also imagine that honest discussions such as these would reduce the placebo effect significantly, as the patients' belief in the drugs would be reduced. In the end, this conceivably could lead to massive failures of anti-depressants. This would, as it were, pull back the curtain to reveal that the Great Wizard is really just an ordinary person.

But this change at the point of the doctor-patient interaction in actuality is not nearly enough, as the nature of the drugs themselves would not change. More honesty from doctors comes much too far down the line. Reform needs to begin at the pharmaceutical company level, where true ethics and science should be practiced. The Categorical Imperative should be embraced. I am arguing for corporate honesty and for companies to be open about the drug development process and the problems with their products. Only then could I see the beginning of the genuine pursuit of effective ADs, if such a thing is in

fact possible. Only by renouncing their current practices and adopting legitimate ones could drug companies take a step towards the creation of a kingdom of ends, in which *both* the companies *and* their customers would benefit. Kant would be pleased.

### **The Anti-depressant Enterprise: A Hegelian Analysis**

#### **The Hegelian View: Deception, Duties of the State, the Free Market, and the Citizen**

It is most productive for the present purposes to view Georg F. W. Hegel as a man of his times, which he certainly was. He lived at a time when the modern notion of a nation-state had emerged and was growing. Knowledge about the rest of the world was being gained by Europeans, and this was driving to some extent European academic development in various fields, including philosophy. Hegel's intense interest in history put him in a position to evaluate the state of philosophy in his time, and he appears to have used that position to great effect. His view of ethics, as put forth in *Elements of the Philosophy of Right* (1991), represents a broadening of the ethical perspective of Kant, whose concern was more with *individual* ethics—as had previously been the case in most of ethics—than with *societal* or *governmental* ethics. Hegel changed this, providing an approach to the last two issues.

In summarizing in this section the portions of Hegel's work that apply to my topic, I follow Hegel in his developmental path as found in *The Philosophy of Right*. In the next section, I apply these concepts to the ethical problems I outlined in the first section. Rather early, Hegel discusses forms of wrong (*das unrecht*) in the sense of contracts. He includes here a brief discussion of *deception*. Hegel (1991, p. 118; §87) says: "(w)hen the universal is thus reduced by the particular [individual] will to a mere semblance [a subjective appearance], and, in the case of contract, is reduced in the first place to a purely external community of wills, this constitutes *deception*." The addition refers to this as the "second level of wrong", saying: "the deceived person is given the illusion that he is receiving his right" (1991, p. 118; §87) when in fact this is not the case. Hence, deception is ethically and morally wrong and prohibited, as it robs others of their rights. He then addresses the particular versus the universal regarding *welfare* (1991, p. 153; §125):

(s)ubjectivity, with its *particular* content of *welfare*...also has reference to the universal.... This [universal] moment, initially posited within this particularity itself, includes *the welfare of others*—

or...the welfare of *all*. The welfare of *many other* particular beings in general is thus also an essential end and right of subjectivity.

Thus, an individual's concern for her own welfare entails concern for the welfare of others, too. Hegel notes that one's subjective ends may or may not be in accord with universal ends.

Next, Hegel endorses an economic system centered on the concept of the *free market* (Hegel, 1991, §184). He does not use this terminology; the economy is the "system of needs" (Hegel, 1991, §189) and there is no use of the word "market" in the English translation. Nonetheless, Hegel sees the free market as an integral part of civil society. In the Editor's Introduction, Allen Wood says that (Hegel, 1991, p. xviii): "civil society is the realm of the market economy" but that civil society is not *reducible* to the economy. However, Hegel understands that a completely free market will inevitably lead to massive economic inequality (Kain, 2014-15; Neocleous, 1998). Hegel (1991, p. 222; §185) says: "civil society affords a spectacle of extravagance and misery as well as of the physical and ethical corruption common to both." And it is for this very reason that the state must regulate the market economy, making it less free but more fair and equitable.

Serving a role such as this regulation is the part of the state government that Hegel calls the "police" (*polizei*; Neocleous, 1998)—not having its more recent meaning. In defining the third moment of civil society, Hegel (1991, p. 226; §188) says: "(p)rovisions against the contingency which remains present in the above systems [needs, justice], and care for the particular interest as a *common* interest, by means of the *police* and the *corporation*." Again, "corporation" does not have the more contemporary meaning for Hegel (Neocleous, 1998). Here, Hegel is saying that governmental regulatory agencies are a necessary mechanism for the balancing of individual (particular) and societal (universal) needs (Neocleous, 1998; Kain, 2015-15). This can be viewed or reworded as restraining capitalism in the name of the public good. And it is the state alone that can insure this outcome through its regulatory agencies, the police.

Hegel (1991, p. 237; §206) holds that the state: "has the universal interests of society as its business" and that (Hegel, 1991, p. 259; §229—addition): "(a)ccount should be taken of my welfare, of my particularity, and this is the task of the police and the corporation", essentially echoing his earlier point. Even more strongly, he states (Hegel, 1991, p. 260; §230): "the right *which is actually present in*

*particularity* means...that the livelihood and welfare of individuals should be *secured*—i.e. that *particular welfare* should be *treated as a right* and duly *actualized*.” This is a very strong ethical position that the state has as its *primary* duty the welfare of its individual citizens—a *raison d’être*, one might say. For Hegel, the police play a central role in multiple aspects of the state’s duties to its citizens—such as, for example, protection from systematic fraud.

