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What is really known about psychological alterations produced by psychiatric drugs?

David Jacobs [a] and David Cohen [b,*]

[a] *Center for the Study of Psychiatry and Psychology-Southwest, 528 Fourth St., Encinitas, CA 92024, USA*

[b] *Professor, School of Social Work, and Researcher, Groupe de recherche sur les aspects sociaux de la santé et de la prévention (GRASP), Université de Montréal, Montréal, QC, Canada, H3C 3J7*

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Abstract. This paper argues that information about psychiatric drugs derived from conventionally conducted randomized controlled clinical trials (RCTs) is inadequate to form an accurate picture of drug-induced psychological alterations. Two main lines of argument are presented. The first concerns the disparity between adverse effects established in RCTs and the broader range of adverse drug reaction reports which derive from non-RCT formats. The second concerns the contention that information about drug-induced psychological alterations obtained from RCTs is too limited to address the meaning of observed "target symptom" reduction which occurs during the course of the (typically very brief) investigation. The paper considers the possibility that nominal "therapeutic" drug effects may only be part of a larger, inadequately discerned picture of drug-induced psychological toxicity.

1. Introduction

Most of what is considered "known" or "established" about the psychological effects of psychiatric drugs derives from randomized clinical trials (RCTs) in which a psychotropic drug is used as medication to treat patients with a specific diagnosis. Mainly because of the presumed control of bias imparted by randomization and by "blinding" researcher and subject, the RCT has come to be regarded as perhaps the most valid procedure for making causal inferences about the effects of drugs, and thus about the pros and cons associated with a specific medication-disorder match [3]. However, this paper's main contention is that conventionally conducted RCTs in clinical psychopharmacology cannot produce a realistic picture of the psychological alterations brought about by psychotropic drugs used as medicine.

By "conventionally conducted RCTs", we refer to investigations with the following typical characteristics:

(a) about six to eight weeks' duration;
(b) where data on patients' clinical status and drug effects derive mainly from structured, pre-established questionnaires;
(c) where data gathering on adverse effects occurs during brief, focused encounters between researcher and subject;
(d) where the researcher is not well acquainted with the subject before the initiation of drug treatment;

*Correspondence: Dr David Jacobs: jacobsan@aol.com; Dr David Cohen: david.cohen@umontreal.ca.

(e) 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
(f) where only data obtained while subjects are treated is considered relevant.

By "psychological alterations", we mean the impact on thinking, feeling, and behaving brought about by a psychotropic drug's full spectrum of neuropharmacological activity.

The main contention is supported by three related discussions centered on clinical illustrations of drug-induced untoward psychological effects reported in the course of various types of clinical research. These illustrations mostly concern the popular drug fluoxetine ("Prozac") but the issues we raise are meant to apply to all psychiatric drugs. First, we explicitly take note of the disparity which exists between "adverse" or "side effects" identified in RCTs and adverse drug reaction (ADR) reports which derive from non-RCT clinical research and from ordinary clinical practice. Second, we argue that this disparity indicates that conventionally conducted RCTs under-represent drug-induced psychological alterations. Third, building upon the previous two points, we examine the proposition that an expanded appreciation of psychological or behavioral ADRs may undermine the conventional (and foundational) view that psychiatric drug treatment brings about a "main" therapeutic effect and independent, mostly somatic "side effects". In short, we ask in this paper whether "therapeutic" drug effects are seen as such only because the "big picture" concerning what the drug has actually brought about has not been fully discerned in RCTs. Throughout the paper, we make some methodological suggestions – all of which have been previously put forth by psychopharmacology pioneers or occasionally used in contemporary studies – to attempt seriously to attain this "big picture".

2. The disparity between adverse reactions seen in RCTs and non-RCTs

Adverse drug reaction (ADR) reports from day-to-day clinical practice or "open" drug trials are published in nearly every issue of psychiatric journals as case studies or letters to the editor. This continuous stream of clinical observation indicates that the range and severity of ADRs established for psychiatric drugs in RCTs is far from complete. Yet, it is accorded relatively minor importance. For example, Gram's [10] authoritative review of fluoxetine distinguishes clearly between side effects established in "clinical trials" – listed as "nausea, anorexia, loss of weight, nervousness, tremor, anxiety, insomnia, diarrhea, and sexual dysfunction" (p. 1357) – and "suspected (rare) adverse drug reactions" based upon "case reports". The implications are that alleged ADRs described in case reports are (1) not necessarily true drug effects, and (2) uncommon.

