# MAOIs treat psychotic depression — the nature of evidence

> RCTs are largely sales gimmicks, beguilingly tricked up as a verisimilitude of science
>
> ~ Ken Gillman 2020

After my creation of the above quotation, I learnt that Milton (in 'Comus, a mask', presented at Ludlow castle, in 1634, before the Earl of Bridgewater, then Lord President of Wales, had come up with a similar but more elegantly phrased sentiment 400 years ago. The words are spoken by 'the Lady' to Comus (wicked son of Bacchus, who is trying to seduce her).

> This juggler would think to charm my judgment, as mine eyes, obtruding false rules pranked in reason's garb

RCTs are indeed 'Pranked in reasons garb'.

## Introduction

In 2006 the British Journal of Psychiatry published [1] '*Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis*' (188, 410-415).

It did not even mention MAOIs for psychotic depression because they found no relevant studies.

**It might strike observers as bizarre that psychiatrists have been at work on this for decades, yet no decent studies of MAOIs in melancholic and psychotic depression have ever been published.**

One of the authors, Willem Nolan, is coincidentally the doctor who successfully treated a psychotically depressed professor of psychiatry with TCP; this same professor was himself vehemently anti-MAOIs and lectured and wrote about those views — this remarkable story, which was unknown to English-speaking doctors until I published it on my website, is a 'must-read'. Much to his credit this professor did a U-turn after his favourable response to MAOIs.

I responded to that Wijkstra-Nolen paper by publishing a summary of my audit of my treatment of psychotic depression with MAOIs. It was published as an e-letter, but after some years it disappeared from the BJP website [2]. Since then, in my general psychiatric practice, I have treated more cases of psychotic depression with TCP with success, even when ECT had failed.

For decades I have been puzzled by the readiness of psychiatrists to give dopamine antagonists, antipsychotic drugs — anti-what-sort-of-psychosis, one might ask — to patients with severe depression, especially those designated as having 'psychotic' depression. The evidence that this strategy is effective is paltry. That error of giving antipsychotic drugs is compounded because patients who get put on them may not be taken off them subsequently; even when they fail to provide benefit: a serious mistake that is frequently made.

## Methodology

If you have an understanding of Bayesian reasoning you would have to consider it is probable, as an a priori assumption, that dopamine deficiency, not dopamine excess, is likely to be related to melancholic and psychotic depression — and that therefore dopamine antagonists would be the wrong treatment. It would be logical to suppose that drugs like tranylcypromine, that increase dopamine, are a

Address for correspondence: ken.psychotropical@gmail.com
Website: https://psychotropical.com

better bet. There is a detailed commentary about the much-neglected role of dopamine in depression in the commentary 'Dopamine and depression' here.

My experience of using tranylcypromine monotherapy in psychotic depression — one supposes other MAOIs might be similarly beneficial — indicates clearly it is a good strategy with few side-effects — certainly a lot less than ECT.

There are some differences in treatment response that are sufficiently clear that you do not need a double-blind trial to demonstrate them (think penicillin, and, have a laugh, parachutes (1)).

> Modern clinicians appear to have lost faith in their own clinical judgement

An RCT is an inappropriate and impractical methodology for some purposes and scenarios, as the limited quality of the available studies demonstrates — half a century down the track without decisive results, not exactly an advertisement for success. On a more substantive note, it is relevant to be aware that many commentators have noted the overreliance on RCTs and the problems with that methodology: these are discussed at length in another commentary. Such as:

> **Ashcroft** [3] 'autonomous of the basic sciences…blind to mechanisms of explanation and causation'
> **Pearl** (the Turing prize-winner) 'Causality is the key: there is no way of doing science without causality, it is the sine qua non for all understanding and progress' [4-6].
> **Solomon** [7]; 'Emphasis on [RCTs] has eclipsed other necessary research methods.'
> **Berwick**, 'we have overshot the mark with EBM and created an intellectual hegemony that excludes other important research methods from recognition.' [8].
> **Sir Michael Rawlins** [9]: 'the notion that evidence can be reliably placed in hierarchies [as all guidelines do] is illusory … striking effects can be discerned without the need for RCTs*… has important limitations of which four are particularly troublesome: the null hypothesis, probability, generalisability, and resource implications.'

More importantly, not only do you not require an RCT, but an RCT is not the most suitable or applicable methodology. A different investigational technique is required, one that takes account of basic science, and dissects cause-effect relationships by manipulating the key causal intervention, and measuring the outcome of that, in relation to its strength and duration (cf. Pearl [6, 10]): that constitutes a discerning tool — an RCT does not.