An excellent example of systematic fraud is the production, marketing, and sale of ineffective, defective, or dangerous products. Although he does not address product safety or related issues head-on, Hegel does address “private actions” that become public and “can wrong or harm other people or actually does so” (Hegel, 1991, p. 260; §232). (This generally fits the case I raise.) In reality, harm from the actions may or may not occur, but exposure to risk is the inherent harm done and this is the basis for police authority in the matter (Hegel, 1991, §233). All of this is part of the over-arching claim that facilities, functions, products and services meant for public use “require oversight and advance provision on the part of the public authority” (Hegel, 1991, p. 261; §235).

Probably most directly relevant to the present application is the next section, §236, almost all of which is important to my issue. Here, Hegel sets out the case of possible

differing interests of producers and consumers [that] may come into collision with each other, and even if, *on the whole*, their correct relationship re-establishes itself automatically, its adjustment also needs to be consciously regulated by an agency which stands above both sides (Hegel, 1991, p. 261; §236).

The automatic correction Hegel cites here appears to be a reference to the market economy, but Hegel finds that mechanism alone to be inadequate for his purposes, e.g., doing right by the individual(s) directly involved. He goes on to say that the right of police to regulate in this manner springs *first* from the fact that when everyday commodities are publicly marketed, they

are offered not so much to a particular individual as such, as to the individual in a universal sense, i.e., to the public; and the task of upholding the public’s right not to be cheated and of inspecting market commodities may, as a common concern, be entrusted to a public authority (Hegel, 1991, p. 262; §236).

But the *second*, more important factor is that interactions and thus interdependencies within society are a complex multitude, and this necessitates an over-arching authority that can take into account the larger picture to protect public safety, or at least minimize public harm (Hegel, 1991, p. 262; §236). Hegel comments that individual will and interests “invokes the freedom of trade and commerce against regulation from above; but the more blindly it immerses itself in its selfish ends, the more it requires such regulation to bring it back to the universal” (Hegel, 1991, p. 262; §236). In the addition to this section, such legitimate police functions are listed; included in this list is *public health*.

### **Application of the Hegelian View to the Anti-depressant Enterprise**

I begin the application of Hegelian thought to the Anti-depressant Enterprise with the topic of *deception*. Repeatedly throughout the development in the first section above, I have labeled a certain industrial practice deceptive and thus unethical. This might seem to be an unwarranted equation on my part, but as I wrote above, Hegel considers deception to be a form of wrong. In this respect, he agrees with Kant—who despised deception at the personal level. No doubt, Hegel would despise the wider, social level of deception displayed by the untruthful practices of the pharmaceutical companies I have summarized. My first example of this is the representation of ADs as scientifically developed and proven, when this is anything but the case.

My other examples are from the political/economic area and include the issues discussed earlier in this thesis: ghost authorship by non-physicians and general falsification of authorship; a compromised FDA, intertwined financially with the industry it regulates; the suppression by industry of negative studies, or the file-drawer effect; and the absence of true informed consent. All of these are deceptive, and this alone is enough to condemn Big Pharma and anti-depressants. This is, however, only the first step. Hegel’s second relevant topic is *welfare*, that of both the individual and the public. We recall that Hegel’s position is that individual welfare entails public welfare. On a corporate (in the contemporary sense) and business level, the *company* can be seen as playing the role of the individual in this application. It is evident from this Hegelian perspective that the individual (company) is putting profit over public interest.

And if we view this point from the perspective of individual *persons*, it is also abundantly clear that in this case corporate interests depart severely from a depressed person’s interest: the depressed person could not be less interested in corporate profits, desiring instead an effective, affordable, safe product to

meet her needs. On the other hand, the company needs only to establish the *perception* that its products are effective—essentially, it would seem, taking credit for the placebo effect as much as for their drugs' effectiveness—and enjoying the sales that follow without concern for consumer welfare. This is a fine example of the “differing interests of producers and consumers [that] may come into collision with each other” (Hegel, 1991, p. 261; §236).

Thus, there is an obvious need for the close monitoring and, if necessary, intervention on the part of the police (FDA) from the Hegelian perspective as well as my own. Yet, I have presented a significant amount of evidence that the FDA is not doing its job at all well; it is failing to police the pharmaceutical industry with enough zeal to prevent the many problems I have identified. These include the familiar issues: inadequate product safety and effectiveness, thus posing a threat to public health; the allowance of false advertising regarding this safety and effectiveness; inadequate transparency in the drug development process; the lack of financial insulation of the FDA from the industry's influence; pro-industry bias in FDA policies and their enforcement—the *inadequate regulation of the market economy*. Hence, the state is failing to perform its duties.

This leaves us with the final issue, that of the *free market*. Hegel recognizes that a completely free market will result in massive economic inequality, and that this is an ethically untenable situation. Such recognition is not held by everyone in our contemporary world. In fact, the market economy is often seen as a mechanism that is pro-consumer in nature. For example, recall that from Chapter Four, in discussing the role of the market in the performance of basic science, Barker and Kitcher (2013) emphasize the central role of autonomy in science. They find that government is untrustworthy, as previously discussed. And what of the market economy?

