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Randomized Controlled Trials of Antidepressants: Clinically and Scientifically Irrelevant

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This contribution to the "antidepressant debate" (republished here from a 2007 article in the now-defunct journal, *Debates in Neuroscience*) focuses on the validity of randomized controlled trials. We argue that: (a) randomized controlled trials do everything possible to methodologically stamp out high placebo response rates rather than reveal the clinical implications, (b) assessing a psychoactive drug's effects greatly exceeds the purpose of a randomized controlled trial, requiring substantial investigation on normal volunteers, (c) made-up psychiatric diagnostic categories destroy the purpose and logic of the randomized controlled trial as a medical experiment, and (d) adverse drug reactions remain under-studied, under-recognized, and under-appreciated, in parallel with the muting of subjects' voice and the reliance on surrogate measures of efficacy. The standard psychopharmacotherapy trial has lost virtually all clinical and scientific relevance, and needs complete revamping. The backdrop for the discussion is American biopsychiatry's insistence that personal difficulties must be viewed as the expression of idiopathic somatic diseases, and the pharmaceutical industry's dominance of the entire drug treatment research enterprise.

The present article, a contribution to what has been called "the antidepressant debate" (Moncrieff, 2002), stems partly from an article (Jacobs and Cohen, 1999) in which we endeavored to address topics receiving little attention in medical and psychiatric journals: whether psychiatric drugs' "therapeutic"

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effects might be more sensibly considered "toxic" (e.g., Breggin, 1997); how to understand the large disparities (in range, incidence, severity) between adverse drug reactions reported in randomized controlled trials and from other treatment venues; and the reluctance of the psychopharmacotherapy field as a whole to study psychiatric drugs as *psychoactive* drugs, that is, drugs with diverse, diffuse, and variable effects on mental life regardless of why they are used.

The concerns and methodological suggestions voiced in Jacobs and Cohen (1999), falling outside of "normal science" as it was then and is still understood, were not taken up by psychiatric drug research. Nevertheless, in the intervening years, changes from without — investigative reporting, criminal and product liability cases, whistle blowing and leaks, and the actions of regulatory bodies outside the United States — greatly contributed to an unmistakable crisis of confidence in all industry-sponsored drug research (Medawar and Hardon, 2004). This led the former editor of the *British Medical Journal* to propose that medical journals cease publishing all clinical trials, and simply critically evaluate them for readers (Smith, 2005). In psychiatric drug research, the revelatory writings of one man, David Healy, based on his access to otherwise inaccessible internal industry documents in the course of appearing as expert witness in numerous cases, greatly contributed.

In the present paper we revisit and reformulate some of the concerns and suggestions covered in our 1999 article, and we try to expand the boundaries of the usual debate by arguing that: (a) fully assessing a psychoactive drug's psychosocial consequences vastly exceeds the comparatively minuscule purpose of a randomized controlled trial, (b) adverse drug reactions remain under-studied, under-recognized, under-reported, under-appreciated, in parallel with (c) the muting of subjects' voice and the reliance on surrogate measures of efficacy, and that (d) essentially *made-up* psychiatric diagnostic categories destroy the logic and purpose of the randomized controlled trial as a medical experiment. This suggests to us that the standard psychopharmacotherapy randomized controlled trial has lost virtually all clinical and scientific relevance, and needs complete revamping — something easier said than done.

To remind readers, randomized controlled trials refer to investigations with the following typical characteristics: (a) random assignment of psychiatric patients to treatment or placebo or comparison group, (b) about six to eight weeks' duration, (c) where the researcher is not well acquainted with the subject before the initiation of drug treatment, (d) where data on patients' clinical status and drug effects derive mainly from structured, pre-established questionnaires, (e) where data gathering on adverse effects occurs during brief, focused encounters between researcher and subject, (f) where no information about drug effects is obtained from individuals who know the subject well and are able to observe the subject in diverse and natural settings, and (g) where only data obtained while subjects are treated are considered relevant.

Neglecting the Placebo Response

The randomized controlled trial has become the standard test for drug manufacturers to establish the efficacy (and some of the safety) of drugs for specific indications (i.e., "mental disorders" listed in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* [DSM-IV, American Psychiatric Association, 1994]). Efficacy only means demonstrating *some kind of effect*, or "proof in principle." Randomized controlled trials with large numbers of participants seem to be employed especially when an expected treatment effect is relatively small, or when there is spontaneous variation in the condition being treated (Healy, Langmaak, and Savage, 1999). If a drug is clearly efficacious, it should be efficacious even in small trials, and results of efficacy should be routinely replicable. Clinical trials of SSRIs demonstrate nowhere near this level of efficacy; at best, they show weak, marginal effects in comparison to placebo in the treatment of depression. In other words, placebo effects are usually quite large in antidepressant clinical trials, which poses a problem in the assessment of drug effects beyond placebo.