RCTs and EBM are as comfortable with a meta-analysis of whether people who see aliens see them as predominantly green, or predominantly blue — the reality or meaningfulness of the data and subject matter is irrelevant to an RCT-ologist. If you think that is a facetious comparison, then I invite you to delve into the meta-analyses that psychologists have done concerning parapsychology [11-13] — and remember that they have been stuck on that nonsense for many decades (they have PhD's, and doubtless they think they are clever). It is worth noting, e*n passant*, that parapsychology, P values, and meta-analysis have been intertwined for most of 20th century science. They a constitute a prime example of poor research and the limitations of statistics — a point of view that has only recently been given the prominence it deserves, by, *inter tot alia*, these authors [14-17].

An eminent and sensible statistician, Professor Sir David Speigelhalter, recently bemoaned the fact that the statement put out by the statistical association about P values has not changed anything.

According to the ASA's statement, p-values and significance testing are routinely misunderstood and misused, resulting in insights which are meaningless flukes

Pearson and Fisher, the parents of P values, might have been usefully employed using their tests to see if the nuts and bolts coming from one factory differed significantly in size from those from another factory, but the P value has had a stultifying and negative influence on medical science methodology for far too long. Its adherents exhibit an irrational antipathy to Bayesian logic, or considerations of causality — causality being the key to good science.

Causality is the key to science — RCTs cannot do causality. Ergo, they are not good science

P-values have been damaging. Thus, I was delighted to see this title of a (2019) publication spruiked by no lesser body than the Royal Society 'The reign of the p-value is over' [18]. But I am surprised the author, Halsey, did not cite Pearl. Unfortunately, like the announcement of Mark Twain's death, this pronouncement may prove premature.

One must concede that Fisher himself did attempt to excuse himself from the egregious misuse of his statistical tools by saying in one lecture:

> To call in a statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of [19]

Since I wrote the first version of this commentary some years ago, I have further extended my recognition and understanding of the serious problems associated with RCTs and, thus, evidence-based medicine: I have therefore written several commentaries that elaborate the multifarious concerns about RCTs; those commentaries are intimately concerned with the nature of scientific evidence — fundamental epistemological considerations.

I quote the eminent Professor John Ioannidis from his recent editorial [20] discussing the removal of Peter Gøtzsche from the Cochrane group, under unsatisfactory and controversial circumstances; he said:

> Despite valiant efforts to make them more evidence-based, guidelines, recommendations and exercise of policy power unfortunately remain among the least evidence-based activities, impregnable strongholds of expert-based insolence and eminence-based innumeracy [20].

Guidelines: impregnable strongholds of expert-based insolence and eminence-based innumeracy

It is refreshing to see someone as distinguished as Ioannidis expressing clear and forthright opinions about such matters, without weasel-words, equivocation, and the usual pandering to propriety.

Certain basic presumptions, like the necessity for RCTs, and the supposed superiority of RCTs, shape our opinions and knowledge, often in unrecognised ways; that makes them an insidious influence: this is discussed in detail in those other commentaries, see especially the 'Bias in science' section.

In brief; a proper understanding of science and scientific methodology highlights the fact that RCTs are not the gold standard that they are erroneously held to be, and that 'real world' clinical observation and experiment of the effect of treatments such as MAOIs and ECT is often a more valid and a superior investigational methodology. The multifaceted epistemological considerations underpinning that viewpoint are detailed in those other commentaries.

> Experiments that are agnostic and impotent about elucidating causality, as are RCTs, are poor experiments

When I used to help doctors starting in research in London many years ago, I would ask them, concerning their proposed research, what sorts of results they might expect, or hope for. Then I would ask them what they would conclude from those various possible sets of results. The answer to that question usually led me to say to them, 'so what'. Whatever the results were, it was not going to lead to an explanation of any mechanism, nor an indication of what other experiment might follow to advance knowledge — it merely showed that one thing was a little bit different, possibly 'significantly' different, to another thing, occasionally, in some cases, some of the time, if they were lucky. Does that ring a bell? Does it describe most of the trials that have been done on antidepressants in the last four or five and you should see a screen similiar to the one below. decades?

I am 're-publishing' my previous publication (below) which was in response to a paper 'Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis' that appeared in the British Journal of Psychiatry in 2006. It was published as an e-letter, but after a few years it disappeared from the BJP website [2].

I felt then that it was important to document my experience, and again now, to ensure it remains 'on the record' (since the BJP have, rudely, 'unpublished' it without informing me); it is appended below.

## *Leeches to treat anaemia*

Allow me to explain why it is that I have long been puzzled by the readiness of psychiatrists to give DA antagonists, aka, anti-dopaminergic or 'antipsychotic' drugs, to patients with severe depression.

A considerable amount of basic science evidence from various disciplines, one could say a massive amount of evidence, has accumulated over the last 50 years, pointing to the fact that depression has to do with under-activity in the brain, mental and physical slowness — brady-phrenia and brady-kinesia, not dissimilar to Parkinson's disease — reflecting under-activity of neurotransmitters, especially dopamine. Those are basic and crucial observations to which RCT-based methodology is unreservedly 'blind'.

Dopamine undoubtedly plays a key role in motivation, motor activity, cognition and pleasure, which are central to severe depression, as reprised recently — I have expanded on the theme of DA and depression in a video and in other commentaries.

