**The 60-year old paradigm for testing psychiatric drugs should change**

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***Abstract***

*Since the 1950s, the paradigm for testing psychiatric drugs has been the double-blind, placebo-controlled trial where a psychiatrist assesses the effect using rating scales. The underlying assumptions for using this paradigm are not met. The universal use of short-term trials with ineffective blinding, subjective outcomes assessed on rating scales with unclear clinical relevance, and in patients who were already in treatment with a similar drug before randomisation, which causes harm in the placebo group because of withdrawal effects, has produced a huge literature with misleading results. Sixty years of psychiatric drug trials have been largely wasted and have resulted in tremendous harm for the patients. We explain why we need a new paradigm, with a focus on unbiased designs, objective outcomes, harms and patient views.*

*The paradigm for testing psychiatric drugs looks appealing and there has been little attention to the fact that the underlying assumptions for using it are not met, and that its use has led to tremendous harm for the patients [1-3]. We describe here the major fallacies.*

**Bias caused by the trial design**

Whether the trials are truly double-blind is so rarely discussed that current research practice resembles what Thomas Kuhn has called a period of normal science where anomalies are seen as noise rather than as falsifying the theory [4]. However, the blinding is virtually always compromised due to the conspicuous and common side effects of the drugs [3]. The fact that ineffective blinding can bias the psychiatrists’ observations so that they fit with their expectations is also ignored although the consequences can be huge. In 1964, NIMH-funded investigators reported in a large placebo-controlled trial that phenothiazines reduce apathy, improve motor movement and make patients with schizophrenia less indifferent [5], although psychiatrists had correctly reported the exact opposite a decade earlier and that these effects were harms of the drugs [6].

Another important bias in virtually all drug trials is induced because the patients were already on a similar drug before being randomised. Withdrawal symptoms are therefore inflicted on patients in the placebo group and they can include abstinence depression or psychosis [2,3,7]. Trials with washout periods before randomisation cannot avoid this problem as some drug-induced changes in the brain are irreversible, and those that are reversible may take a long time to come back to normal [2,7,8].

In addition to these important biases, the interaction between researchers and patients may not be the same in the two compared groups. This interaction, which is rarely standardized in trials, varies substantially [9]. Five of 19 principal investigators found it acceptable to encourage patients to “*vent their feelings about a current stressor”*, and ten of the researchers found it acceptable to praise patients for positive changes they have made in their lives, and behavioural advice is also common [9]. As many patients receiving an active drug experience side effects, they might spend more time with the psychiatrist talking about symptoms, thoughts, feelings and worries than patients on placebo, which could create a therapeutic relationship with the psychiatrist and thereby a form of psychotherapy. Similarly, researchers may ask patients to tell about their experiences more often if they are on active drug.

These interactions could be an important source of bias. It has been shown that the variance in the outcome depends more on the therapeutic alliance than on whether psychotherapy or pharmacotherapy was used [10]. The better the agreement between physician and patient about what is important in being cured from depression, the better the outcome with regard to positive affect, anxiety and social relationships [11]. Another study showed that one third of psychiatrists performed better with a placebo than a third of the psychiatrists did with an antidepressant [12]. The better psychiatrists were also more effective when prescribing an antidepressant [12], which indicates that the effect depended mainly on the characteristics of the psychiatrist and not on whether the drug was active or placebo.

**The fallacies in using rating scales**

Self-reports are relatively rare in psychiatric drug trials. By far, most reported data on rating scales are those generated by psychiatrists [13,14]. This suggests that psychiatrists are more trustworthy than patients but is this correct?

Since the experience of the suffering and of the effect of psychoactive drugs is subjective, the patients’ perspective should prevail. Patients also have more information than their doctors when they evaluate the outcome and they frequently report harms of the drugs [3]. Moreover, they may remember what it is like for them to be in good mental health (condition 1); they know what it is like to have a mental health problem (condition 2); and they know what it is like to be under influence of a psychoactive drug (condition 3).