Kirsch, Moore, Scoboria, and Nicholls (2002) reanalyzed all data obtained from the Food and Drug Administration's (FDA) evaluations of the 47 randomized controlled trials funded and submitted to it by the makers of the six most widely prescribed antidepressants approved by the FDA between 1987 and 1999. The reanalysis found that 82% of the response of medicated patients was duplicated in placebo-treated patients, despite the FDA allowing the replacement of subjects on two of the drugs who were not improving after two weeks into the trial, and the concomitant administration of benzodiazepines to patients in over half the trials (a practice that went unreported in publications of these trials). On the chief outcome measure, the Hamilton Depression Rating Scale (HAM-D), the mean difference between drug and placebo groups was a minute 1.8 points on the 50-point version of the scale (a clinically insignificant but statistically significant difference).[1]

We conducted a MEDLINE search on August 12, 2006 for past-year English-language first-time publications of double-blind, placebo-controlled randomized trials of any SSRI. This yielded seven reports of one geriatric, one pediatric, and five adult trials of five different SSRIs, conducted in three countries. Six trials involved depressed patients (one trial included women with breast cancer)

[1]An extensive re-analysis of this FDA dataset by Kirsch, Deacon, Huedo–Medina, Scoboria, Moore, and Johnson (2008) found virtually identical results. Focusing on the relationship between baseline symptom severity and later effectiveness of antidepressants or placebo, the researchers found that antidepressants were associated with a better outcome only among the very small subset of trial patients who scored in the highest range of the HAM-D (score above 28, indicating more severe depression). However, this was shown to be associated with a waning of the placebo effect, rather than increased responsiveness to antidepressants, among these patients.

and one trial looked at weight restoration in individuals diagnosed with anorexia nervosa. In no trial did the SSRI exceed placebo response on the primary endpoint. In three trials, placebo-treated patients fared statistically significantly better (Moreno, Teng, Almeida, and Tavares, 2006; Musselman et al., 2006; Schatzberg and Roose, 2006), and in four trials, placebo and SSRI group scores did not differ statistically (Fava et al., 2005; Gastpar, Singer, and Zellek, 2006; Wagner, Jonas, Findling, Ventura, and Saikali, 2006; Walsh et al., 2006).

The high placebo response rates in both data sets were observed despite most studies' use of placebo-washout or placebo run-in periods, wherein all subjects are abruptly discontinued from any medications they may be taking and placed on a pill placebo, so that early placebo responders can be identified and excluded from those who will then be randomized for the study. For example, in the 47 trials reviewed by Kirsch and colleagues (2002) any subject whose HAM-D score improved 20% or more during this period was excluded from the study. Since the point of all these trials was to compare the efficacy of active medication treatment to placebo treatment, it is by no means clear what the rationale could be for excluding positive placebo responders. It is also unclear whether removing early placebo responders increases drug–placebo differences at trial's end, but there is yet another issue. Because abrupt discontinuation induces a state of withdrawal (Warner, Bobo, and Warner, 2006), trials that begin with a washout "introduce a bias against the subjects who advance to the placebo arm" (Jackson, 2005, p. 32). In at least some subjects, these trials in effect compare a centrally active drug against placebo in reducing symptoms of drug withdrawal. Subjects randomized to take the drug — which should mitigate withdrawal effects — could outperform subjects randomized to take placebo in various ratings of (withdrawal induced) distress. Unfortunately, the issue is not discussed in the literature.

Also, high placebo response rates were observed despite the placebos being "inert" (e.g., flour), rather than "active" (e.g., diphenhydramine). Psychotropic drugs may have certain effects, such as dry mouth or increased heart rate, which can serve as cues to patients and clinicians about which treatment condition they are in. One way around this problem is to use placebos without pronounced psychoactive effects but with a somewhat similar profile of "side effects" as the drug being tested. These placebos are commonly called active placebos, and results from earlier trials showed that active placebos produced greater placebo response (Fisher and Greenberg, 1993). It was proposed that active placebos' physical effects might trick subjects into thinking that they were taking "real" medication, thus amplifying the placebo response. Conversely, in a study using inert placebos, the truly outstanding adverse effects are likely to derive from the group on medications, which would give clinicians a cue about which treatment condition subjects are in, and might tilt clinicians' observations toward amplifying the medication response. Two reviews

of these earlier trials (Moncrieff, Wessely, and Hardy, 2004; Petovka et al., 2000) have not settled the matter of the precise role of inert vs. active placebos, and Quitkin (2003) suggests ignoring the matter altogether because the studies are dated. But the issue remains relevant: If inert placebos produce equivalent or superior response than antidepressants in the latest available randomized controlled trials, might not active placebos vastly outperform antidepressants? We cannot answer this question because we could not find a single randomized trial comparing an SSRI with an active placebo. By comparison, in neurology, trials of pain treatments frequently use active placebos. This void in the psychiatric literature makes no scientific sense — but is understandable from a political economy perspective, wherein the commercial imperatives of the pharmaceutical industry — which sponsors the bulk of all neuroscience research (Dorsey et al., 2009) — shape the pursuit of knowledge.