2.1. Cause and effect in the non-RCT format

Notwithstanding the importance of the RCT format to provide evidence that the test drug is in and of itself a source of clinical improvement, certain case reports offer compelling evidence that a drug provokes the appearance of psychopathology. For example, King et al. [17] report that in a 30-week period, six of 42 children (14%) treated with fluoxetine for various psychiatric diagnoses developed new or dramatically intensified self-injurious ideation or behavior. Have the authors observed a genuine drug effect or would the so-called ADRs have emerged in these six children without fluoxetine, presumably as a consequence of how their psychopathology was developing? One 14-year old girl treated for obsessive-compulsive disorder not only made a suicide attempt after five months on fluoxetine, but in hospital on 40 mg/d of fluoxetine began pulling out her hair, slamming her limbs into objects, and burned herself with

a lighter. The pattern of behavior first emerged on fluoxetine, abated when fluoxetine was discontinued, emerged again at a later date following renewed fluoxetine treatment, and once again cleared when fluoxetine was discontinued.

King et al. [17] nevertheless insist that whether or not the observed reactions are real ADRs remains in doubt without data from untreated or alternately treated groups. They imply that if some patients in a similarly composed untreated or alternately treated group exhibit comparable symptomatology, then the question of whether or not their six young patients really exhibited an ADR could be answered in the negative. This reasoning fails to recognize that similar patients treated without fluoxetine might deteriorate and become self-injurious by other routes. Should this occur, fluoxetine as a cause of *de novo* self-injurious behavior is by no means ruled out. The question is: why did these fluoxetine-treated patients develop the self-destructive behavior observed? For cases where fluoxetine rechallenge produced similar consequences, it is difficult to avoid concluding that the drug brought about self-injurious behavior.

Most published ADR reports do not involve rechallenges with the suspected agent. Typically, a clinical phenomenon (not originally present and not part of the patient's history) emerges following initiation of drug treatment and clears following discontinuation of drug treatment. Teicher, Glod and Cole [25] describe such a sequence (with a single drug), with the additionally convincing features that the individual concerned was not a psychiatric patient, had no psychiatric diagnosis, had never before been treated with psychotropic drugs, and was not a "substance abuser". She received fluoxetine in the hope that it might provide relief for a four year history of chronic fatigue. After one month of fluoxetine treatment at 20 mg/d, she developed obsessive, all-consuming impulses to kill people she loved as well as herself. Although fluoxetine was discontinued on day 31, the symptoms persisted for six months before beginning to abate. At six months, norfluoxetine (a metabolite of fluoxetine) was still detectable in her blood.

Debating whether or not fluoxetine may be implicated as the cause for the behavior they reported, King et al. [17] speculate (on the pro side of the issue) that the drug may play a causative role because of its multifaceted psychotropic effects (agitation, disorganization, excitation, etc.). Teicher et al. [25] make a similar point, that the chemical substance does not so much induce a specific thought or impulse as it *interferes with normal thought processes* so as to bring about a drug-induced obsessive-compulsive state. Both comments recognize that fluoxetine is a psychotropic substance which can bring about diverse and variable (across individuals, and in the same individual over time) psychological alterations. Indeed, King et al.'s [17] final remark could serve as the foundation principle for psychopharmacology: "Like all psychotropic agents, the behavioral and neuropharmacological effects of fluoxetine are complex and variable" [17, p. 185].

2.2. Incidence estimates in RCT and non-RCT format

As Gram [10] notes, "rare serious drug reactions with fluoxetine are to a large extent based on case reports, and the incidence rates are unknown" (p. 1358). Indeed, most adverse drug reaction reports (unlike the King et al. report above) do not provide information allowing estimates of incidence. Gram's conclusion that the "suspected (rare)" fluoxetine ADR she cites are rare is evidently because they have not been recognized in RCTs. However, if a drug has been studied in an RCT format at multiple sites and by different research teams over time, why even a low frequency ADR – especially if genuine – has escaped recognition in previous RCTs comes to mind as a fundamentally important scientific and clinical question.