In other medical domains, the researchers usually have a clear concept of what a healthy body is (condition 1) and there are often objective signs and symptoms of the disease (condition 2). A successful treatment then means that the signs and symptoms have disappeared (condition 1). In mental health, this is not the case. There are many ways of being in good mental health, and many of these might be viewed by psychiatrists as being pathological. The criteria in DSM-5 for what it means to have a mental disorder are so broad that most healthy people could get one or more diagnoses if tested according to just a few of this manual’s many disorders [3], which one of us has confirmed when testing healthy people attending courses. It is therefore problematic that researchers compare the number and severity of symptoms that many of us have on rating scales before and after the administration of a drug.

This leads us to some fundamental but overlooked problems in psychiatric research and practice. Psychiatric drugs do not improve brain functions but disable some of them [2]. This could be therapeutic if mental illness was caused by an over- or underactive brain area for which there was a specific drug that could reverse the situation. Yet, no such brain abnormalities have been found to be the cause of mental illness [2,3] and the drugs have many effects that might be labelled as healthy or unhealthy depending on the context. Therefore, it is pretty arbitrary when psychiatrists call some of these changes beneficial and others harmful; categorizing findings in this way is a normative exercise that leads to disagreements.

Further, researchers and clinicians have no data on what it means for a particular patient to be in good mental health (condition 1), and drugs that have widespread effects in the brain [2,3,15] and elsewhere in the body cannot bring the patient back to condition 1. They bring the patient to condition 3, an unknown territory where the patient has not been before. It is therefore misleading to talk about antidepressant and antipsychotic drugs, which implies that the drugs can cure the patient in a similar fashion as antibiotics cure infections.

Condition 3 is qualitatively different from conditions 1 and 2, and it is difficult to know whether it is better or worse than condition 2, or better or worse than if the patient had received placebo, no treatment or psychotherapy. The implicit assumption that the rating scales will provide the answer is flawed for several reasons.

It is implicitly assumed that when patients exhibit fewer symptoms on the chosen rating scale, they have returned towards condition 1. This assumption is unlikely to be correct, and it is also far too simplistic to focus on a rating scale result and call much else that happens for side effects that the patient will have to live with in order to obtain the assumed benefit defined by the psychiatrist. It is also doubtful to use the same scale before and after the drug is administered because condition 3 should be studied as a new, unknown state that requires an open investigation of the complex effects in areas that are not necessarily included in the items on the rating scale.

Rating scales do not measure specific drug effects. The Hamilton Depression Rating Scale, for example, contains three items on sleep, two on anxiety and one on agitation summing up to a maximum of 16 points on the 52-point scale [16]. Any sedative - including alcohol, benzodiazepines and neuroleptic drugs - would be expected to show an effect on depression using this scale because they have effects on sleep, anxiety and agitation [16]. We do not recommend alcohol because of its many other psychological and physical effects, which include the development of dependence, but exactly the same argument can be used against prescribing psychiatric drugs, as they can also cause dependence [2,3,7] and have many other unwanted and potentially dangerous effects. Another problem with the Hamilton scale is that unwanted effects such as emotional numbing and caring less for oneself and others [2,3,17,18] might cause patients to have fewer feelings of sadness and therefore a lower Hamilton score although these effects are not desirable.

The meaning of score changes is rarely discussed. Instead, conclusions of drug trials often state - even when it is totally wrong [19] - that a clinically relevant improvement in the score was obtained with no discussion about what clinical relevance means, let alone what the patients’ perspective was [20]. The results on rating scales do not have much, if any, relevance for outcomes that matter for patients whose concept of remission include functioning, coping ability, being satisfied with oneself and being able to enjoy a meaningful life [21,22].

Psychiatrists routinely use a 50% reduction in a score as a success criterion, but this approach is so problematic that it should not be used. One of the problems is that it counts the number of patients who cross a certain line for benefit and ignores the patients who get worse [14]. Therefore, any useless treatment that increases the variance in responses compared to placebo will seem effective.

Despite all the biases inherent in the trial design and the use of rating scales, the benefit from psychiatric drugs is generally so small that it is of doubtful clinical relevance [3]. In recent submissions to the FDA, neuroleptics were only 6 points better than placebo on the Positive and Negative Syndrome Scale [23] while the smallest ef­fect that can be perceived on this scale is 15 points [24]. Similarly, the effect of antidepressants is smaller than the minimally relevant effect, also for very severe depression [14].