As the reader will recall, this question is also, if somewhat indirectly, addressed by Barker and Kitcher. They propose that if governments cannot be relied upon to direct science in a way that is beneficial to all of society, then maybe the so-called “invisible hand” of the free market could act as a democratizing force. But the authors identify profit as a major interference in this scenario, and we have seen exactly how that factor is manifested at every level of the AE. So, no, the free market is hardly the solution, and in fact it was the free market that exploited the AD explosion to generate vast profits for Big

Pharma but little relief for patients. The “invisible hand of the market” cited by Barker and Kitcher seems to have taken over the regulatory process to a significant degree. The fox resides in the henhouse.

### **Implications**

In view of my development in this section, I find that both the government and the market economy have failed to provide medications for depression that are scientifically sound, safe, and effective. Corporations have discovered the power to pressure scientists to arrive at the conclusions they prefer, as Barker and Kitcher state regarding governments, or to effectively replace the scientists with their own people for publication purposes. The government stands by relatively idly as it watches these abuses occur, and in some ways is even complicit with the illicit corporate agenda. While the pharmaceutical industry wallows in tremendous profits, individuals with depression continue to hunt for the drug that will lift them out of their nightmare. Many of them will hunt until they are out of options, without finding what they need.

I see the solution to the ethical thicket surrounding the treatment of depression in a manner similar to that of Lexchin (2013), quoted in Chapter Three, in that money needs to be separated from the research and development process—the funding of clinical trials is a central issue, if not *the* central issue. Capitalism has been insufficiently constrained in this realm and needs to be roped in. Corporate greed has done a great disservice to the public; the few have profited at the expense of the many. Hegel would almost certainly acknowledge all of this.

I believe he would find the situation morally repugnant, as do I and many others, and a blatant violation of his vision and system of ethics in multiple ways, including the ones I have outlined in this chapter. Although two centuries have passed since his writing, we can credit Hegel for being ahead of his time in terms of anticipating some of the problems of the nation-state and of the market economy. Thus, Hegel’s vision of the crucial role of the police in the modern political-economic world is prescient, relevant, and to be given the attention it deserves, although that does not seem to be happening currently in the world of the psychiatry of depression.

### **Conclusion**

In this chapter, I have considered two ethical perspectives from the school of German Idealism. Kant’s individual, personal standpoint showed that the inherent dishonesty at work within the AE makes

the entire enterprise unethical. Hegel's societal, community standpoint in application to the AE gives the same result as the Kantian analysis. Thus, the ethical views of these two major thinkers yield in application to the AE the same conclusion we reached with the simple common-sense view of ethics. This is both reassuring and unsurprising. All of this was predictable, even after the first chapter of this thesis.

The weight of these two analyses is not to be underestimated. As I said earlier, Kant's system is a standard one for biomedical applications. Ethicists in this field rely on Kantian deontology as a way to navigate ethical dilemmas. We have seen in this thesis that the Kantian approach is easily applicable to the AE, especially after four chapters of development regarding the unethical practices of the AE. To my knowledge, Hegelian ethical analyses are not within the scope of biomedical ethics. However, the picture presented in this chapter demonstrates clearly that Hegel's approach is certainly applicable. Further, the Hegelian view is a perfect complement to the Kantian picture such that ethics from both the personal and societal standpoints are considered. Thus, the ethical analyses in this chapter come from different directions but converge on the same outcome. The common-sense approach employed by me and many of the cited authors in prior chapters agrees with these two formal ethical analyses, and again this is a strong reinforcing point for the conclusions I have reached. Any ethical system that would absolve the AE of ethical wrongdoing would be an incredible deviation from what we hold innately to be fair and just—not to mention moral and ethical. So, after all the work of the first four chapters that indicated major ethical problems, we see that these indications were exactly on point.

## Chapter Six

### Conclusions and Commentary

In this final chapter, I first summarize my findings in the prior five chapters, then state my conclusions from the thesis overall. Finally, I discuss some of the future directions of AD research. This last part is very important, since the failure of the AE to this point seems to be driving an increase in animal research on depression. As the reader will recall, I reviewed the methodology behind rodent research for ADs in Chapter Two, and found the entire process to be invalid. Thus, I will be highly critical of these new efforts in AD research.

### Summary

Chapter One was an introductory overview of the Anti-depressant Enterprise and the host of scientific and ethical problems that lies within the AE. I divided these problems into two broad categories. The *scientific/empirical* evidence category included the following considerations: (1) uncertainty over the *mechanism* of anti-depressant action; (2) related to the first point, *changes* over time in the purported anti-depressant mechanism; (3) the effectiveness of *placebos* versus anti-depressants in clinical trials; and (4) the *side-effects* of anti-depressants. The *political/economic* evidence category included the following factors: (1) funding for clinical trials provided by the drug companies themselves—*conflict of interest*; (2) the highly selective reporting and publication of trial results—*publication bias*; (3) the *ghost authorship* of published trials; and (4) the lack of true *informed consent* by patients in drug trials and in the doctor's office. All of the factors above render the AE unscientific. From the ethical point of view, with the science of anti-depressants thus undermined, it is deceptive to make claims for the effectiveness of these drugs and for a scientific basis for their mechanism and use.

