Twenty-nine legal ways to distort the results of a randomized controlled trial

1) A biased sponsor (a drug company) is looking for compliant investigators who will produce the desired results. Roughly 90% of clinical trials are sponsored by the private industry (are biased from the start).

https://clinicaltrials.gov/

Amsterdam JD, McHenry LB, Jureidini JN: Industry-corrupted psychiatric trials. *Psychiatr Pol* 2017, **51**(6):993–1008.

Spielmans GI, Parry PI: From evidence-based medicine to marketing-based medicine: evidence from internal industry documents. *Bioethical Inquiry* 2010, **7**:13–29.

Jureidini J, McHenry LB: The illusion of evidence based medicine. *BMJ*, 2022, https://doi.org/10.1136/bmj.o702

The sponsor (drug company) is a client of a contract research organization (CRO), which often conducts a trial for the drug company. Thus, the CRO aims to please the client and cannot be trusted to obtain unbiased results. **The sponsor typically gets the results that it paid for.**

Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S: Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006, **163**(2):185–194.

Oostrom T: Funding of clinical trials and reported drug efficacy. *Journal of Political Economy* 2024, **132**(10):3298–3333.

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L: Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2017, **2**(2):MR000033.

Turner E: Unraveling the Bundles of Research Bias: Is What you Read the Truth, the Whole Truth and Nothing but the Truth? *Mad in America Continuing Education*, Accessed October 7, 2018.

Wang AT, McCoy CP, Murad MH, Montori VM: Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. *BMJ* 2010, **340**:c1344.

Sismondo S: Epistemic corruption, the pharmaceutical industry, and the body of medical science. *Front Res Metr Anal* 2021, **6**:614013.

2) As a consequence of #1, people writing the research article are under pressure to put a positive spin on the results. **The abstract embellishes or distorts the results in the main text.**

Boutron I, Dutton S, Ravaud P, Altman DG: Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA* 2010, **303**(20):2058–2064.

Alasbali T, et al.: Discrepancy between results and abstract conclusions in industry – vs nonindustry-funded studies comparing topical prostaglandins. *Am J Ophthalmol* 2009, **147**(1):33–38.e2.

3) The Results section embellishes or distorts the actual raw data.

Boutron I, Dutton S, Ravaud P, Altman DG: Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA* 2010, **303**(20):2058–2064.

4) The original raw data in a clinical trial are often inaccessible (kept secret permanently), thus enabling #2 and #3 above.

Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G: Open clinical trial data for all? A view from regulators. *PLoS Med* 2012, **9**(4):e1001202.

Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, Abi-Jaoude E: Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015, **351**:h4320.

5) Incorrect selection of patients for the trial; to be precise, participants in a typical clinical trial are not representative of the general population of patients: the trial participants will be taking only one drug and currently have only one disease. Only 5-15% of real-world patients are allowed to participate in a trial because eligibility criteria are too strict. A substantial percentage of real-world patients have several diseases and take three or more medications. Adverse effects of these drugs are later treated with additional drugs. **Therefore, the results of most trials are not applicable to real-world patients.**

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

Rothwell PM: External validity of randomised controlled trials: 'To whom do the results of this trial apply?' *Lancet* 2005, **365**(9453):82–93.

6) Selective publication of clinical trials (not publishing trials that yield negative results: so-called publication bias).

Stefaniak JD, Lam TCH, Sim NE, Al-Shahi Salman R, Breen DP: Discontinuation and non-publication of neurodegenerative disease trials: a cross-sectional analysis. *Eur J Neurol* 2017, **24**(8):1071–1076.

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R: Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008, **358**(3):252–260.

Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B: Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003, **326**(7400):1171–1173.

Howland RH: Publication bias and outcome reporting bias: agomelatine as a case example. *J Psychosoc Nurs Ment Health Serv* 2011, **49**(9):11–14.

Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T, Kerekes MF, Gerken M, Wieseler B: Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010, **341**:c4737.

Turner EH, Knoepflmacher D, Shapley L: Publication bias in antipsychotic trials: an analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Med* 2012, **9**(3):e1001189.

Ghaemi SN: The failure to know what isn't known: negative publication bias with lamotrigine and a glimpse inside peer review. *Evid Based Ment Health* 2009,**12**(3):65–68.