Finally, it is axiomatic in clinical research that subjects' and researchers' expectations may bias their ratings, which is the reason for the double-blind randomized controlled trial (Elwood, 1998). However, subjects might still recognize their treatment because of physical characteristics of drug or placebo, desirable or adverse effects of the active drug, or cues given by the clinician (Desbiens, 2002). Since most randomized controlled trials in psychiatry are said to be double-blind (Perlis et al., 2005), knowing whether the blind is violated seems vital to interpret results. Researchers could ask patients and clinicians to guess which substance they received and estimate how much this differs from a chance guess, or re-analyze results according to patients' or observers' guesses. The FDA does not require such checks and less than one in 40 published controlled trials mentions some effort to ensure blindedness (Even, Siobud–Dorocant, and Dardennes, 2000) — a sign that editors and peer reviewers also ignore the issue.

In tightly controlled trials, inert placebo "benefits" up to half of Major Depressive Disorder patients who take placebo in exactly the same way that antidepressants are estimated to benefit up to half of patients who take them — by reductions in the scores of clinician-rated symptom scales, starting with the first week of treatment and every week thereafter (Walsh, Seidman, Sysko, and Gould, 2002). Naturally, why this occurs is a key question in psychopharmacotherapy research. Yet, it is obvious that the field as a whole, at least that large portion of it that is funded and controlled by the pharmaceutical industry, is less interested in answering this question than in methodologically stamping it out.

Avoiding to Study Psychiatric Medications as Psychoactive Drugs

Psychopharmacotherapy clinical trials differ greatly from the usual case in medicine since the treatment depends on the drug being a *psychoactive* substance

expected to alter, via its neurophysiological effects, mental and emotional life or behavior for the duration of the treatment (often suggested by medical experts to last indefinitely). The drug has certain (largely unknown) effects on the central nervous system but it is being used as a treatment in a clinical trial only because it has produced states such as sedation, agitation, or catalepsy in earlier animal (preclinical) and normal human (Phase 1) studies leading to the open trials (Phase 2) and randomized controlled trials (Phase 3) on diagnosed individuals. The overriding question thus becomes: What psychosocial alterations and medical consequences (neurological and others) does the regular use of a centrally active drug bring about short- and long-term?

A uniform answer is impossible because the drug will not affect everyone identically. Answering the question includes distinguishing desirable from undesirable effects, identifying unambiguously adverse effects and withdrawal effects. One must also ascertain the drug's psychosocial effects on normal volunteers *prior* to testing the drug with psychiatrically diagnosed individuals, because multiple co-present personal difficulties confound the determination of these effects and distinguishing between possible desirable and undesirable drug effects becomes very problematic. For example, do SSRIs have "antidepressant" properties or "emotional numbing" properties (Moncrieff and Cohen, 2006)? If the data collected during the controlled trial are mute on whether the drug treated group has "improved" on the basis of effects that could be construed as neuropathological (emotional muting, unconcern, euphoria, etc.), just as easily as therapeutic (decreased preoccupation with symptoms, lifting of depressed mood, etc.), then results from placebo-controlled randomized trials mean little, even if "favorable." As we previously discussed (Jacobs and Cohen, 1999), randomized controlled trials are simply not designed to allow observers to make a distinction between, say, "improved mood" while on a SSRI as a return to normal from a depressed state or as a sign of drug-induced frontal lobe damage (Hoehn–Saric, Lipsey, and McLeod, 1990). If the individual is taken seriously as someone whose distress can only be understood historically and contextually, then on the face of it the drug treated person has no *reason* to feel less distressed except for the action of the drug itself, but its effects might not stand close examination. The randomized controlled trial, again, is simply not designed to evaluate the *nature* of "reduced" distress induced by a drug. Obviously, then, individuals without psychiatric diagnoses must be enrolled in this evaluative effort.

The necessity to document the drug's neurological and psychosocial effects on normal volunteers prior to its investigatory clinical use is minimally recognized at best. Phase 1 studies conducted by pharmaceutical companies and sometimes submitted to the FDA as part of the drug approval package seem to have a shadowy existence in terms of how and why they are conducted, how data are collected, coded, and interpreted, what is actually reported to the

FDA, and who has access to the original data (Healy, 2004). What does seem clear that Phase 1 studies are primarily conceived and conducted as toxicology studies (and sometimes as "abuse liability" studies), not as *human psychoactive drug investigations* — for which no established study method exists.

Nonetheless, in addition to normal volunteers, other informants who know the subject well and can observe the subject in her natural environment should also contribute information. The consequences of drug discontinuation, also from multiple informant perspectives, must be investigated. Finally, subjects' accounts once definitely off the drug (e.g., several months after the last dose) must be compared to their accounts under the influence. (Studies with these features are actually conducted today, but only with drugs that investigators and society unambiguously label *psychoactive* [e.g., Griffiths, Richards, McCann, and Jesse, 2006].) Without such information from undiagnosed normal volunteers, diagnosed persons have no realistic basis on which to decide to be treated or not with the drug. Unfortunately, the passage of time since the publication of a famous study of dextroamphetamine effects on normal prepubertal boys (Rapoport et al., 1978) illustrates how little impact the demonstration had regarding assumptions of somatic pathology and "therapeutic" drug effects in the psychiatric literature on "Attention-Deficit/Hyperactivity Disorder."