Patient views on psychiatric drugs are less positive than those of their psychiatrists. When evaluated by psychiatrists, antidepressants seem to have a small effect on depression in children and adolescents (standardised mean difference 0.28), but not when evaluated by the patients in the same six trials (standardised mean difference 0.06) [25]. In adults, a similar discrepancy is seen [26].

We find it unlikely that drug treatment results in happier and more fulfilling lives for the patients. In fact, the sharp rise in the usage of psychiatric drugs has been accompanied by a sharp rise in number of people on disability pension because of mental health problems in all countries where this relationship has been examined [1].

**The biasing impact of the power imbalance**

The discussion of symptoms is an interpretative process where researchers and patients interact. The ineffective blinding may therefore affect not only the researchers’ ratings but also the patients’ self-reports by biases inherent in social processes.

People in distress are often unsure of what to make of their feelings [27] and depressed people have noted they have no vocabulary for it [28, 29]. They are also likely to have dealt with their distress for a while [29,30], to have felt helpless [2], to be less certain about their experiences and more eager to find a meaning [31], and to be more dependent on their doctors’ views, as also illustrated in qualitative studies (table 1) [32-34].

Because of their authority, psychiatrists have a subtle impact on participants in trials [32,35]. The power of professional language and the power to label [36] may make certain answers more likely than others. For example, rating sleep and appetite in collaboration with patients might make sleep and appetite more salient and more often reported henceforth. There is also a risk that the patients will answer the researchers’ questions in accordance with what they think the researchers would want to hear as a kind of social reinforcement. Since the patients have agreed to enrol in a trial, they are probably motivated to cooperate with the researchers, providing further grounds for socially desirable answers.

This social desirability bias would be expected to be particularly problematic in psychiatric research where the power imbalance can be extreme because forced treatment is allowed. Also in clinical practice, patients may try to fine-tune their expression of symptoms in order to be heard [37] and they may find it difficult to challenge what their doctors say [32]. Depressed patients are concerned with how others evaluate them and with being normal [32,35,38]. This could result in a kind of Hawthorne effect, in which people modify their behaviour or thoughts in response to their awareness of being observed.

Psychiatric drugs often cause sexual dysfunction [3], which illustrates how social desirability effects may influence reporting. In one study, only 6% of patients on antidepressants reported sexual dysfunction spontaneously whereas 41% had such problems when asked explicitly [39]; in another study, the numbers were 38% and 71%, respectively [40]. Sexual dysfunction is a private matter that is difficult to discuss; patients might not attribute the sexual difficulties to the drug; and they might wish to provide “good” answers to the researcher. Open-ended questions are often praised for being neutral, but such data illustrate that the interpretation of both open-ended and closed-ended questions can be difficult. Direct questions can lead to overreporting.

The power imbalance means that the researchers’ observations and interpretations are prioritized over the patients’ perspective. It is therefore very difficult to produce results in support of the null hypothesis of no drug effect. Even when patients’ self-reports clearly show that the drugs do not work, the psychiatrists routinely ignore this, report a therapeutic effect according to themselves, and prescribe the useless drugs [3,14,25,26].

Not uncommonly, the power imbalance leads to outright arrogance. In a survey of 493 patients with closed-ended questions, 82% agreed that, “*As long as you are taking antidepressants you do not really know if they are actually necessary*” [41]. Around 40 % of the patients agreed that the treatment could alter their personality and that they had less control over their thoughts and feelings. The psychiatrists refused to believe what the patients had told them; they called them ignorant and negative and felt they needed “psychoeducation.”Yet, their partners had the same opinion as the patients about antidepressants.

**Medication spellbinding**

Psychoactive drugs may increase the patients’ confusion [2], and patients may feel uncertain about the validity of their own decisions in relation to antidepressant use because both depression and antidepressants change the way a person feels about themselves and their world [33].

Psychoactive substances may render the patients totally unaware of the fact that they can no longer think clearly or evaluate themselves. This lack of insight into their feelings, thoughts and behaviours is called intoxication anosognosia, or medication spellbinding [2,42]. Medication spellbinding is usually ignored, both by the patients and their doctors, which is surprising as the effects of marijuana are well known and as everybody knows that people who have drunk too much alcohol cannot judge their ability to drive. Patients taking psychiatric drugs may act violently in an out of character fashion and may only understand that this was due to the drugs after they have come off them [2,3,7,42,43]. Children and adolescents receiving SSRIs may experience apathy accompanied by a lack of insight, which increase with increasing doses [44–46]. Even patients with tardive dyskinesia caused by neuroleptics very often lack insight about this [2,47] and it is also frequently overlooked by their psychiatrists [2,3].