In fact, any and all of the following words or phrases could be used to describe the medical and corporate practices I reviewed: dishonesty, deceitfulness, deception, misinformation, manipulation, willful withholding of vital information, and lying. The entire system is money-driven, rather than patient-centered. After briefly presenting summary evidence for the eight categories above, I made the preliminary conclusion that the psychiatry of depression is in fact very far from science. This in itself constitutes a case of *unethical behavior* since ADs are represented by drug companies both to physicians and to the public at large as scientifically based and proven when in fact this is far from the case.

Chapter Two argued that the choice of a rodent model—specifically a mouse model for human psychopathology, and Major Depressive Disorder (MDD) in particular—is not just odd but in fact wholly inappropriate on both the scientific and (especially) the philosophical levels of analysis and is probably the source of many highly problematic issues in the use of anti-depressants in humans. For a depressed person, her diagnosis is made according to a clinical interview, the patient’s behavior in session, and possibly psychometric testing—all of which are unavailable for an animal model. The only choice, then, is to use the *behavior* of an animal model to assess the effectiveness of drug candidates. In this kind of experiment, an MDD-like state is first induced in the animal, which is then treated with the experimental drug. Here I focused on one very popular approach: the olfactory bulbectomy (OBX) model of depression.

The reasoning behind this methodology is contradictory and invalid. The chain of illogic begins with the assumption that, because humans experience decreased olfactory sensitivity when depressed, removing the olfactory bulb of the mouse brain will produce a depressed mouse. This claim reverses the arrow of causality found in the human experience, and simultaneously leaps from humans to mice. Thus, the claim is invalid. But there is much more that invalidates the AE at the animal model stage. In the example discussed in Chapter Two, there was a chain of inference following this initial massive error. The inferential chain was that electrophysiological measurements correlated with tail suspension test results, which correlated with forced swimming test results, which purported to be diagnostic of depression in mice; furthermore, this supposed mouse depression was claimed to correlate with human depression—a reversal of the interspecies leap of faith made at the outset. In addition to this, there are four kinds of validity identified by researchers as important: face, predictive, etiological, and construct validity. At best, it seems that animal research in AD development can meet only one of these four. This is woefully inadequate for application of such candidate drugs to humans.

Finally, we examined the human experience of depression from the phenomenological perspective as well as the clinical definition. In inspecting the criteria and phenomena of human depression, we found that the human experience is deep, complex, and crucially involves aspects of existence that are exceedingly difficult to attribute to a rodent. This was especially true for suicidal ideation and suicide attempts. In humans, this is a crucial aspect of MDD since it can lead to death, but it seems quite clear that no such analogous process could occur in the much simpler brain of rodents.

Thus, the claim that human and mouse depression are correlated, and even the claim that mice can experience anything as complex as human depression, are impossible to support logically or empirically.

To conclude the summary of Chapter Two, we saw that the chain of inference leading from rodent research to human clinical trials, then to approval and marketing of anti-depressants, appears highly questionable on its face and at each step; and when closely examined, is filled with logical, empirical, and interpretive problems. The drugs yielded by this process thus also inherit the uncertainty arising from the development process. The flaws in the developmental methodology may lie behind the obvious flaws in the drugs themselves. Since we are marketing anti-depressants to *humans*, the presumed efficacy of a drug candidate in a presumably depressed *mouse* is an inadequate basis. The rodent model of human depression, for all its convenience, is quite simply *too simple* to accurately mirror the human condition.

With this analysis as background, we then closely examined in Chapter Three the human clinical trial step in AD development and found at least as many problems in this arena as with the prior one. The ethical issues appeared to arise with Phase III of the four-phase randomized clinical trial (RCT) process. These Phase III studies have a short follow-up period, shorter than the typical period of drug use in clinical practice. The number of participants is limited to several hundred or thousand participants. So, Phase III trials assess a drug's effects for too short a follow-up time and for far fewer people than the number who eventually will take the drug. These are glaring problems, particularly for depression—a long-term condition, affecting millions of people. But FDA approval to proceed to Phase IV depends mainly on providing two successful clinical trials. Since negative trials do not count, David Healy suggested that one hundred trials could be run that provided only two successful ones, and the drug would be approved by the FDA. But this is clearly an anti-scientific practice and is thus invalid.

The problems continued with Phase IV, which follows the approval of the drug, since safety and effectiveness have not been completely determined in the first three phases. The results from use in the general population constitute Phase IV, meaning that patients using a relatively new AD are actually participating in a clinical trial, but are almost always unaware of this. Thus, informed consent is destroyed. This is highly unethical. We also identified and explored three other unethical practices relating to the RCT and publication process: (2) conflict of interest, created by companies sponsoring the trials of their own drugs; (3) publication bias, wherein drug companies publish only successful trials, obscure the

negative trial results in publications to make them look positive, or withhold the data completely; and (4) ghost authorship, giving researchers authorship credit while the manuscript is actually written by drug company employees with a favorable bias toward the drug. All four of these practices distort the research and clinical picture painted by RCTs, making a scientific evaluation of a potential AD nearly impossible due to these distortions. Thus the RCT process, as it currently stands, is invalid scientifically and is unethical.