7) Measurement of parameters that do not matter to patients (so-called surrogate measures), to make a useless drug appear beneficial. For example, a drug can be approved for cancer treatment if it shrinks the tumor, even if it worsens quality of life and does not extend life.

Shaughnessy AF, Slawson DC: What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes. *BMJ* 2003, **327**(7409):266.

Nilsson S, Mölstad S, Karlberg C, Karlsson JE, Persson LG: No connection between the level of exposition to statins in the population and the incidence/mortality of acute myocardial infarction: an ecological study based on Sweden's municipalities. *J Negat Results Biomed* 2011, **10**:6.

8) Presentation of relative metrics not absolute results. Relative metrics look much more impressive. For example, you may see in a scientific article that "addition of radiotherapy to surgery offers a relative reduction of recurrence risk by 20%." Sounds great! But if you look at absolute metrics, this result is modest: The risk of recurrence of 5% is reduced to 4%. In other words, 100 people should suffer the adverse effects of radiotherapy in vain to prevent 1 case of cancer recurrence. The risks are not worth the tiny benefit. I used to get a flu shot every year in the fall until I looked at the evidence. I was appalled to find that virtually all studies about the effectiveness of influenza vaccines present the results in the deceptive relative way, by showing a relative risk reduction instead of absolute numbers. The absolute risk reduction is ridiculously small: an approximately 2% incidence of influenza is reduced to a 1% incidence. To be precise, 71 people should get a flu shot to prevent one case of influenza, assuming that the presented data are 100% truthful (unrealistic assumption). You should also keep in mind that dozens of other viruses cause influenza-like illnesses against which this vaccine cannot work. Furthermore, these effectiveness studies show that flu vaccines have failed to provide any benefit in some seasons and do not help some segments of the population.

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

Diamond DM, Ravnskov U: How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol* 2015, **8**(2):201–210.

Cochrane Review: Vaccines to prevent influenza in healthy adults. 2016. https://www.cochrane.org/CD001269/ARI_vaccines-prevent-influenza-healthy-adults

9) Other unusual ways to analyze the data to hide adverse effects or exaggerate benefits.

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

Montori VM, Jaeschke R, Schünemann HJ, Bhandari M, Brozek JL, Devereaux PJ, et al.: Users' guide to detecting misleading claims in clinical research reports. *BMJ* 2004, **329**(7474):1093–1096.

Safer DJ: Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *J Nerv Ment Dis* 2002, **190**(9):583–592.

Gilbody S, Wahlbeck K, Adams C: Randomized controlled trials in schizophrenia: a critical perspective on the literature. *Acta Psychiatr Scand* 2002, **105**:243–251.

10) Trying to explain the lack of effectiveness of a drug by an "unusually strong placebo effect." Accordingly, the drug companies then design clinical trials that try to exclude "placebo-responders" or minimize their effect on the final results: the so-called sequential parallel comparison design. Incidentally, the placebo effect does not exist, it is fully explained by random changes in the state of health and by the natural course of a disease. Therefore, there is no such thing as "placebo responders."

Hróbjartsson A, Gøtzsche PC: Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010, (1):CD003974.

Hróbjartsson A, Gøtzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001, **344**(21):1594–1602.

11) Failing to mention that the use of a placebo is an imperfect and inexact method. Patients often guess correctly that they are in the active-drug group because of the adverse effects of the drug. Blinding of investigators is not perfect either and usually fails because experienced physicians know the typical adverse effects and easily identify the patients taking the active drug. Therefore, double-blind randomized clinical trials should not be presented as rigorous and mathematically exact scientific proof. Additionally, because there is no such thing as a placebo effect, patients do not need to be blinded regarding which treatment they get. A no-treatment control group known to patients can be used when possible.

Hróbjartsson A, Gøtzsche PC: Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010, (1):CD003974.

Hróbjartsson A, Gøtzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001, **344**(21):1594–1602.

Kirsch I: The emperor's new drugs: medication and placebo in the treatment of depression. *Handb Exp Pharmacol* 2014, **225**:291–303.

12) Ghostwriting of scientific articles. Let's say a pharmaceutical company conducts a clinical trial through a contract research organization (CRO) and wants to publish the results. If it shows the real authors of the clinical trial, then the readers will not take the findings seriously because all the authors have massive conflicts of interest: they are employees of the drug company and CRO. To give more scientific weight to the research article, the drug company hires fake authors, i.e., academic physicians who work at a university and are not affiliated with the drug company. Now 10 to 20 independent respectable scientists appear as coauthors of the article, along with one or two real authors (employees of the private industry).