The main biasing effect of medication spellbinding probably is that the harms of psychiatric drugs are underestimated.

**Harms of the biomedical model**

In the psychological literature, being uncertain about one’s feelings and engaging in interpretative work on negative thoughts and feelings is a response style called rumination, and it is considered a characterizing mechanism in depression [48]. Since offering interpretations to ruminating patients may temporarily relieve their distress [48], patients may readily accept these interpretations regardless of their meaningfulness for the patients’ lives and experiences. When the predominating paradigm among psychiatrists is the biomedical model, it is not surprising that patients may have a medical understanding of their disorder, e.g. that it is being caused by a chemical imbalance in the brain or a gene defect, and that a drug may fix their problem.

This influence on patients is unfortunate, as psychiatrists generally hold scientifically unsupported beliefs about causes [2,3]. Only 0.4% of 2813 British psychiatrists believed that schizophrenia primarily has social causes; around half believed it primarily has biological causes while another half believed it to be a balance between biological and social causes [50]. In contrast, those diagnosed with schizophrenia primarily listed psychosocial causes like pressure at work or school, parental style in childhood, personality factors, family conflicts and psychological trauma [51, 52]. Another survey found that 75% of psychiatrists endorsed heredity as a cause of schizophrenia (and 66% endorsed stress as a cause) [53]. Yet, no convincing biological or genetic abnormalities, which psychiatrists tend to emphasize, have ever been found to characterize the most common mental disorders [2,3,7]. The evidence clearly shows that the psychosocial factors that patients and the general public emphasize [3] are important, e.g. adverse childhood experiences are associated with a high risk of psychosis and displays a marked dose-response relationship [54].

It has never been shown in reliable research that patients become ill because they have a chemical imbalance in the brain, and it is not even remotely likely that this is the case [3]. Nonetheless, psychiatrists often tell this myth to their patients, for all kinds of mental disorders [3,55], and in one survey, 80% of the patients affirmed that “*Antidepressants correct the changes that occurred in my brain due to stress or problems*” [41]. This myth is very harmful. When patients with a past or current depression received a bogus test showing that their depression was caused by a chemical imbalance in the brain, they experienced more prognostic pessimism, expected to be less able to regulate negative mood, and viewed pharmacotherapy as more likely to be effective than psychotherapy [56].

Taking a pill might elicit beliefs that are consistent with pill-taking behaviour in general to avoid cognitive dissonance [57] but in psychiatry, these beliefs are often harmful. Taking a pill “to correct a chemical imbalance” might teach patients new ways of interpreting their experiences, e.g. women beginning to take SSRIs showed a pattern of phases, which entailed redefining themselves as people with a biochemical disease [35,58].

It seems that all psychoactive drugs can cause dependence and abstinence symptoms [2,3,7], which, somewhat ironically, *is* a truly biomedical phenomenon, which might be called a iatrogenic, artificial chemical imbalance. Many patients have difficulty stopping their medication [2,3,7,32,33,41,58]. The psychological dependency can also be important and some patients refer to the chemical imbalance in their brain as the reason for not stopping [59] - not as something their psychiatrist has inflicted on them but as the cause of their disorder.

**A new paradigm for psychiatric drug trials**

The universal use of the short-term, placebo-controlled trial of psychiatric drugs with ineffective blinding, subjective outcomes assessed on rating scales with unclear clinical relevance, and in patients who were already in treatment with a similar drug before randomisation has produced a huge literature with misleading results, which has harmed patients immensely [1-3]. This must stop.

As noted above, patients are in a psychologically abnormal state when they enter a drug trial; during the trial they are in a socially abnormal state talking to a researcher about their mental lives; and when the effect is being evaluated, they are in a biologically abnormal state because they are taking a psychoactive drug. Clearly, when the patients feel uncertain about their introspection so should the researchers who interpret what happens.