But the biggest issue emerging from the clinical trial process concerns placebos and their very large effect on depression as measured during RCTs. The placebo effect turned out to be the major clue leading to the resolution of the many paradoxes presented by ADs. I employed Brody's definition of the placebo effect: "(a) change in the body (or the body-mind unit) that occurs as the result of the symbolic significance which one attributes to an event or object in the healing environment" (Brody, 2000, p. 9). The ideas of the symbol, the healing environment, and the power of patients' expectations are all important in generating the placebo effect. Further, the idea of the natural disease course is crucial, for MDD follows a variable course that complicates the interpretation of AD action. Finally, the presence of AD side effects—which had been a paradox at the outset of this thesis—was found through the analysis to be the key to understanding the entire picture of apparent AD action.

In reviewing the most important studies of ADs, we saw that the work of David Healy and Irving Kirsch was vital in unraveling the confusing picture presented by ADs. Both researchers presented data suggesting that if there was any true drug effect for ADs, it was very small. Kirsch's work demonstrated that there was in fact no drug effect after all; any improvement in a patient's depression was due to the placebo effect combined with the disease course. In light of the findings in the first three chapters, I suggested that the following scenario is at work behind the scenes: ADs have no legitimate drug effect. Instead, they induce side effects. The psychological result of the side effects is a *symbol* to the depressed person that healing has begun. This interpretation on the part of the patient induces the placebo effect.

The PE is superimposed on the natural course of depression, and initial ingestion of the drug is both a marker in time and the beginning point of side effects—but absolutely no therapeutic effect. Thus, if a person's course is heading downward at treatment initiation, the continuing symptoms will be wrongly interpreted as side effects of the drug—since the assumption is that the drug is working—and if the

person's course is upward at initiation, the subsequent improvement will be wrongly credited to the drug. In other words, the drug is assumed to be effective; therefore, all changes following treatment initiation are attributed to the drug. The putative latency period of effectiveness of ADs is thus seen as just the normal disease course. The mistakes in interpretation spring from the assumption that the drug is effective.

We thus saw that the false assumption of drug effectiveness lies behind the paradoxes of ADs. Side effects attributed to drug activity are in fact only the continuation of the disease course; this is why the side effects of ADs are often symptoms of depression: they *are* symptoms of depression. Suicidality is the most dangerous aspect of depression, and has been a claimed side effect of ADs. But we saw that suicidality is, again, just a continuation of the disease course, unabated by AD administration. This illustrates the foolishness of assuming drug activity, then attributing the continued disease course to the drug's effects. I concluded that the key to the past successes of ADs has been the keeping of this gigantic secret from doctors and the public.

Views from science and the philosophy thereof were addressed in Chapter Four. First, we saw that a logical analysis again spelled doom for the AE. I began with a close logical analysis of the overall concept behind ADs, what I called the Neurotransmitter (NT) Theory of Depression (NTD). The general claims of the NTD are that people with depression have insufficient levels of one or more NTs available in neuronal synapses, and that by readjusting the supply of NTs one can reverse the effects of depression. But, as I pointed out, there is no known standard as to what the synaptic level of NTs *should be* for a normal person, much less for a depressed person; similarly, patients prescribed ADs never have the NT levels in their synapses checked before diagnosis. If depression is caused by NT levels that are too low, then I asked, too low compared to what? There is no basis for comparison.

A second form of logic, statistical reasoning, again refutes the NTD. This conclusion is based on the statistical fact that the majority of drug trials for a given drug are negative. By statistics, this shows that there is no statistically significant effect of ADs. In fact, as we traced this reasoning further, we found that at least in the most extreme cases (such as Healy's example of a drug failing 98 of 100 trials), the drug is *statistically proven to fail*. Yet, drugs with such trial records may be approved nonetheless, due to the low FDA bar for approval. This represents a crushing failure of the NTD. Further, in the clinical setting,

the doctor puts a depressed patient through a series of drug trials with an  $n$  of one. This is pure experimentation with no guidance as to what might work for a given patient. Since the drugs work only by placebo, this set of trials may be simply a search for convincing side effects. Many patients go through several drugs during these trials, and can suffer great harm while their depression is unaffected or even worsened.

The NTD fails every time it is tested. The RCT results, including the placebo effect, demonstrate this, as does the analysis in the previous paragraphs. And theoretically, the NTD is deeply lacking: (1) it cannot account for how depression is initiated by experiences; (2) it cannot explain spontaneous recovery; and (3) it cannot explain the effectiveness of psychotherapy. It appears that the primary cause of MDD is experience, even if the experience triggers some kind of genetic effect on NTs. And we have seen that NT levels appear to be unrelated to MDD. In fact, logic yields a deeper conclusion: if NT imbalances do not *cause* depression, then neither will they *maintain* depression. The putative NT imbalance would be a *symptom* of MDD, not the *cause*. This is a crucial point. Rarely if ever does treating the symptoms of a disease actually cure the underlying disease. And clearly, even if ADs do “rebalance” NTs, this would have no effect on mood. Then, by analogy, treating an NT imbalance is as effective against MDD as Nyquil is in killing the common cold virus.