The question cannot be answered with certainty. There is the critical issue of the large numbers of subjects needed to expect detection of a low frequency ADR in a short-term study. Other sorts of considerations may be pertinent. First, an RCT involves major financial and professional stakes in the test drug.

After each phase in the drug development strategy, it becomes much more costly to abandon a project. This implies that bias increases along the route up to and including RCTs – which is of course one of the potent arguments in favor of the RCT format, which "blinds" researcher and subject. Unfortunately, as most actual psychopharmacotherapy researchers probably realize, there are ample reasons to believe that procedurally blinded researchers in psychopharmacotherapy RCTs are unblind in fact [7,19,20]. Indeed, we are mystified about how much the research community still appears convinced that the conventional double-blind arrangement achieves its intended aim, especially in psychopharmacotherapy studies. In a wholly representative example, Cohn and Wilcox [5] describe their double-blind study of fluoxetine, imipramine, and placebo as including dosage adjustment based upon weekly interviews about effectiveness and side effects. This means that some fluoxetine-treated patients complain to the researchers about unpleasant states which began after fluoxetine initiation. The researchers, familiar with the effects of fluoxetine, adjust these patients' dosages accordingly, and yet are still presumably blind as to the drug status of all patients.

Second, as Herxheimer [12] observes, "the systematic collection, investigation, analysis, and interpretation of data on adverse drug reactions, has developed slowly, and is still lagging far behind the development of clinical trials" (p. xix). For example, researchers exercise much discretion in (1) classifying subjects' complaints or researchers' observations as "consistent with the subject's psychiatric condition" or as "drug reaction", and (2) how to name a drug reaction. Both points are illustrated in a fluoxetine ADR observed by Lipinski, Mallya, Zimmerman, and Pope [18] during early open trials. The authors admit that a first case of fluoxetine-induced akathisia was not recognized until well into the trial by a nurse, and it was only from then onward that the researchers began to see akathisia as such in patients. Lipinski et al. do not discuss how they characterized the same patients' behavior before they realized that fluoxetine could produce akathisia.

In light of these brief considerations, we question whether it is defensible to hold up what has or has not been recognized in RCTs as the gold standard on the question of ADRs. Some forms of ADR reports, such as those involving rechallenges, have more credibility than data from an RCT format concerning a specific individual's drug reaction. Correctly estimating the incidence of an ADR is complex in its own right but should not be conflated with determining whether a reported ADR is genuine.

Having said this, it is rarely the case that an ADR report seems directly relevant to the contention, most consistently (though not exclusively) put forth by Peter Breggin [1,2], that the so-called therapeutic effects of a psychiatric drug are actually part of its toxic effects. Reports of drug-induced akathisia, mania, psychosis, panic, and so on, take for granted that the drug has a main therapeutic effect and separate, independent side effects. We address this question in the remainder of the paper.

3. How is a psychiatric drug's "main" effect determined?

A hypothesis-testing RCT can be viewed as a formal test of the alleged therapeutic drug effect which served as the basis for the open trials leading to the RCT. Thus an RCT is designed specifically to test a drug's efficacy for the treatment of a certain condition. In this manner the drug's "main effect" is already built into the entire design and objective of the RCT. But the *meaning* of observed or reported "target symptom(s)" reduction brought about by a psychotropic drug may be far from self-evident. It is precisely with regard to meaning that the question can be raised concerning the drug's "main" effect and whether sufficient effort and ingenuity have been directed to detect the drug's *full range* of psychological effects. This latter question is just where psychopharmacotherapy RCTs diverge – and ought to diverge – from

RCTs in all other areas of medicine. The issue of a drug's full psychological effects is by no means easily addressed. Nonetheless, it is part of our main contention in this paper that research in clinical psychopharmacology has failed to squarely face up to the complexities involved in coming to grips with the issue. A clinical illustration follows.

3.1. The ambiguity of "doing better" on a psychiatric drug

The question of what "feeling less depressed" means when this is brought about by a psychotropic drug is raised as problematic in what begins as an ADR report by Hoehn-Saric, Lipsey and McLeod [13]. Three patients treated for depression with fluoxetine are depicted as becoming euthymic (normal mood) and developing symptoms resembling the effects of frontal lobe lesions: "apathy, flatness of affect, lack of emotional concern, loss of motivation and initiative, and difficulty foreseeing the outcome of an action" (p. 345). The symptoms were not in evidence before drug treatment was initiated and they remitted following its discontinuation.