Amsterdam JD, McHenry LB, Jureidini JN: Industry-corrupted psychiatric trials. *Psychiatr Pol* 2017, **51**(6):993–1008.

Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, Abi-Jaoude E: Study 329 continuation phase: Safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression. *Int J Risk Saf Med* 2016, **28**(3):143–161.

13) Comparison with a wrong dose of another drug. The dose of the comparison drug is set too high if the drug company is trying to show that its product is safer, or the dose of the comparison drug is set too low when the drug company is trying to prove that its product is more effective.

Safer DJ: Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *J Nerv Ment Dis* 2002, **190**(9):583–592.

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

14) Miscoding of data. In a clinical trial of an antidepressant, patients may drop out for various reasons. Let's say a patient commits suicide and she simultaneously had complaints of nausea. The drug company can register only nausea as an adverse effect and the reason for the dropout. This is a good way to hide serious adverse effects.

Maund E, Tendal B, Hróbjartsson A, Lundh A, Gøtzsche PC: Coding of adverse events of suicidality in clinical study reports of duloxetine for the treatment of major depressive disorder: descriptive study. *BMJ* 2014, **348**:g3555.

Healy D: Time to abandon evidence-based medicine? *YouTube.com*, at 12 min in the video. Accessed December 26, 2017.

15) Mislocation of data. Adverse events that did not occur in the placebo group during the trial are falsely assigned to the placebo group. For example, before the trial, there is often a "washout" period, when the patients stop taking previously taken drugs and stay without any drugs for some time, so that the effects of the drug being tested are not mixed with the effects of the previously taken drug. Adverse events such as suicide that occur during this washout period will be incorrectly assigned to the placebo group by the drug company, even though the placebo treatment has not started yet. Similarly, after the trial, a patient from the placebo group may be put on some drug and will commit suicide. The drug company will falsely assign this suicide to the placebo group, so that the placebo group looks worse than the treatment group. Through mislocation and miscoding of data, adverse events are made to appear statistically insignificant. A drug company adds just enough false adverse events into the placebo group to make the difference between the placebo group and treatment group statistically insignificant (in terms of the adverse events). Readers of the study see that there is an increase in the number of adverse effects with the drug, but the drug company convinces the readers that this finding is an illusion because it is not statistically significant.

Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, Abi-Jaoude E: Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015, **351:**h4320.

Healy D: Time to abandon evidence-based medicine? *YouTube.com*, At 12 min 30 sec in the video. Accessed December 26, 2017.

16) Misrepresenting adverse effects of drugs as symptoms of the disease. Drug companies claim that suicide is a symptom of depression not the effect of their drugs. As pointed out by David Healy, clinical trials yield misleading results when both the drug and disease cause the same symptom. Through key opinion leaders, drug companies also have propagated the notion that cognitive deficits and flat affect are negative symptoms of schizophrenia rather than adverse effects of neuroleptic drugs. This notion is now in textbooks.

Not so bad pharma. David Healy's review of the book Bad Pharma by Ben Goldacre.

Lacasse JR, Leo J: Serotonin and depression: a disconnect between the advertisements and the scientific literature. *PLoS Med* 2005, **2**(12):e392.

Albert N, Randers L, Allott K, Jensen HD, Melau M, Hjorthøj C, Nordentoft M: Cognitive functioning following discontinuation of antipsychotic medication. A naturalistic sub-group analysis from the OPUS II trial. *Psychol Med* 2019, **49**(7):1138–1147.

Allott K, Yuen HP, Baldwin L, O'Donoghue B, Fornito A, Chopra S, Nelson B, Graham J, Kerr MJ, Proffitt T, Ratheesh A, Alvarez-Jimenez M, Harrigan S, Brown E, Thompson AD, Pantelis C, Berk M, McGorry PD, Francey SM, Wood SJ: Antipsychotic effects on longitudinal cognitive functioning in first-episode psychosis: a randomized, triple-blind, placebo-controlled study. *medRxiv*, 2022, posted February 21, https://doi.org/10.1101/2022.02.16.22271103

17) Misrepresenting withdrawal effects of a drug as a relapse of the disease; alternatively, **the use of abrupt discontinuation of a drug** (with the ensuing withdrawal effects) **to make the placebo group look worse than the treatment group**. This method also helps to hide adverse effects of a drug.