The bias caused by lack of blinding has been assessed in systematic reviews of trials in all diseases that had both a blinded and a non-blinded observer. It was 36%, on average, measured as the odds ratio [60], and 68% when the outcome was assessed on a scale [61]. We should ensure that the trials are better blinded. When the placebo contained atropine, which gives similar side effects as antidepressants, not even the psychiatrists were able to record any benefit from the drugs [3,62]. To avoid cold turkey effects, we should also ensure that only treatment-naïve patients are recruited.

We therefore raise two testable hypotheses: Are the relatively small beneficial effect of psychoactive drugs observed in trials spurious? Do these drugs have any genuinely helpful effects, on average?

We should require outcomes that matter to patients and which are not subjective and prone to bias. As important outcomes, patients mention quality of relationships, return to normal levels of functioning and quality of life [21,22,63,64]. In DSM-5, major depression is present when the patient exhibits 5 or more of 9 possible symptoms that *“cause clinically significant distress or impairment in social, occupational, or other important areas of functioning*” [65]. Given how the disorder is defined, it makes little sense that drug trials do not use the same outcomes. The same argument can be used for trials of other psychoactive drugs.

Quality of life combines the patients’ perception of the benefits and harms of drugs while avoiding reports about their emotional life, which may be confusing for patients in distress. It should be interpreted cautiously, however, as it is a self-report measure that can be influenced by social desirability bias, the power imbalance, and other biases, which include selective reporting. At our centre, we looked at 70 antidepressant trials [64,381 pages of clinical study reports we obtained from the European Medicines Agency) [66] and found that selective reporting of quality of life is extensive, not only in published trial reports but even within the study reports [67). We also found that 12% more patients drop out of the trials when they are on a drug than when they are on placebo, which means that the patients think placebo is a better pill than the drug [67,68]. This, and other evidence, e.g. the harmful effect of the pills on people’s sex life [3], makes it highly likely that quality of life is worse on an antidepressant drug than on placebo. More generally, we have not found any reliable research that suggests that quality of life is improved when patients come on psychoactive drugs.

The most important of all outcomes - suicide attempts, suicides and other deaths - have often been selectively reported [1,3,69]. Currently, only about half of deaths and suicides that occur in trials of psychoactive drugs are reported in medical journals [70]. We must ensure full reporting of all results and access to anonymised raw data. Until that happens, it can be useful to review critically the trials already carried out despite all their flaws. We have recently found, for example, that antidepressants increase the risk of suicide at all ages [71,72], which was confirmed in a 2019 meta-analysis of FDA data [73]; that SSRIs increase aggression in children and adolescents [74], which is an important finding considering the many school shootings where the killers were on SSRIs; and that behavioural psychotherapy halves the risk of a new suicide attempt in people acutely admitted after a suicide attempt [75].

**Implications for the use of psychoactive drugs**

Considering all the substantial biases in psychiatric drug trials, it is a strong finding when patients say that their drugs do not work. It is also a strong finding when psychiatrists report effects in trials of antidepressants and neuroleptics on rating scales that are lower than what is clinically relevant. We believe similar arguments can be raised against all psychoactive drugs.

Therefore, also considering the many serious harms of psychiatric drugs, which we still know too little about because the vast majority of trials are short-term and the harms are selectively reported, it would be rational to reduce their use to a minimum, in acute situations and only if the patients agree to being treated. Forced treatment cannot be defended scientifically, legally or ethically and must stop [3].

The prevailing paradigm has not served psychiatry well [76], and we have explained why. We have suggested improvements in trial designs and clinical practice and that a totally new paradigm is needed.

Table 1. Quotes from qualitative studies of patients with depression.

*“Most of the participants found it difficult – and sometimes impossible – to challenge the therapist’s authority during the consultations: ‘When I sit in front of a doctor or someone with great knowledge, well, then I believe all that’s being said’”* [32].

“*The participants’ perspectives … were characterized by continual uncertainty regarding depressive symptoms and the effects of the medicine, which required extensive – and sometimes anxiety provoking – interpretative work”* [32].

“*they struggled to determine the extent to which they should rely on their judgments about the value of antidepressants or accept the expertise of others to do this for them”* [33].

“*A striking theme throughout the data was patient uncertainty about whether taking SSRI medication had led to an improvement in health”* [34].

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