How were these untoward psychological effects recognized? At first, the authors did not observe anything in their contacts with the patients which struck them as an ADR. As they saw it, fluoxetine actually brought about "euthymia". However, unrestricted by a research protocol, Hoehn-Saric et al. listened to and noted what their patients said. Patients were free to provide spontaneous commentary about their life and how they fared on fluoxetine as their views evolved over time. As a result, Hoehn-Saric et al. began to see these patients from the perspective of clinical neurology rather than clinical psychopharmacology – in terms of drug-induced neuropathology rather than drug-induced clinical improvement. That the clinical data which instigated this shift in perspective were slow to emerge and not immediately recognizable as neurological symptoms is not unusual in clinical neurology. Since Hoehn-Saric et al. cite Stuss and Benson's [23] classic text on the frontal lobes, we note that Stuss and Benson conclude that symptoms of frontal lobe dysfunction are so variable and often so subtle that diagnosis by any means other than individualized case study may be inadequate (p. 216).

The point here is that an individualized case study approach to the question of drug-induced neuropathology is beyond the methodological scope and interest of conventional, hypothesis-testing RCTs. Four decades ago, Freyhan [8] had already expressed concern that investigations which substituted pre-established rating scales for protracted, open-ended, "comprehensive observation" would inevitably misrepresent the full consequences of psychopharmacological treatment. He pointed out in great detail that information obtained in the former manner in large scale RCTs may operate to foreclose identification of "the actual spectrum of neuropharmacological activity" brought about by the treatment or test drug, with the consequence that what became "established" about the drug in RCTs could be quite misleading. In effect, Freyhan argued that the requirements for generating uniform data (e.g., asking all subjects in all experimental groups to respond to the same pre-established list of what researchers/manufacturers regard as likely side effects) in order to make statistical comparisons between experimental groups may be accomplished only by reducing observational sensitivity. Thus, one of Hoehn-Saric et al.'s patients, a 50-year old woman who worked as an illustrator, eventually complained that she could only complete projects with persistent reminders from others. The authors could not directly observe this, and it took time before the patient brought this to their attention. They finally interpreted this as fluoxetine-induced apathy, but only in the context of individualized knowledge of this patient before and during fluoxetine treatment.

In sum, the relatively unstructured "speech situation" for the patient in treatment, which permits a flow of narrative about everyday life and the manifold effects of the drug which the patient knows he or she

is taking, becomes a structured and narrowly focused question-and-answer session about symptoms of the condition being treated and various side effects in the treatment research situation, with researchers and subjects ostensibly unaware of who receives the test drug. Moreover, the patients in the study by Hoehn-Saric et al. only slowly realized that their drug-induced condition had become problematic. In one case, six months elapsed before there were explicit complaints from the patient. This period contrasts conspicuously with the six to eight week duration of most RCTs (during which a substantial proportion of subjects will drop out).

We turn now to Hoehn-Saric et al.'s ambivalence about whether the frontal lobe dysfunction-like effects they (eventually) discerned should be regarded as toxic effects unrelated to fluoxetine's antidepressant action (literally, "side effects"), or if they are in fact an important part of what is taken to be the therapeutic ("main") effect. This is hardly wordplay, since Hoehn-Saric et al. understand that what looks clinically like frontal lobe dysfunction is psychologically and socially impairing for their patients – whether or not the patient feels "less depressed" on the drug. Presumably this is why, in addition to the patients' own concerns and complaints, Hoehn-Saric et al. discontinued treatment. On the other hand, the authors kept one of the three patients on fluoxetine. This patient felt far less depressed on fluoxetine but had also become impaired as described above. The authors write that "she continued on Prozac because of the substantial improvement in her mood, but we slowly tapered the dose" (p. 345). The frontal lobe lesion-like symptoms were then described as "partially improved".