We then examined the scientific concept of reproducibility. Scientific results are useless unless they can reliably be reproduced with the same methods in other settings. But again, the results of RCTs show that any apparent success of ADs in RCTs is not reproducible. In fact, it is the failure of these drugs that is easily replicated. This is scientific doom. It is also philosophical doom, as laid out by Popper and his concept of falsifiability. I phrased this concept as: a theory can provide any number of tests with positive outcomes, but this does not verify the theory—which can never be fully and finally verified; the true test of a theory is its ability to generate hypotheses that can be empirically tested, and have a chance to fail those tests. RCTs are the mechanism by which the NTD is shown to be false by the application of ADs to MDD.

Delving deeper into the philosophy of science, we saw that Kuhn’s theory of scientific revolutions is based on the history and sociology of science, and prescribes the way in which science naturally undergoes major shifts (revolutions) as necessary in the face of accumulated anomalies that the status-

quo paradigm cannot explain. Such anomalies induce disruption and chaos in what Kuhn calls “normal science” that lead to new ideas, new methodology, and a new understanding of old data as well as the anomalous data. The underlying phenomenon here is identified as a paradigm change, a change in the scientific worldview, brought on by anomalies.

But we saw that in the case of the AE, there were no anomalies that caused the sharp paradigm shift from psychotherapy to psychopharmacology for depression. Instead, there was opportunity—in the form of replacing psychotherapists with pills—that would spell billions in profits for drug companies, as well as expanded case loads and profits for psychiatrists. Thus, the paradigm shift for ADs was not one that could be called natural in the Kuhnian sense. Rather, it was artificially induced by the extra-scientific forces of politics and economics. Thus, we see that anomalies are not the only pathways to scientific revolutions, if the pharmacology of depression can be called science. There are other forces that, while not scientifically legitimate, can also do the job. But the problem with this is that in the process, science is thwarted along with its goals.

Finally, in Chapter Five, we saw the results of applying two ethical systems to the AE: those of Kant and Hegel. I chose Hegel to complement the Kantian analysis because Hegel gives an ethical view from the standpoint of society, while Kant’s is predominantly from an individual perspective. In this way, I gave a more complete analysis—on both the personal and societal levels. First, regarding the individual, I invoked Kant. The AE process described in this thesis to some degree reduces the patient’s status to one not too far above an experimental laboratory animal. The experimental procedure in the doctor’s office differs, of course, but the patient is still seen as the locus of an experiment in curing depression. And the main goal of industry is to sell drugs. Thus the medical-industrial complex, in the case of the psychiatry of depression, almost appears to be designed to use people as means to its *own* end, *not* to treat people as ends in themselves. This is a basic violation of Kantian deontology.

One of Kant’s major ethical principles is that people should not be treated merely as a means to another’s purposes, but as ends in themselves; this is one of the formulations of the Categorical Imperative (CI). There are several interrelated concepts: (other formulations of) the CI, truth-telling, rationality, internal causality (freedom of the will), dignity, duty, and beneficence. All of these concepts can be subsumed under, and logically derived from, the single concept of *autonomy*. In the *Groundwork*,

Kant seeks a single, supreme principle of morality and identifies this principle as autonomy of the will. From this principle, Kant derives another that he calls a kingdom of ends, wherein all people live in accordance with the Categorical Imperative yet maintain their individual autonomy. In this kingdom, all treat others as ends in themselves; in this world, no one treats anyone else merely as a means to one's own end.

For Kant, rationality is the ruler in this kingdom. Rationality and freedom of the will work together, along with beneficence, under the canopy of autonomy to make morality possible. Intimately involved also are dignity and duty; intention—as opposed to outcomes—is the primary ethical factor. If one acts out of duty as the sole motivation or intention, one is acting morally. Kant holds that autonomy is the ground of dignity, and morality is the relation of actions to the autonomy of the will. Of all these interrelated concepts, the ethical tool provided by Kant is his Categorical Imperative, in all its forms. Kant even provides examples wherein he uses this tool to illustrate its application in real life through hypothetical examples.

We saw that two of Kant's examples relate strongly to the AE as I have portrayed it. The first was the lying promise, wherein a person borrows money with the promise, but not the intent, to repay it. The consequence of this, if universalized, is that no one could ever trust anyone else's promise—with grave implications for society. Thus, the lying promise is unethical. In the case of the AE, I have illustrated in myriad ways how the claims about ADs are false, and this falsity is well-known to those who manufacture, market, and sell ADs. The falsity may also be known to prescribing doctors, but clearly not to patients. By selling ADs via the claim that they are clinically proven to be effective, Big Pharma is engaged in a lying promise: companies are happy to take one's money, but their promise of a cure in return is a lie.

Kant's second example was a person who was doing well in life, but refused to help others while also renouncing help from others. In this case, the individual is ignoring Kant's claims that we have a duty to be beneficent to others and promote their happiness. But beyond these factors, Kant emphasizes the CI. This person's stance would be self-contradictory since at some later time there might well be need for assistance, but this would be unavailable. Therefore, this person's stance is unethical. Also, in this example the person in question is not treating others as ends in themselves. In the case of the AE, this second example applies because the company is not displaying any form of beneficence. It is not

concerned with the welfare of patients, but only with its own financial welfare. Patents are merely means to profitable ends.