Are Randomized Controlled Trials in Psychopharmacotherapy Just Infomercials?

We hope to have made it clear enough that ascertaining the full physical, psychological, and social consequences of taking a psychoactive substance daily for a long period of time constitutes a very complex undertaking. Standard, short-term psychopharmacotherapy trials are not designed for this undertaking, but for the much narrower purpose of showing treatment superiority of one drug over inert placebo or non-inferiority to another drug used to treat the same condition. This is precisely why randomized controlled trials have little relevance to clinical practice. In practice, antidepressants are prescribed to very severe cases, very mild cases, pregnant women, frail older people, illiterates, people who would never accept to take a placebo — all cases that are excluded from the vast majority of randomized controlled trials (Seeman, 2001). In practice, drugs can be prescribed for months and years, not the average 6–8 week duration of the controlled trial. In practice the majority of people treated with an SSRI are multiply symptomatic and are prescribed more than one psychoactive drug simultaneously (Silkey et al., 2005). The effort made in controlled trials to exclude many people who will actually be exposed to the drug in clinical practice and to limit exposure to one indicated disorder opens an unbridgeable gap between research and practice.

In research studies and in clinical practice, that so many suffering people treated with "safe and effective" medications soon decline to continue taking

them (e.g., 42% of adults who initiated antidepressants between 1996 and 2001 discontinued them within one month, and only 28% continued beyond three months [Olfson et al., 2006]) invokes only laments regarding non-compliance on the part of many psychiatrists (Mitchell, 2006). In somatic medicine, it may be that clinicians usually know that the burden of the treatment is less than the burden of the disease in the long run, even if the patient does not know this. But in psychiatry, course, outcome, and response to treatment vary in the extreme. People treated with antidepressants may fare worse in the long run than people not treated (Moncrieff and Kirsch, 2006). The burden of the drug may be severe and long-lasting while the severity of the condition may be mild and transitory. This reality is continually obscured by disease mongering, meaning the relentless expansion of defining human distress in all its guises and at all levels of severity as "diseases" requiring drug treatment.[2]

The drug treatment literature mostly ignores the existence of psychotherapy or psychosocial interventions. Psychotherapy research itself has been distorted in order to compete with the supposed rapid efficacy of drug treatment (Weston, Novotny, and Thompson–Brenner, 2004). Exposure to centrally active drugs, even for long periods, is typically regarded as the first and only option — drugs are compared to inert placebo or to other drugs (how fairly one drug is compared to another depends a great deal on who sponsors the study [Heres, Davis, and Maino, 2006]). Such is the commitment to regarding personal difficulties in the emotional realm as the visible signs of an endogenous, idiopathic somatic disease requiring drug treatment that ". . . life style modifications, which is widely practiced [in medicine] for the prevention of relapse [in various real somatic diseases] is not even considered in clinical psychiatry . . ." (Fava, 2002, p. 129).

In sum, the typical psychopharmacotherapy clinical trial might reasonably qualify as an infomercial: a communication aimed to promote a product in a supposedly objective manner, but actually divorced from reality. In the typical infomercial, the product performs well during impractical tests, its defects and disadvantages are not hinted at, and the approving observers have been bought.

Adverse Drug Reactions: Under-studied, Under-recognized, Under-reported, Under-appreciated

We noted in an earlier paper (Jacobs and Cohen, 1999) that serious adverse drug reactions are rarely if ever reported in published trial reports, in contrast to an unending stream of reports of serious adverse drug reactions appearing in psychiatry journals based on open trials, retrospective chart reviews, case reports, and other observations made in clinical practice. With respect to SSRIs, the

[2]*PLoS Medicine*, volume 3, issue 4, 2006, features six essays on disease mongering.

list includes delayed orgasm/ejaculation and anorgasmia (Csoka and Shipko, 2006; Landen, Hogberg, and Thase, 2005; Stimmel and Gutierrez, 2006), suicidal ideation (Mosholder and Willy, 2006), lethargic/apathetic frontal lobe syndrome (Garland and Baerg, 2001; Hoehn–Saric et al., 1990), growth suppression (Weintrob, Cohen, Klipper–Aurbach, Zadik, and Dickerman, 2002), hostility, aggression, and violence (Healy, Herxheimer, and Menkes, 2006; Jain, Birmaher, Garcia, Al-Shabbout, and Ryan, 1992), withdrawal reactions (Warner et al., 2006), and various forms of behavioral toxicity (Wilens et al., 2003). We conjectured that this obvious and glaring disparity (if one elects to notice it) in rates and types of effects between types of studies could be understood at least in part on the basis of sponsorship and the resultant bias that sponsorship creates.