Here, Hoehn-Saric et al. seem to abandon the position that a desirable reduction in distress is only one aspect of evaluating the clinical impact of a drug on the patient as a person. They speculate in a final comment that the reason why SSRIs seem more *effective* in anxiety disorders than other drugs is precisely *because* SSRIs induce frontal lobe dysfunction. Hoehn-Saric et al. first referred to euthymia *and* frontal lobe dysfunction as separate but contemporaneous drug-induced conditions, but then explicitly entertained the idea that the latter may be an important ingredient of the former. This is precisely Breggin's point, namely: (1) toxic effects can appear salutary if clinical attention is confined to a narrow enough sector of what the drug has brought about, and (2) insufficient effort and ingenuity have been brought to bear in psychopharmacotherapy research on the matter of apprehending the full psychological effects of psychoactive drugs used as medicine.

4. Researchers' limited observational opportunities in RCTs

The complexity brought about by using a psychotropic drug clinically may be amplified by minimizing the researcher's opportunities for observation. That researcher and subject are strangers in RCTs and only meet briefly during the short time frame of the investigation creates an impoverished set of observational opportunities for the researcher. We have not found an explicit discussion of this point in the literature. We surmise that the situation is dictated by the logic of the experimental design: if the researcher does get to know the subject in depth during the course of the investigation, it could be argued that a psychotherapy-like component has been added to the drug treatment and any clinical gain observed cannot be clearly attributed to the test drug. For the purpose of noticing somewhat subtle drug effects, however, this is a serious drawback to the standard RCT. The RCT outpatient format actually leaves it up to the subject to report subtle drug effects which he or she may not discern (as in the Hoehn-Saric et al. report) until long after the usual RCT period is over (assuming the subject remains on the drug), or which he or she may never discern (reduced cognitive abilities, etc.).

One way to distinguish between therapeutic or toxic/adverse effects is to administer doses of a psychotropic drug to normal subjects. Here, one asks if the drug brings about "behavioral toxicity" [24] such

as emotional indifference which could be construed as symptom relief if the drug was used for clinical purposes. However, this method does not address whether subjects are able to discern possible untoward drug effects in a timely manner. One might therefore make arrangements for people who know subjects well and can observe them under natural conditions to serve as sources of information about drug effects. Judd, Hubbard, Janowsky, Huey and Attewell [15] used the foregoing method in a study of the effects of lithium carbonate on normals. The researchers cited two previous "anecdotal" observations:

(1) Schou's [21] report describing how he and his associates ingested 1,850 mg/day for several weeks and felt that increased mental effort was required to initiate physical tasks (inertia), as well as experiencing indifference, passivity, decreased response to environmental stimuli with a sensation of being separated from environmental stimuli by a "glass wall", etc.
(2) Judd and Hubbard's [16] non-blind observations of the "dulling and blunting" effects of lithium in nine normal males who received therapeutic doses for two weeks.

Judd et al. [15] wished to determine if these observations could be "objectively demonstrated in a well-controlled clinical study" (p. 347). They carried out a double blind, placebo vs. lithium crossover study, counterbalanced for order. The data derived mainly from self-rated lists of adjectives and short phrases administered at the end of the two week placebo period and the two week lithium period. Compared to the end-of-placebo ratings, many significant mean differences were obtained at the end of the lithium period, in the direction of greater distress, dysphoria, and impairment.

Before the study began, each subject was asked to designate a "significant other", also "blinded", who would be called upon to render judgments (based upon whatever relationship the significant other had with each subject in their everyday lives) about the subject's psychological condition at the end of each two week period. These judgments were compared to those made by "trained observers" on the basis of "a short personal interaction" with subjects followed by simply watching them fill out the research instruments. The judgments consisted of rating a list of adjectives describing an individual's present psychological state thought to be amenable to behavioral observation, e.g., happy, angry, grouchy, drowsy. Subjects also rated the list for themselves on the day the observers made their evaluations. Although subjects indicated that the effects of lithium were profoundly noticeable and dysphoric, the trained observers were unable to distinguish differences between the subjects' behavior or mood on or off lithium, while ratings by significant others were highly consistent with the subjects' self-ratings on and off lithium.