Tsai AC, Rosenlicht NZ, Jureidini JN, Parry PI, Spielmans GI, Healy D: Aripiprazole in the maintenance treatment of bipolar disorder: a critical review of the evidence and its dissemination into the scientific literature. *PLoS Med* 2011, **8**(5):e1000434.

Récalt AM, Cohen D: Withdrawal confounding in randomized controlled trials of antipsychotic, antidepressant, and stimulant drugs, 2000-2017. *Psychother Psychosom* 2019, **88**(2):105–113.

Moncrieff J, Jakobsen JC, Bachmann M: Later is not necessarily better: limitations of survival analysis in studies of long-term drug treatment of psychiatric conditions. *BMJ Evid Based Med* 2021, doi: 10.1136/bmjebm-2021-111743

18) Changing the declared hypothesis of the study after completion of the trial and the result is negative. One hypothesis (so-called primary endpoint) is declared during registration of a trial with the government. Let's say a clinical trial measures 15 clinical parameters in patients, and there are four methods to analyze statistical significance of the results. To obtain regulatory approval of the drug, one of these 15 clinical parameters must be declared as the main hypothesis (primary

endpoint) before the trial. Suppose the main hypothesis turned out to be wrong after the trial is completed (according to all four methods of statistical analysis). In other words, the clinical trial yielded a negative result and the government agency will not approve this drug for this disease. Not to worry, the sponsors of the trial still have 56 more ways to win (15 x 4 = 60 combinations and minus 4). Because many different parameters are measured during the clinical trial, some of them will improve by chance. When the trial is published in a scientific journal, the authors falsely claim that they had a different hypothesis; they do not report the negative result, and instead they report this accidental positive result. (This approach is forbidden for obtaining approval of the FDA but is allowed for publication in a scientific journal.) Because of the way statistical significance is measured traditionally, one of 20 trials will produce a random meaningless but statistically significant result. Thus, in a clinical trial, the sponsors can obtain three statistically significant results automatically by design (15 x 4 = 60 combinations divided by 20). These results are most likely random and meaningless, but they will be reported as a real clinical finding. As you will see in the next trick, the sponsors/investigators actually have far more ways to win and can publish 20 to 50 original research papers from a single trial. The vast majority of these "scientific" findings of course are accidental and do not mean anything, but they serve as deceptive advertising for the drug in question. They can also be used to justify off-label prescription of the drug in question.

Roest AM, de Jonge P, Williams CD, de Vries YA, Schoevers RA, Turner EH: Reporting bias in clinical trials investigating the efficacy of second-generation antidepressants in the treatment of anxiety disorders: a report of 2 meta-analyses. *JAMA Psychiatry* 2015, **72**(5):500–510.

McGauran N, Wieseler B, Kreis J, Schüler YB, Kölsch H, Kaiser T: Reporting bias in medical research - a narrative review. *Trials* 2010, **11**:37.

Bourgeois FT, Murthy S, Mandl KD: Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med* 2010, **153**(3):158–166.

Lancee M, Lemmens CMC, Kahn RS, Vinkers CH, Luykx JJ: Outcome reporting bias in randomized-controlled trials investigating antipsychotic drugs. *Transl Psychiatry* 2017, **7**(9):e1232.

19) Analysis of subsets of patients with certain characteristics (so-called subgroup analysis). In this way, you can always find something positive in a trial that produced a negative result. Let's say you can find 10 subgroups in your study population of 1000 people (women who have had only one child, white males between ages of 40 and 50 who never smoked, etc.). Continuing our example from the previous trick, now we have 600 combinations (15 x 4 x 10) and approximately 30 of them will yield a statistically significant result automatically by design (600 divided by 20). Thus, 30 positive research articles can be published from a single clinical trial (this is so-called salami slicing). Virtually all these findings are due to chance, but the readers of these scientific studies will be led to believe that these are real benefits of the drug in question.

Spielmans GI, Biehn TL, Sawrey DL: A case study of salami slicing: pooled analyses of duloxetine for depression. *Psychother Psychosom* 2010, **79**(2):97–106.