By waiting for patients to complain about a drug effect, or by asking about unpleasant effects in open-ended questions — rather than by systematically eliciting reports from patients and extending the observation period — rates of side-effects may appear to be substantially low (Safer, 2002). In outpatient trials, subjects are typically evaluated once a week or less often, during relatively brief encounters with clinicians who do not know them. In the first 11 published reports of ADHD trials of atomoxetine, ten reports described the methods for eliciting adverse effect information in no more than the following: "open-ended questioning," "unsolicited reports," "self-report," "spontaneous report from parent or child," or no methodology. The criteria for *reporting* the adverse effects in the publication varied as much: "reported in at least 5% of patients in any treatment group," "occurring in >10% of treatment group," "most frequent," "most common," "reported in at least 5% of treatment group and statistically significantly more frequent than placebo," or no criteria (Cohen, Hughes, and Jacobs, 2009). Such derisory methods underscore the irrationality of overemphasizing the validity of the causal standard or conventional placebo-controlled trial design in detecting true adverse effects or, conversely, of systematically questioning the drug-induced status of effects observed in routine clinical practice or reported in uncontrolled case studies. (On the other hand, even unmistakable effects observed in the placebo-controlled randomized trial, such as double the rate of suicidal ideation in depressed youths treated with antidepressants [Mosholder and Willy, 2006], can also be intensely questioned — but, seemingly, only if they disturb the relentlessly promoted portrait of the drugs as safe and effective.)

Another source for the disparity between randomized controlled trial and other treatment venue reports of adverse drug effects may be widespread polypharmacy in ordinary clinical practice. For example, based on challenge–dechallenge for 533 consecutive inpatient admissions over a 14-month period, an 8.1% rate of antidepressant-induced psychosis or mania was observed (Preda, MacLean, Mazure, and Bowers, 2001). Assessment (such as it is) of a drug's adverse effects in a randomized controlled trial is a poor guide to what will

occur when the same drug is combined with other psychoactive drugs. Indeed, among these inpatient admissions, polypharmacy was the rule. Many if not most of these patients would have been excluded from an antidepressant clinical trial because they were taking multiple drugs. However, patients deliberately excluded from clinical trials are nonetheless prescribed, in clinical practice, the same drug that cannot be studied on them — along with other drugs — for the same indication or other indications. Thus, clinical trials may simply miss noticing adverse effects that frequently happen under more realistic treatment circumstances. Of note, the authors of the report conveyed a message of rapid remission of mania or psychosis once dechallenge of the antidepressant was instituted and other drugs were substituted. The three clinical examples provided in their text all have rapid happy endings, but no follow-up is described. We did not detect any interest in the impact on the patient, from the patient's own perspective, of an antidepressant-induced psychosis or mania severe enough to require hospitalization. Indeed, we are unaware of any report published in a psychiatry journal of adverse drug reactions, regardless of severity and incidence, that recommends more than "increased vigilance" on the part of prescribers. But it is uncertain what increased vigilance should mean or what it can accomplish in clinical practice. It is widely recognized that only a minuscule fraction of adverse drug reactions are reported to the professional literature or to regulatory bodies (Lexchin, 2006), so it is probably safe to conclude that professional estimates of an antidepressant's "safety in use" (an FDA expression) represent a gross underestimation.

Medawar, Herxheimer, Bell, and Jofre (2002) compared two sources of accounts of antidepressant adverse effects: first-person accounts sent by patients to Social Audit, and "Yellow Card" reports sent in by physicians to the U.K.'s Committee on Safety of Medicine. Different portraits of drug safety emerged from these different sources. "[Yellow Card reports] are mainly written in doctors' own words, usually a translation into medical shorthand of what the patient says. This often entails some misunderstanding or misinterpretation [on the part of Committee on Safety of Medicine coders] and inevitably omits much detail, especially the personal and social consequences of unwanted drug effects. These emails [sent to Social Audit] recorded major problems for relationships, employment and locomotion (e.g., driving)" [p. 167].

What Is Treated in an Antidepressant Drug Randomized Controlled Trial?

Up to now, we have been critiquing technical aspects of conventional clinical trials. The fundamental critique, however, is simply that antidepressants do not treat a specific, identifiable disease, disorder or condition called Major Depressive Disorder. Although such a construct is contained in the *DSM-IV*, a distinct depressive disorder cannot be validated with respect to etiopathogenesis, patho-

physiology, distinctive symptomatology, course, outcome, or response to treatment. Some biological psychiatrists have regularly noted that aggregating a group of subjects on the basis of non-biological diagnostic criteria and then pretending that the group so aggregated really suffers from the same medical condition, will delay the hoped-for discovery of biological bases of this condition (van Praag, 1998, 2000). Since *DSM-III*, the *DSM* system has rested on the medically conventional principle that psychopathology can be divided into distinct categories, and has postulated hundreds of autonomous disorders (though it has also stated in its introduction that such distinctions cannot be supported empirically — but this has been ignored [Jacobs and Cohen, 2003]). No psychiatric disorder construct began its official existence on the basis of convincing evidence of ontological reality and it has become increasingly clear that such constructs simply do not conform to evidence (Caine, 2003; Hyman, 2003; Merikangas, 2003; Widiger, Thomas, and Coker, 2003). As a *scientific* taxonomy, *DSM* is on the way out because valid case identification ("Who has what disease or disorder?") has proven to be a chimera (but this does not impact on the need for the *DSM* as an *administrative* document).

