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Randomized controlled trials of antidepressants: clinically and scientifically irrelevant

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Abstract This contribution to the "antidepressant debate" focuses on the validity of randomized controlled trials (RCTs). We argue that: (a) made-up psychiatric diagnostic categories destroy the purpose and logic of the RCT as a medical experiment, (b) RCTs do everything possible to methodologically stamp out high placebo response rates rather than reveal their clinical implications, (c) assessing a psychoactive drug's effects greatly exceeds the RCT's purpose, requiring substantial investigation on normal volunteers, and (d) adverse drug reactions remain understudied, under-recognized, and underappreciated, in parallel with the muting of subjects' voice and the reliance on surrogate measures of efficacy. The standard psychopharmacotherapy RCT 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.

Keywords randomized controlled trials · psychopharmacotherapy · psychoactive drugs · diagnosis · placebo response · adverse drug reactions · disease model · conflicts of interest · pharmaceutical industry

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Introduction

We were invited by the editors of this journal to contribute to what has been called "the antidepressant debate" [1] on the basis of a 1999 article [2] in which we endeavored to address topics receiving little attention in medical and psychiatric journals: whether psychiatric drugs' "therapeutic" effects might be more sensibly considered "toxic" [3]; how to understand the large disparities (in range, incidence, severity) between adverse drug reactions (ADRs) reported in randomized controlled trials (RCTs) and from other treatment venues; and the reluctance of the 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.

Our concerns and methodological suggestions, 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 U.S.—greatly contributed to an unmistakable crisis of confidence in all industry-sponsored drug research [4]. Recently, for example, the former editor of the *British Medical Journal* proposed that medical journals should cease publishing all clinical trials and simply critically evaluate them for readers [5]. 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 earlier article, and we try to expand the boundaries of the usual debate by

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 [17] and in an RCT testing fluoxetine for depression in children and adolescents [18], exactly four-fifths of subjects meeting the diagnostic criteria for MDD were also diagnosed or diagnosable with other DSM disorders, in which case, the MDD diagnosis was rarely primary. In each instance, in what way would these persons be considered to suffer from "the same disorder"?

The RCT 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 describe ahead. We have stressed that the key concept for understanding an individual's personal problems is *story*, not category or clinical entity. Clinicians or researchers may routinely suppress or ignore story and highlight (usually) one context-less feature, so as to conceptually create a clinical entity or category. This does not, however, render the people thus homogenized *the same* in the manner that the clinicians or researchers wish for and that the design of the RCT in medicine requires. If this argument has validity, then the whole point of conducting an antidepressant RCT breaks down.

Neglecting the placebo response

The RCT has become the standard test for drug manufacturers to establish the efficacy (and some of the safety) of drugs for specific DSM-IV indications. Efficacy only means demonstrating *some kind of effect*, or "proof in principle". Large RCTs seem used especially when an expected treatment effect is relatively small or when there is spontaneous variation in the condition being treated [19]. 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 selective serotonin reuptake inhibitors (SSRIs) demonstrate nowhere near this level of efficacy; at best, they show weak, marginal effects in comparison to placebo in the treatment of MDD. In other words, placebo effects are usually quite large in antidepressant RCTs, which poses a problem in the assessment of drug effects beyond placebo.

Kirsch et al. [20] reanalyzed all data obtained from the Food and Drug Administration's (FDA's) evaluations of the 47 RCTs 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 2 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 (HAMD), the mean difference between drug and placebo groups was a minute 1.8 points on the 50-point or 62-point versions of the scale (a clinically insignificant but statistically significant difference).

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 including women with breast cancer) and one 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 [21–23], and in four trials, placebo and SSRI group scores did not differ statistically [24–27].

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 et al. [20], any subject whose HAMD score improved 20% or more during this period was excluded from the study. As the point of all these trials is 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 [28], trials that begin with a washout "introduce a bias against the subjects who advance to the placebo arm" [29, 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 on placebo in various assessments of 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 have certain effects, such as dry mouth or increased heart rate, which

distress, upset, anxiety, etc., induced by a drug. Obviously, individuals without psychiatric diagnoses must be enrolled in this effort.