Since the study demonstrates that lithium brings about untoward psychological alteration in normals which could easily be seen as "desired therapeutic changes" in certain psychiatric conditions, and since the issue of *who* is observing the subject under *what conditions* can hardly be ignored, it is noteworthy that psychopharmacotherapy research in the main has not incorporated these methodological refinements. Still, Judd et al. [15] do not address the problem of recognizing drug effects which are not reported to the researcher by the subject. Comparing evaluations by trained observers and by significant others depended upon subject self-evaluations as a standard. No observer evaluations were requested which bear on the issue of the possible disparity between what an observer can notice and what a drugged person can notice about himself or herself. The prior observations of Judd and Hubbard [16] were of this nature, that is, observations *about* lithium-drugged subjects which would probably not be forthcoming from the subjects themselves – i.e., "we anecdotally noted an overall dulling and blunting of various personality functions. . ." (p. 347). Needless to say, the issue of recognizing subtle drug effects is crucial for developing a comprehensive, realistic picture of what is brought about by psychotropic drugs used as medicine.

5. Limitations of drug effect descriptions while "under the influence"

Judd et al. [15] did not seek information about drug effects from subjects following discontinuation of the drug. Standard procedure in RCTs conducted for efficacy purposes suggests that "Post-treatment evaluations should be continued weekly for up to four weeks" [14, p. 369]. Such evaluations would probably suffer from the same limitations which, as we have argued, characterize evaluations during treatment, but this is difficult to assess given how *rarely* post-treatment evaluations are reported in published RCT reports. Yet, post-drug recovery descriptions of drug effects, although admittedly complicated by the necessity to draw upon memory, may add crucial information which is otherwise unavailable. Some drug effects may interfere with providing witness until the person is no longer under the influence of the drug.

Cohen [4] illustrates the importance of retrospective drug depictions from what is apparently the first use of chlorpromazine in psychiatry, in 1951, when French psychiatrist Leon Chertok injected an unspecified amount of chlorpromazine into his colleague Cornelia Quarti and voice-recorded her comments. It is evident from Quarti's written account that she drew upon the voice-recording some days later as an aid in reconstructing what she experienced on the drug, and that the consequences of chlorpromazine rendered her unable to produce a report while in the grip of the drug. Similarly, Schou's [21] descriptions of his experiences with lithium make it reasonable to wonder whether they were written after the effects of lithium wore off. Golombok, Parmala, and Lader [9] report that people who had been on long-term benzodiazepine treatment often spontaneously comment that they did not realize how psychologically impaired they had become until they had successfully withdrawn.

One need not decide which account of drug effects, contemporaneous or retrospective, is more or less trustworthy or free of bias. As Zinberg [26] has pointed out in the context of studying drug-induced alterations in consciousness, every methodological choice influences the quality and quantity of information obtained. The aim of systematic study should be to acquire information in a variety of ways, so that the complexity of the subject matter can emerge and consistencies and inconsistencies can be noted. If drug depictions when no longer "under the influence" appear inconsistent with self-reports while the drug is biologically active in the person, this feature of psychopharmacology should not be obscured but rather, made a specific object of study.

The above consideration is strikingly illustrated in a study by Healy and Farquhar of the subjective and behavioral responses of healthy volunteers randomized to either one dose of 5 mg of droperidol, 1 mg of lorazepam, or placebo and submitted to a few cognitive tests [11]. Three methods of data collection were employed, which turns out to have made all the difference in identifying the drug effects. First, experimenters directly questioned all subjects during the testing sessions and kept notes. "Second, all subjects were interviewed individually in the weeks following the testing sessions. Third, two focus groups were convened in which 12 of the 20 affected subjects participated" (p. 114). In summary, the single dose of droperidol induced akathisia in all 20 subjects, as well as various other unpleasant effects lasting for several days for some subjects, but none of the subjects on lorazepam or placebo had an adverse experience. Of relevance to our discussion, however, is that "only two of those who took droperidol reported discomfort during the testing session" in response to direct queries. The researchers challenged the other 18 subjects on the "discrepancy between their reports of no undue discomfort at the time of testing and subsequent reports of extreme distress". All 18 subjects "reported that even when they were denying discomfort they had been acutely restless, impatient or dysphoric. There was "a feeling that they didn't want to be affected and that not acknowledging a problem might help it go away". Healy and Farquhar further comment that "there appeared to be some awareness of an altered state, but an unwillingness or

inability to admit to this altered state, owing in part to the rapidity of its onset and in part to a more general difficulty in pinpointing the distinctive features of an unusual experience" (p. 116).