Careful study of the timing and appearance of clinical symptoms indicates the importance of history and context (Leff, Roatch, and Bunney Jr., 1970) yet Major Depressive Disorder is conceptualized and presented in the *DSM-IV* as an endogenous medical illness with numerous possible guises that the physician/diagnostician must detect, unconnected to the patient's social history and current social-interpersonal situation. But depression as a distinct medical illness is simply *made up*, and so all reports of treating "it" in placebo-controlled trials begin by fundamentally distorting the nature of the research subject's complex and multifaceted problem. It is only via curtailing and editing what the subject actually says about his problem that a distinct condition "emerges." The *DSM*'s Axis IV allows the examination of social and environmental conditions, but the overall commitment to a strictly medical view of "psychiatric disorders" is such that the diagnosis need not include any of these considerations. As a result of clinicians' curtailing and editing speech, people who "meet *DSM-IV* criteria for Major Depressive Disorder" are in effect reduced to caricature so as to be fitted into what a randomized controlled trial logically demands — that for all intents and purposes groups of subjects are *the same* on factors (other than the treatment) that could influence the outcome that the trial aims to assess (Elwood, 1998). Real patients, however, present complaints and behaviors that have no respect for categorical boundaries as delineated in the *DSM* mental disorders (Mirowsky, 1990). Nonetheless, participants in a psychoactive drug clinical trial must qualify for such a disorder. Considerations of prognosis, course, outcome, and response to treatment are too variable to play a role in psychiatric diagnosis. This state of affairs is simply incompatible with the logic of the medical treatment randomized controlled trial.

So, what is actually being treated in antidepressant drug trials? The answer is: complex cases of emotional suffering that presumably include conspicuous states of depressed mood, feeling demoralized, despondent, dispirited, and so on. The attempt to define or discover what depression *really* means as a medical–psychiatric illness proposes there is an "it" to discover — for example the inability to produce insulin in Type 1 diabetes — that is separate from language use, meaning, context, and social interaction. But, we repeat, there is simply no concept or recognition of depressed mood stripped of a personal account in its unique context. A broader, culturally diverse perspective drives this home (Mezzich et al., 1999). Depression may be part of many medical conditions, but this does not mean that everyone who looks or feels depressed suffers from the same medical condition, or that looking or feeling depressed is a symptom of any medical condition. Whether seen as a sign of a real medical disease, or understood as a feature of a person's account of their circumstances, it makes no sense to refer to depression as an independent illness (Jacobs and Cohen, 2003).

What subjects in an antidepressant drug clinical trial share is that their emotional suffering can be described with expressions from the family of words that include "depression." This bears little resemblance to patients diagnosed because they share the same somatic pathology believed or known to result from the same somatic cause. For example, both in a nationwide epidemiological survey (Kessler et al., 2003) and in a randomized controlled trial testing fluoxetine for depression in children and adolescents (Emslie et al., 1997), exactly four-fifths of subjects meeting diagnostic criteria for Major Depressive Disorder were also diagnosed or diagnosable with other *DSM* disorders, in which case the depression diagnosis was rarely primary. In each instance, in what way would these persons be considered to suffer from "the same disorder"?

The randomized controlled trial was developed in and for medicine, but is applied in psychiatry at the cost of obscuring what is being treated, with several far-reaching consequences as we have described so far and continue ahead. We have stressed that the key concepts for understanding an individual's personal problems is personal account and context, not category or clinical entity. Clinicians or researchers may routinely suppress or ignore the subject's own complex version of her problem and highlight (usually) one context-less feature so as to conceptually create a clinical entity or category. This does not, however, render individuals homogenized in the manner that clinicians or researchers wish for and that the design of the controlled trial in medicine requires. If this argument has validity, then the whole point of conducting an antidepressant randomized controlled trial breaks down.

The Research Subject's Muted, Absent, or Interpreted Voice

If the only way to realistically depict the subject or patient's "personal difficulties" (*DSM-IV*'s Axis IV uses this expression) is in terms of a complex tale,

including *dramatis personae*, then it is unrealistic to become too committed — in advance of hearing the patient's account and awaiting further developments — to a fixed idea or measure of a happy ending (i.e., therapeutic benefit), such as a 30% reduction in the baseline score of a rating scale. This is by way of asserting that bringing a relevant clinical story into existence (one that addresses "what's the matter?" with this person), along with addendums (which address how the person is doing now following *x* amount of treatment), must honor that no single official version of the story exists. Certainly, the patient's own version cannot be ignored. But in the conventional medical framework of psychiatric drug treatment research, the patient's own voice is either eliminated or relegated to a distinctly inferior position. The subject in a randomized controlled trial is first rendered a "serviceable other" (or caricature) with regard to "what's the problem" in order to be fitted into the trial's requirement of disorder homogeneity, then rendered mute or irrelevant about how he or she is doing during and at the conclusion of treatment. That is, the treating psychiatrist–researcher speaks *for* the research subject both with regard to clinical status and unwanted drug effects (by structuring the research subject's speaking opportunities and by interpreting and translating what the research subject does say).