The necessity to document the drug's neurological and psychosocial effects on normal volunteers before 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 [40]. It 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 his/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* [41]). 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 [42] 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" (ADHD).

Are RCTs 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 major, very complex undertaking. Standard, short-term psychopharmacotherapy RCTs 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 RCTs 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 RCTs [43]. In practice, drugs can be prescribed for months and years, not the average 6- to 8-week duration of the RCT. In practice, the majority of people treated with an SSRI have multiple symptoms and are prescribed more than one psychoactive drug simultaneously [44]. The effort made in RCTs 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 both 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 1 month, and only 28% continued beyond 3 months [45]) invokes only laments of noncompliance on the part of most psychiatrists [46]. In 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 [47]. 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 (see *PLoS Medicine*, volume 3, issue 4, 2006, featuring six essays on the topic).

Mostly, the drug treatment literature ignores the existence of psychotherapy. Psychotherapy research itself has been distorted to compete with the supposed rapid efficacy of drug treatment [48]. Exposure to centrally active drugs, even for a long time, is usually 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 is paying for the study [49]). Such is the commitment to regarding personal difficulties in the emotional realm as the socially visible signs of an endogenous, idiopathic somatic disease that requires 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..." [50], p. 129].

In summary, 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

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 4 uses this expression) is in terms of a unique story that includes history and *dramatis personae*, then it is unrealistic to become too committed—in advance of hearing the story and awaiting further developments—to a fixed idea or measure of a happy ending (i.e., therapeutic gain, progress, benefit), such as a 50% reduction in baseline score of a rating scale. This is by way of asserting that bringing a relevant "clinical" story into existence (a story that addresses "what's the matter?" with this person) and addendums to the story (which address how the person is doing now after x amount of treatment) must honor that there is no single official version of the story. 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 an RCT is first rendered a "serviceable other" (or caricature) with regard to "what's the matter" to be fitted into the RCT'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/reporting 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 seems so compelling that it is rarely discussed. Why a disparity routinely exists between the researcher-interpreted version of the treatment outcome and the subjects' own version—albeit limited by the instruments the researcher provides [65, 66]—also remains usually undiscussed. From start to finish of an antidepressant RCT, 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 [67]. But in psychiatry, little objective scientific knowledge can be brought to bear on how the patient looks, behaves, and what he or she says, so one cannot confidently regard the patient's own view of his or 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. We have emphasized, in this section, that the patient's own voice is muted or absent both with regard to what is the problem and with regard to the pros and cons of treatment. A main reason for quantification of the patient's views is to analyze group scores statistically, as the patient will not naturally use numbers when trying to convey his or her impressions. 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, and criticisms of conventional drug treatment methodology and findings frequently amount to presenting information narratively which is held to have been lost or overlooked or buried by its transformation into scores on one or more scales. It may be tedious to solicit narratives 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 to examine even summaries of their discourse. Nevertheless, the patient's voice is lost in the usual approach to collecting and analyzing data. We believe it sensible 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 every section 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 [4, 68–72]. Because the RCT constitutes the principal hurdle that drug manufacturers must pass to have their products approved for marketing, they need, in the USA, to only produce two RCTs showing their drug's superiority to placebo and/or equivalence to an existing drug for the same indication to generate potentially astronomical profits. This means that the design, conduct, analysis, and publication of clinical trials are *marketing* issues for drug manufacturers [73]. 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

Of course, changes from without are unceasing and powerful, but there is no obvious indication of where the field is headed. Two related trends are apparent: 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 completely beyond the traditional confines of medical research (made possible by the Internet and its ability to give direct, uninterpreted voice to laypersons) [101]. 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: (a) "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" [102]; (b) "*Like all psychotropic agents*, the behavioral and neuropharmacological effects of fluoxetine are complex and variable" [103, our italics].

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