20) Clinical trials can be combined by enrolling the same patients in two or more trials. Adverse events in the treatment group of the first trial will be assigned to the placebo group in the second trial because those patients will be assigned to the placebo group in the second trial. Thus, the adverse events in this spurious placebo group will seem to be as bad as those in the treatment group. This is a good way to hide adverse effects of a drug. Using this technique, drug companies successfully obfuscated the fact that antidepressant drugs increase the risk of suicide. (That the name "antidepressants" is incorrect—because these drugs worsen depression and make it chronic—is a separate topic, see the next point.)

Healy D: Time to abandon evidence-based medicine? *YouTube.com*, At 42 min in the video. Accessed December 26, 2017.

Whitaker R: Do Antidepressants Work? A People's Review of the Evidence. Madinamerica.com, March 11, 2018.

Amendola S, Plöderl M, Hengartner MP: Did the introduction and increased prescribing of antidepressants lead to changes in long-term trends of suicide rates? *Eur J Public Health* 2020, doi: 10.1093/eurpub/ckaa204

Turabian J: Psychotropic drugs originate permanent biological changes that go against resolution of mental health problems. A view from the general medicine. *J of Addict Dis & Ment Heal* 2021, **1**(3):1–5.

Vittengl JR: Poorer long-term outcomes among persons with major depressive disorder treated with medication. *Psychother Psychosom* 2017, **86**(5):302–304.

Lagerberg T, Matthews AA, Zhu N, Fazel S, Carrero JJ, Chang Z: Effect of selective serotonin reuptake inhibitor treatment following diagnosis of depression on suicidal behaviour risk: A target trial emulation. Neuropsychopharmacology. *Neuropsychopharmacology* 2023, doi: 10.1038/s41386-023-01676-3

Plöderl M, Amendola S, Hengartner MP: Observational studies of antidepressant use and suicide risk are selectively published in psychiatric journals. *J Clin Epidemiol* 2023, doi: 10.1016/j.jclinepi.2023.07.015

21) Incorrect duration of a clinical trial. For example, clinical trials of antidepressants usually do not last more than 6 weeks, but they are prescribed to real-world patients for several years, even for life. The drug company can also choose the duration of a trial so that the benefits exceed the adverse effects if it is known in advance that adverse effects appear much later than the beneficial effects or vice versa. Brilliant journalist Robert Whitaker made a frightening discovery: short-term clinical trials of antipsychotic drugs (~6 weeks) show a small benefit, whereas long-term outcomes of treatment with antipsychotics (1-3 years) are dismal: many or even most of unmedicated patients fully recover after the first psychotic episode, as compared to only a small minority of medicated patients. In other words, antipsychotic drugs make schizophrenia chronic.

http://pubmed.gov/30862219/ http://pubmed.gov/27269768/ http://pubmed.gov/28277310/ http://pubmed.gov/22130905/ http://pubmed.gov/21920710/ http://pubmed.gov/23824214/ http://pubmed.gov/25066792/ http://pubmed.gov/17502806/ http://pubmed.gov/17360921/ http://pubmed.gov/12796222/ http://pubmed.gov/21300943/ http://pubmed.gov/1565705/ http://pubmed.gov/6101522/ http://pubmed.gov/352976/ http://pubmed.gov/12695732/

http://pubmed.gov/831535/ http://pubmed.gov/167596/ https://doi.org/10.1093/schizbullopen/sgad032 http://pubmed.gov/38021372/ http://pubmed.gov/38647464/

Because most of clinical trials show only a small benefit of antipsychotics short-term, hardly different from a placebo, this small benefit should be correctly interpreted as negative efficacy owing to the numerous distortions described in this document. It can be concluded that the name “antipsychotic drug” is incorrect because these chemicals worsen psychosis (despite temporary sedation) and make psychosis chronic. The main cause of chronic schizophrenia is antipsychotic drugs (my conclusion). Robert Whitaker has also found a ton of scientific literature showing that antidepressant drugs make depression chronic:

http://pubmed.gov/4700934/ http://pubmed.gov/1417430/ http://pubmed.gov/15219472/ http://pubmed.gov/20616621/ http://pubmed.gov/16699380/ http://pubmed.gov/7915039/ http://pubmed.gov/8559954/ http://pubmed.gov/10221291/ http://pubmed.gov/12633120/ http://pubmed.gov/21459521/ http://pubmed.gov/7625458/ http://pubmed.gov/9463600/ http://pubmed.gov/10198504/ http://pubmed.gov/10771465/ http://pubmed.gov/15518594/ http://pubmed.gov/18087204/ http://pubmed.gov/21328195/ http://pubmed.gov/21779273/ http://pubmed.gov/28903116/ http://pubmed.gov/29680831/ http://pubmed.gov/30853919/ http://pubmed.gov/31205190/ http://pubmed.gov/37491091/

and because short-term effects of antidepressants (~6 weeks) are almost indistinguishable from a placebo, these drugs must have negative efficacy short-term if we take into account the numerous distortions of clinical findings. Consequently, the name “antidepressant” is incorrect because these chemicals do the opposite. The main cause of chronic depression is antidepressant pills (my conclusion).

Kirsch I: The emperor's new drugs: medication and placebo in the treatment of depression. *Handb Exp Pharmacol* 2014, **225**:291–303.

Gøtzsche PC, Young AH, Crace J: Does long term use of psychiatric drugs cause more harm than good? *BMJ* 2015, **350**:h2435.

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

Sharma T, Guski LS, Freund N, Meng DM, Gøtzsche PC: Drop-out rates in placebo-controlled trials of antidepressant drugs: A systematic review and meta-analysis based on clinical study reports. *Int J Risk Saf Med* 2019, **30**(4):217–232.

Gøtzsche PC and Healy D: Restoring the two pivotal fluoxetine trials in children and adolescents with depression. *Int J Risk Saf Med* 2022, **33**:385–408.

Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA: The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* 2022, doi: 10.1038/s41380-022-01661-0

Moncrieff J, Cooper RE, Stockmann T *et al.* The serotonin hypothesis of depression: both long discarded and still supported? *Mol Psychiatry* 2023, doi: 10.1038/s41380-023-02094-z

Additionally, Robert Whitaker has compiled lists of studies showing that stimulants and benzodiazepines do more harm than good in the long run.

Whitaker R: Thomas Insel Makes A Case for Abolishing Psychiatry. Subsection "The Research That Insel Dared Not Mention" Madinamerica.com, April 30, 2022.

Consistently with these observations, renowned psychiatrist Peter Breggin has stated on many occasions that psychiatric drugs are neurotoxins and cause all kinds of abnormal thinking and behavior (he is talking about human-invented [patented] chemical psychiatric drugs; there is no reason to believe that this is true for herbs, e.g., valerian and St. John's wort).

Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W: 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol (Phila)* 2018, **56**(12):1213–1415.

WARNING: Although chemical psychiatric drugs are harmful, they should not be discontinued abruptly because they cause dependence, and sudden quitting will cause even more harm. Slow tapering of the dose is needed (at least 3-4 months), and several drugs can be discontinued simultaneously. In my experience, sedative herbs and adaptogens (e.g., ginseng) do not cause dependence and withdrawal symptoms even after many months of daily use.

Given that most of current medical knowledge is badly distorted, the effects opposite to "widely known benefits" are likely to be true for many other drugs and medical interventions: statins worsen cardiovascular diseases and overall health, metformin worsens diabetes and makes it chronic, etc.

Diamond DM, Ravnskov U: How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol* 2015, **8**(2):201–210.

Nilsson S, Mölstad S, Karlberg C, Karlsson JE, Persson LG: No connection between the level of exposition to statins in the population and the incidence/mortality of acute myocardial infarction: an ecological study based on Sweden's municipalities. *J Negat Results Biomed* 2011, **10**:6.

22) Stopping a trial too early or too late (compared to the approved protocol). This approach can help to find a random combination of results that is better than the results that will be obtained when the protocol is followed exactly. This approach can also help to hide adverse effects.

Goldacre B: Bad Pharma. 2013. *Farrar, Straus and Giroux*, 448 pp.

Califf RM, DeMets DL: Principles from clinical trials relevant to clinical practice: Part I. *Circulation* 2002, **106**(8):1015–1021.

Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH: Ethical issues in stopping randomized trials early because of apparent benefit. *Annals Internal Med* 2007, **146**(12):878–881.

Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al.: Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010, **303**(12):1180–1187.