The taken-for-granted necessity for the psychiatrist–researcher to authoritatively interpret what the subject says and how the subject appears, and to present the interpretation as the primary outcome appears so compelling that it is rarely discussed. Why a disparity routinely exists between the researcher-interpreted version of the treatment outcome and the subject's own version — albeit limited by the instruments the researcher provides (Healy, 2003; Lasalvia, Ruggeri, and Santolini, 2002) — also remains usually undiscussed. From start to finish of a standard antidepressant trial, the subject's or patient's own views of personal troubles and treatment effects are regarded in the usual medical fashion, that is, as possibly useful information to be expertly evaluated (McHugh and Slavney, 1998). But in psychiatry little objective scientific knowledge can be brought to bear on how the patient looks, behaves, and what she says, so one cannot confidently regard the patient's own view of her status at the conclusion of treatment as expendable. In familiar medical treatment research parlance, this renders the preferred or exclusive reliance on the psychiatrist's–researcher's evaluations tantamount to a "surrogate" outcome indicator.

In previous sections we have made some suggestions regarding more realistic study of drugs thought or hoped to exert an antidepressant effect. In this section, we emphasize that the patient's own voice is muted or absent both with regard to what distresses him and with regard to the pros and cons of treatment. A main reason to quantify the patient's views is to analyze group scores statistically. The researcher creates numerical scores to represent the patient's problem at the start of treatment, during treatment, at the end of treatment, and also lists side effects in terms of presence or absence (rarely, of intensity), all for the purpose

of statistical analysis. The extent to which it is reasonable to represent psychological matters numerically is, of course, a critical topic in the history of psychology as a research field. Probably few would suggest that nothing of importance is lost in the numerous translations of the patient's attempt to convey information through discourse into numbers. Criticisms of conventional drug treatment methodology and findings frequently amount to presenting, in a narrative form, information that is held to have been overlooked or buried by its transformation into scale scores. It may be tedious to solicit first-person accounts from research subjects and to present what the subjects actually said in the ultimate report to the various interested parties, and it may be time consuming for readers to examine what patients actually said or even summaries of their discourse. Nevertheless, it is indisputable that the patient's voice is lost in the usual approach to collecting and analyzing data. We believe it crucial that ethnological drug treatment studies be recognized as a critical component of the overall drug treatment research enterprise so that the voice of the patient is not lost from what is known about drug treatment safety and efficacy.

The Current Status of Scientific Research, Government Protection of the Public, and Expert Medical Opinion

In the sections above, we omitted a focused discussion of conflicts of interest and the industry's dominance of psychiatric drug treatment research as a whole, although this forms the backdrop for every topic addressed so far in this article (Abramson, 2004; Angell, 2004; Cohen, 2005a; Kassirer, 2005; Medawar and Hardon, 2004; Moynihan and Cassels, 2005). Because the randomized controlled trial constitutes the principal hurdle that drug manufacturers must pass in order to have their products approved by the FDA for marketing, manufacturers need only produce two randomized controlled trials showing their drug's superiority to placebo and/or equivalence to an existing drug for the same indication in order to generate potentially astronomical profits. This means that the design, conduct, analysis, and publication of clinical trials are *marketing* issues for drug manufacturers (Smith, 2003). Unquestionably, the very purposes of these once-presumably scientific activities are (for the bulk of clinical trials today) to gain FDA approval of a drug and then to alter physicians' prescribing behavior to increase the drug's market share (Mirowski and Van Horn, 2005). Recognition of this fact has led to a crisis in the perceived integrity of all clinical trials, notably those involving the SSRIs (De Angelis et al., 2005; "Depressing Research," 2004; Giles, 2006; Medawar and Hardon, 2004; Quick, 2001). In contrast with the rest of medicine, however, only belatedly was the extent of the crisis publicly acknowledged in psychiatric journals (Freedman et al., 2006; Perlis et al., 2005).

Here follows, in dense form, a brief overview of the topography of the crisis, focusing on the SSRIs, and how different social actors contribute to it and are caught in it.[3] All the members of the *DSM-IV* and *DSM-IV-TR* panels on Mood Disorders and Schizophrenia and Other Psychotic Disorders had financial ties to drug companies (Cosgrove, Krimsky, Vijayaraghavan, and Schneider, 2006). More than half of the members of the FDA's 18 expert advisory panels had a direct financial interest in the drug or topic about which they advised the FDA (Fontanarosa, Rennie, and De Angelis, 2004). The FDA forbid its own researcher from publishing findings on the risk of suicidal ideation in children taking SSRIs (Mathews, 2004), and the FDA's own lead counsel attempted to annull a federal judge's order that the makers of paroxetine stop making the misleading advertisement claim that "Paxil is not habit forming" ("Judge: Paxil ads," 2002). Medical schools in the U.S. routinely engage in industry sponsored research that fails to adhere to the International Committee of Medical Journal Editors' standards regarding clinical trial design, access to data, and publication rights (Schulman et al., 2002). In an interview with a reporter, Graham Emslie, the lead investigator in a publicly funded fluoxetine pediatric trial, volunteered that he knew of several pediatric SSRI trials delayed for publication probably because the results were unfavorable. Emslie nonetheless "refused to identify the companies or the drugs involved because he, like other researchers involved in similar research, has signed contracts promising secrecy" (Harris, 2003, p. C4). Pharmaceutical companies or their sub-contractors enlist academics to form expert panels to construct guidelines and algorithms that assert or argue that newer, more expensive drugs (SSRIs and atypical antipsychotics) are more effective and must become first-line treatments, in the absence of definitive data or the presence of contradictory data (Healy, 2006); in some states, such algorithms are promoted by means of covert, illicit cash payments to state officials responsible to make the drugs eligible for government funding (Moynihan, 2004).