Turning now to Hegel, we saw that his main concern was ethics in society, and especially with regard to government and its various subsidiary entities. Hegel condemns deception in the context of contracts, accompanied by the claim that such deception robs people of their rights while hiding behind an illusion. In addition, Hegel maintains that one's self-concern inherently involves the welfare of others. These concerns lead Hegel to charge governments with the duty to prevent such abuses, through regulatory agencies ("the police"). Such agencies are needed to balance the needs of individuals and society. Thus, this is a duty of the state—to protect its citizens. Hegel goes so far as to say that individuals' welfare is the duty of the state, which should protect citizens from such things as systematic fraud.

Applying Hegel's system to the AE, we saw that the lying practices of the AE are prime examples of systematic fraud on a societal scale—and this is a major theme of this thesis. According to Hegel, such deception is unethical and should not be tolerated; it is the role of the police to intervene and end this unethical situation. But we saw in Chapter Three that the FDA is not doing its regulatory duty and is allowing bogus ADs to be marketed to the public. Thus, the state is failing its citizens. In fact, the tolerance of this deception has seemingly become part of the drug-approval process, and this is highly alarming.

Hegel's second important concept for the present purpose was that of welfare of the state's citizens, individually and collectively. Clearly, the AE is not dedicated to the welfare of its patients. This is a breach of trust, as it were, by the government. Individual companies are valuing their profits above the public and individual interests. And governments are allowing this, and even assisting companies in their agenda, given the poor functioning of the FDA and similar agencies in other countries. Thus, producers and consumers have differing interests, and it is the duty of the government to protect people, not companies. The free market needs regulation to ensure that it works for the benefit of the people, and it is the government's role to carry out that regulation. But we have seen that little effort is being expended for this goal.

Overall, Chapter Five illustrated the yawning abyss between current practices of drug companies and the practices that ethics demands. The greed and deceit of Big Pharma having been established, we then saw that the governmental authorities charged with protecting people from such abuse are themselves dishonest and facilitate the harm that corporations carry out against the public. We saw that Kant condemns this AE from the personal, individual perspective; Hegel's system reveals that the AE is also unethical from the societal point of view. Therefore, there is no defense of the AE due to its inherently dishonest nature.

### **Conclusions and Commentary**

This thesis began by outlining a series of issues and problems with the current state of depression treatment. In describing the current state, we saw that there were a series of paradoxes, contradictions, and mysteries associated with ADs. Examples include: the side effects of ADs that resemble depression itself; the long induction period needed for ADs to work; the shifting nature of the theoretical justification for newer forms of AD medications; the fact that some people commit suicide while on ADs; and the placebo effect, discovered through the RCT process, that is almost as powerful as the effect of ADs. These problems and several more lie just beneath the surface of the AE and a little digging revealed them all.

Following the excavation of these problems, empirical studies and philosophical, logical, and scientific reasoning all pointed to the conclusion that ADs are absolutely ineffective as direct treatments for depression. Their efficacy, when such is demonstrated, comes from the placebo effect superimposed on the normal disease course for MDD. In addition, the developmental process for new AD candidate drugs is irretrievably broken by the absurd and nonsensical assumptions and illogic underlying the process. Essentially, the phrase “clinically proven effective” is meaningless. There is no AD effect on depression; the AE is a scam.

In the end we found that the mysteries and paradoxes were due to the *incorrect assumption* that ADs have therapeutic effects. Under that assumption, the issues I have listed above have no ready answers and instead require the invocation of tortured and invalid logical claims that are untestable. Left in this state, there would be no answers to the questions the thesis has uncovered. But, we saw that if we assume—as dictated by both data and logic—the *ineffectiveness* of ADs, the paradoxes and mysteries

are resolved. Doing this requires that we set aside all the propaganda dispensed by Big Pharma, psychiatry, and individual doctors. We must examine the entire picture with fresh eyes, and make objective judgements. This is difficult because we are trained culturally to inherently trust medical professionals and their advice. So, for many people, the evidence and conclusions of this thesis will be difficult to accept or even entertain. This is a cultural weakness, wherein we accept the word of an authority even over and above our own personal experiences. This tendency to avoid critical thinking and challenging authority is directly dangerous to us as individuals and as societies. While that in itself may be depressing, there is still room for action on the part of people. We can refuse ADs and seek psychotherapy instead, wherein we would actually learn about ourselves and improve ourselves instead of resorting to popping pills.

One of the most disturbing aspects of the AE is something I have pointed out a time or two previously: the role of the prescribing doctor in the AE. Here, I expand on my prior comments. There really are only two choices regarding doctors and the AE: either the doctor has been fooled by the corporate propaganda, or the doctor knows that ADs are merely placebos with side effects. In either case, there lies a huge ethical problem. If the doctor is mindlessly accepting the pro-drug propaganda, then she has not done her own research and is informed by only one side of the debate. This is irresponsible, given the ease with which the medical literature can be forced to give up the secret of AD ineffectiveness, and puts her patients at risk. If, on the other hand, the doctor knows the truth about ADs, then she is lying to the patient and intentionally prescribing a placebo. In both these cases, the doctor is behaving unethically. But this happens thousands of times a day in this country alone. This practice needs to be ended via information.