Montori VM, Devereaux PJ, Adhikari NKJ, Burns KEA, Eggert CH, Briel M, et al.: Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005, **294**(17):2203–2209.

Lurie P, Wolfe SM: Misleading data analyses in salmeterol (SMART) study. *Lancet* 2005, **366**(9493):1261–1262.

23) Misrepresenting statistical significance as clinical significance when the effect size is too small. In such cases, the study may say that the effect is "significant" but there is no discussion of effect size and clinical significance.

Kirsch I: The emperor's new drugs: medication and placebo in the treatment of depression. *Handb Exp Pharmacol* 2014, **225**:291–303.

Gøtzsche PC, Young AH, Crace J: Does long term use of psychiatric drugs cause more harm than good? *BMJ* 2015, **350**:h2435.

24) Analyzing only the patients that completed the trial. If all the patients are included in the final analysis, both those that dropped out and those that finished the clinical trial, then the results will be less impressive.

Turner E: Unraveling the Bundles of Research Bias: Is What you Read the Truth, the Whole Truth and Nothing but the Truth? *Mad in America Continuing Education*, Accessed October 7, 2018.

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25) During publication of a multicenter trial: **inclusion of data from a site that was disallowed by the FDA.**

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26) Seeding trials. The real purpose of such clinical trials is not rigorous testing of a drug, but to let as many physicians know about this drug as possible. It's a purely marketing device. In this scenario, the trial includes too many principal investigators and too many small sites (each physician tests the drug only on a few patients).

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30) Changing the definition of the disease after the clinical trial. In this way, some patients can be shifted from the control group to the active-treatment group or vice versa. This approach can make the results look better than they are.

https://tinyurl.com/y3ed3rgc

Conclusions

1) A double-blind randomized controlled trial does not prove anything.

2) Systematic reviews and meta-analyses that have been published to date cannot be taken seriously because they are based on the worst evidence: short-term small changes in symptoms. The best evidence deals with full recovery from a disease after one or more years of treatment as compared to no treatment. Examples of the best evidence: http://pubmed.gov/10368805/ and http://pubmed.gov/17283741/

3) The use of placebos in clinical trials is unscientific and should be discontinued. A no-treatment control is ethical because the usefulness of almost all known medical interventions is unproven.

4) Small-to-moderate effect sizes reported in published clinical trials can be interpreted with high probability as negative efficacy. Huge effect sizes and huge clinical benefits, when confirmed independently, may be true because they cannot be faked so easily. Results of clinical trials may also be true if they involve interventions that have no commercial value (e.g., physical exercise, dietary changes, and other lifestyle modifications) and offer no benefits to the ruling elite (such as funding for government agencies, preservation of government agencies, expansion of the government, a restriction of civil liberties that is widely supported by mass media, and coercive medical procedures widely promoted by mass media, big scientists, and government officials).

5) It appears that statistical methods are not needed to prove that a cancer treatment works. For instance, such a method can be considered effective if in at least one in 10 patients it causes a full recovery (the absence of cancer and a good general state of health) in 5 years or sooner, so that the person is still healthy and cancer free at the 5-year mark. Spontaneous remission of late-stage cancer can be regarded as nonexistent (approximately one case in 50000), whereas the placebo cannot cure cancer and is fully explained by random changes in the state of health and by the natural course of a disease. The diagnosis must be correct too.

6) Clinical trials and government approval are not needed for free medical advice or if a patient wants to try common-sense, easy-to-try, safe or mostly safe, free or dirt-cheap interventions or lifestyle changes. For example, to get rid of severe agitation, a person may choose the horizontal body position (staying in bed all day), elevated air temperature, warmer clothes, a hot bath or sauna, honey, a mixture of sedative herbs, breath-holding exercises, a high-fat diet, a walk in a forest, and avoidance of all CNS stimulants, such as coffee, cacao, tea, ginseng, pungent vegetables, lemon juice, cardio exercise (e.g., climbing five flights of stairs), cold showers, and raw flesh (e.g., sushi, carpaccio, and smoked raw sausages).

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The latest research articles by Nikolai A. Shevchuk:

http://shevchuk-editing.com/publications.html

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Wikipedia is a horrible source of information, but some articles are pretty good:
Logical fallacies
Логическая ошибка

Are you brainwashed? An average person needs several months or years of deprogramming. (русская ссылка)

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