6. Studying psychiatric drugs as *psychotropic* drugs

Psychopharmacotherapy research understands itself as treating distinct medical (psychiatric) disorders. The focus of interest is principally on the illness, not on the host. The goal of treatment is to alleviate, reduce, control the severity of the manifest illness, operationalized as as a list of specific symptoms. The therapeutic drugs are defined in terms of their intended effects on conditions-to-be-treated (antidepressant, antianxiety, antipsychotic, etc.). It is of course appreciated that the drugs are centrally active substances, but as medications defined in terms of their ameliorating effects on specific conditions, they are hardly viewed as *psychotropic*. Unwanted drug effects are seen as inevitable, but within a framework which deflects attention once again from the drugs as psychotropic substances. It would not be an overstatement to observe that the overall psychological impact of the drugs on the host as a total biopsychosocial being, especially in the long run, is construed as essentially a *non-medical* interest [22].

Cohen [4] has pointed out that the entire distinction between main and side effects of psychopharmacological agents is a reification which depends upon slighting the social context and purpose in which a drug is used. So, for example, neuroleptic-induced akinesia and indifference may be valued by multiple parties (including the patient) during an episode of floridly psychotic agitation and ideation, and thus appear undistinguishable from a desired main "antipsychotic" effect. But as time wears on, persistent drug effects of this sort can hardly be seen as compatible with a return to, or even an approximation of, normalcy. The point is made more forcefully in Zinberg's [26] ethnographic study of the effects of heroin on consciousness. The voluntary use of psychotropic drugs outside of medicine shows how a remarkably wide range of drug effects which are manifestly impairing or distorting for most purposes in everyday life may be sought after and relished in the circumscribed context of a "drug experience". But psychiatric drug treatment is not a circumscribed drug experience. The patient is expected to live in, with, and on the total effects of the drug for long periods of time.

Nearly 40 years ago, pioneer psychopharmacologist Jonathan Cole [6] remarked that the then-recent history of therapies in psychiatry "have made psychiatrists aware that major alterations in brain function may produce a variety of end results" (p. 167), though he noted candidly that "The most impressive characteristic of the psychiatric drug literature is the absence of serious concern about adverse effects these drugs may be having upon behavior" (p. 170). We find it striking that Cole raised the exact same methodological issues we raise in our paper: that side effects are curiously seen as independent of main effects, that clinicians may miss subtle undesirable drug reactions, or attribute them to the patients' illness, or not detect reactions which occur only when the patient is at home or at work, or be mostly concerned with non-behavioral forms of toxicity (p. 171). Cole also raised the issue of the disparity between self-reports of subjects who rate themselves as more relaxed and those of significant others who observe deterioration (p. 174). Finally, he questioned the practice of giving normal subjects only a single dose of a test drug, which has no relevance to actual clinical practice (p. 179). We find it even more striking that Cole's points need to be made yet again today.

Psychiatry has attempted to "conventionalize" the use of psychotropic substances as medicine by incorporating psychotropic drug treatment research into a relatively unmodified RCT format. However, this format has serious limitations in learning to understand drug-induced psychological alterations be-

cause, in essence, *it does not direct sufficient researcher interest, effort, and ingenuity at observing and soliciting ADRs*. Specifically:

(1) subjects are not asked to provide a detailed narrative concerning the full effects of the drug, as a "drug experience";
(2) drug-induced psychological alterations of a somewhat subtle nature which the subject may not have noticed, and thus does not report, fall outside the structured data-gathering net;
(3) the typically brief duration of the study may not allow subjects sufficient time to become aware of subtle psychological deficits or impairments;
(4) the researcher has limited observational opportunities to notice various psychological reactions;
(5) no attempt is made to obtain information from people who know the subjects and can observe them under natural conditions; and
(6) retrospective, no longer "under the influence" subject depictions of drug effects are not sought.

We believe that these characteristics essentially leave the weighty question of the psychotropic drug's total psychological effects on the host *outside* the scope of inquiry. This in turn leaves the question open as to whether what appears to be drug-induced symptom alleviation should be seen as a therapeutic or a toxic effect of the drug.

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