But perhaps the deepest, largest, most important point raised by the results of this thesis is that neurotransmitters have nothing to do with free-standing MDD—that is, cases of depression brought on sheerly by experiences. Such MDD cases suggest that this depression is *not biological in nature*. That is, MDD is a phenomenon of the mind, not a dysfunction of the brain. MDD is not biologically caused; neither is it maintained biologically. Realization of this fact would destroy the AE and potentially the companies responsible for it and its exploitation. Personally, I would not bemoan this outcome. Those who live by the lie should also die by it. Many philosophers might also have a problem with my conclusion regarding the

inapplicability of biology, because they might see this as an appeal to mind-body dualism, which is considered philosophical hemlock. An objective mind would not have a problem with this, but instead see it as an anomaly within the status-quo materialist system that undergirds the thought of almost all philosophers today. And such an anomaly demands honest investigation, not rejection.

### **Future Directions**

The reader will recall that Chapter Two opened with a pair of quotes from depression researchers, and one of the quotes highlighted the fact that drug companies were running out of ideas for new ADs. This fact has Big Pharma concerned for its future, since the previous cure for an ineffective AD was the prescription for another AD with the hopes that the new drug would perform better than the old one. By running out of new ADs to try and peddle, the AE is in danger of total collapse. This pressure, brought on fundamentally by the general failure of ADs, is leading to the formulation of new strategies to combat MDD with drugs. Here, I close the thesis by briefly examining two new proposals regarding future AD development.

Cuthbert and Insel (2013) have proposed that the failure of many psychiatric drugs is due to the fact that the DSM and ICD classify disorders on the basis of self-reported or externally observable symptoms rather than the underlying biological mechanisms that generate psychiatric symptoms. They take this to be the fundamental difference between psychiatric and physical medicine, and the reason for psychiatry's lack of progress. The way forward, they claim, is to reconceptualize mental disorders as *brain* disorders, which might then be investigated using methods more familiar to the rest of medicine; the National Institute of Mental Health's Research Domain Criteria (RDoC) approach these authors recommend promises to work by starting with basic brain mechanisms and using those to build a fresh taxonomy, which might then more helpfully categorize patients for the purposes of diagnosis and treatment. The putative goal would be to identify specific brain circuits and biological systems that could be manipulated to cure a psychiatric disorder. This approach has been called "precision medicine."

I find this proposal extremely objectionable. The new RDoC approach is radically reductionistic and physicalist, emphasizing the understanding of the brain as a prerequisite for the taxonomic reconstruction. By emphasizing specific biological systems and brain circuits, the program seems to be tossing aside things such as subjective experience, self-report, and observable behavior. This opens up

the dangerous possibility of rendering the patient's experience moot. Why believe the patient, when there is no supporting evidence? Chronic pain patients face this situation currently, because there are no objective laboratory tests to measure the subjective experience of pain. Doctors therefore typically do not believe patients' reports of chronic pain. Now, depressed people may face the same kind of maltreatment.

Further, and to the point of this thesis, embracing the agenda of the RDoC can only result in an explosion of animal (rodent) research on mental illness and the furtherance of rodent research applied to humans. This thesis has made a very strong case for turning away from animal models of human psychology. The RDoC plan would only intensify this irrelevant branch of research. Finally, if we fully embrace brain science as the key to understanding mental illness, we forfeit the phenomenology and existential nature of human life. We lose our humanity. Mental and physical illnesses differ qualitatively, in that the first involves subjectivity and consciousness; therefore, we should not expect the same paradigm to be effective in both spheres of medicine. Again, psychotherapy is a much more valid tool for depression and other mental disorders, since it involves interacting with another human instead of a drug. Since MDD springs from human experience in the world, it is clear to me that a patient working with a well-trained, informed, empathic therapist would have a much better chance of understanding the life challenges that lie beneath depression. One does not learn from a pill, even if it works. In therapy, however, learning is the goal—learning how to handle negative events, learning about the self in relation to the world, and ultimately learning about one's own life and mind.

A second new approach suggested by researchers involves matching individuals with specific drugs to address their depression. The idea is that clinical trials with an  $n$  of one should not be occurring. Instead, a patient's brain can tell doctors which drug will work. The procedure begins by taking EEG scans of a patient's brain, then selecting a drug based on the EEG results (Wu et al., 2020). In the article cited, the researchers reported positive results when the AD employed was matched to patients with certain EEG patterns. This was a placebo-controlled study, but the authors do not state whether an active placebo was used. If not, then the results are not interpretable due to the lack of a valid comparison. But the more fundamental problem with this kind of work is that any AD such researchers choose to employ has already been rendered invalid by all of the misguided and corrupt aspects of the AE this thesis has brought to light. Perhaps, then, the EEG results merely identify people who are more open to suggestion,

and thus more likely to show a strong placebo effect. In the study I cite, the researchers seem to have no awareness of the deep, problematic issues involved in the AE. And to return to the early part of this thesis, depression researchers and those treating depression need to communicate if there is to be any hope of improved treatments in the future.

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