Professional writers are hired to pen articles of clinical trials or literature reviews, on which prominent academic names appear who might have never seen, let alone analyzed, the raw data (Barnett, 2003; Fugh–Berman, 2006; Hearn, 2004; Mirowski and Van Horn, 2005). These "ghostwritten" articles have wider impact on the field than articles on the same topics that are independently written (Healy and Cattell, 2003). When the Editor of the *New England Journal of Medicine* sought a research psychiatrist with no ties to the drug industry to evaluate an SSRI trial, she could find none (Angell, 2000). When the *American Journal of Psychiatry* published a pediatric randomized con-

[3]The observations in this section were current when this article was first published. Although each one could be replaced with a more recent or egregious instance of the blurring of science and marketing, we saw no reason to update them.

trolled trial of citalopram which reported positive results (Wagner et al., 2004), neither the authors nor the editors disclosed (or knew) that a previous unpublished pediatric randomized controlled trial funded by the same sponsor had observed opposite results (Meier, 2004). When an article in *Journal of the American Medical Association* warned pregnant women not to stop antidepressants because of the risk of re-experiencing depression, most of the 13 authors did not disclose their financial ties to makers of antidepressants (De Angelis, 2006). When all 42 randomized controlled trials of five SSRIs submitted to Sweden's Medical Products Agency as a basis for marketing approval (and unavailable to practitioners) were compared with the reports from these trials actually published in the literature, researchers found evidence of multiple publication, selective publication, and selective reporting (Melander, Ahlqvist–Rastad, Meijer, and Beermann, 2003). A research group on adverse drug events reported, without intentional irony, that "the legal system is becoming an increasingly important participant in postmarketing safety assessments" because lawsuits against manufacturers enable expert witnesses to access company documents that are not normally available to anyone, and although unpublished clinical trials and safety reports from industry would greatly facilitate identifying adverse drug reactions, "these data are not easily obtained" (Bennett et al., 2005, pp. 2137–2138). Drug companies routinely fail to carry out postmarketing safety (Phase 4) studies required by the FDA (Lasser et al., 2002). "[O]nly half of newly discovered serious ADRs are detected and documented in the [Physician's Desk Reference] within 7 years of drug approval" (Bennett et al., 2005, p. 2131). The direct patient adverse drug reaction reporting system created in the Netherlands identified nine new such reactions for paroxetine about 273 days before the same reactions were identified by the Netherlands Pharmacovigilance Foundation based on physician reports (Egberts, Smulders, de Koning, Meyboom, and Leufkens, 1996). Since the 1992 adoption in the U.S. of the *Prescription Drug User Fee Act* (i.e., drug manufacturers seeking product approval from the FDA directly pay the FDA), median approval times for nonpriority drugs decreased from 27 months in 1993 to 14 months in 2001, but as "an inevitable consequence" drug recalls increased from 1.6% for 1993–1996 to 5.3% in 2001 (Fontanarosa et al., 2004, p. 2647).

Conclusion: Whither Drug Research?

American biopsychiatry or neo-Kraepelinism has postulated for the past 30 years that the entire spectrum of "clinically significant" human misery and/or psychosocial deviance is based on endogenous biological faults, and it has enlisted (or become a satellite branch of) the multinational drug industry to promote its postulate. The industry is itself increasingly oblivious to the scientific relevance of its activities as long as they remain profitable, and is only too eager to spend whatever is necessary to maintain the alliance intact (Goozner,

2004). It is difficult to imagine how the psychiatric drug research industry will change from within as long as no actor is pressed to account for the failure to deliver on promises (i.e., to find the biological causes of madness, distress, and misbehavior and to provide safe and effective treatments for them).

Of course, changes from without are unceasing and powerful, but there is no obvious indication of where the field is headed. Two related trends have been apparent for some time: the increasing irrelevance of medical experts and medical intermediaries (encouraged by direct-to-consumer advertising of pharmaceuticals), and the construction of knowledge about psychotropic drugs moving far beyond the traditional confines of medical research (made possible by the Internet and its ability to give direct, uninterpreted voice to laypersons) [Cohen, 2005b]. The implications of these two developments are far from clear. But for our part we suggest that the entire drugs-as-first-line-treatment-for-personal-problems research enterprise has turned a blind eye to two fundamental principles: (1) "In approaching [the issue of exposure to chemicals and toxicity] it is indeed instructive to take as a starting point the extreme position: that the effects of chemicals on organisms are mostly bad" (Summerfield, 1978, p. 335), and (2) "*Like all psychotropic agents*, the behavioral and neuropharmacological effects of fluoxetine are complex and variable" (King et al., 1991, p. 185, our emphasis).

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