> Dopamine plays a key role in motivation, motor activity, cognition and pleasure, all central to depression

Why on earth, one is compelled to enquire, would anybody propose, even in a fevered delirium, that further reducing dopamine with 'antipsychotics', either in Parkinson's or in depression, was a clever idea?

Anyone who suggested using dopamine antagonists to treat Parkinson's disease would be rightly ridiculed, as if they had suggested using leeches to treat anaemia.

It gets worse; antipsychotics generally have a broad spectrum of antagonistic actions at various neurotransmitters, they do not only inhibit dopamine, but they also inhibit other pathways. Remember, the name given to the first antipsychotic, Largactil, was a contraction of 'large actions', meaning it blocked every receptor in sight — its first use was for neurolept-analgesia [21-23].

Way back in 1950 Henri Laborit called it an **ataractic*** — ataraxia; meaning serene, impassive, indifferent.

Ataraxia remains the most accurate description of the action of CPZ-like, DA antagonists. I suspect many psychiatrists think that, because of the 'anti-psychotic' label, there is evidence that such drugs have a specific effect on supposed psychotic symptoms, but this is simply not true.

I have never seen or heard of a trial investigating whether they have a specific, or different, effect on auditory hallucinations, visual hallucinations, ideas of reference, or persecutory delusions.

Scientific rationale, and Bayesian reasoning, would suggest that the evidence for the proposition that lowering dopamine improves depression would have to be strong before it would be logical to even consider it theoretically, never mind act on it by giving such drugs to patients.

Additionally, the RCT evidence that antipsychotics are beneficial in severe depression is poor and probably strongly biased by commercial imperatives [24-29]: it is not logical to accept it, and it is even less logical to act on it. That is especially the case because such drugs have major problems and side effects and the risk-benefit ratio is marginal, at best, even with the most optimistic interpretation of the sparse evidence.

There are major differences in recommendations, about adding antipsychotics to antidepressants for augmentation, between the different guidelines [30] — this indicates a risk of medico-legal difficulties should adverse consequences and ensue.

You would need very convincing evidence to persuade you that leeches were effective for anaemia. So, why are antipsychotics used for depression?

## Reasons for misuse of antipsychotics

Why are antipsychotics used for depression? Why indeed. I suggest there are several reasons that explain the misuse of antipsychotics in depression (I need hardly say 'aside from mega-buck promotion by drug companies').

Labels are used carelessly, they shape our thinking subtly, but powerfully. Words like 'psychotic' are often defined and used imprecisely. The psychotic symptoms of schizophrenia, persecutory delusions and auditory hallucinations, delusions of reference, all contrast starkly with the delusional guilt of depression (which justifies the addition of the word 'psychotic'). Those symptoms are as different as chalk and cheese — one's initial presumption would have to be that it is improbable that any drug could have a specific effect on all three of those distinct types of symptoms. The disconcertingly simplistic idea that drugs for schizophrenia, that are labelled as 'antipsychotics', must therefore be effective in an illness called 'psychotic' depression is not only implausible, but also scientifically naïve, indeed, mindlessly naïve.

The meagre RCT evidence of the minor degree of (short-term) benefit conferred by antipsychotic drugs in severe depression, or psychotic depression, is dubious and equivocal [24-29]. It is more plausibly and readily explainable by the non-specific effects, e.g., sedation and ataraxia. For anyone of Bayesian inclinations the evidence is unconvincing.

* Incidentally, I can state this with confidence because I once stayed with the man who had the original copy of Laborit's diaries, in an extensive private library of antique books, high in the western tower of his old Chateau in Burgundy (he also had some original Marquis de Sade, illustrated). There I viewed, inter tot alia, Laborit's description when he first observed the effects — perhaps I am the only English-speaker alive who has read, the original, in French, in Laborit's own fair hand. I wish I had photographed it, but perhaps my attention was diverted by the wine, the song and …

The idea that dopamine antagonists, either alone, or in combination, effectively treat core symptoms of psychotic depression is baseless — it is widely assumed to be so, but there is no decent evidence to support such a contention — they are not even good for reducing severe agitation. I have seen a number of cases were agitation secondary to severe depression has shown poor response to APs or high doses of benzodiazepines and yet has disappeared within a week or two of starting TCP (see professional career salvaged)

RCTs have been a poor servant to investigational biological psychiatry. Indeed, they have been a thieving and deceptive servant. RCTs represent a methodology that takes no account of causality, which is the *sine qua non* of good science, nor does it take account of the enormous foundation of scientific research and knowledge derived from a swathe of disciplines such as anatomy, physiology, biochemistry, physics, pharmacology …

> Causality is a foreign land to RCTs, like that part of a mediaeval map of unknown regions where it was written 'hic sunt dracones' (here be dragons)

Causality is crucial to the development of knowledge in science and without it science is nothing — there is further discussion on this central issue in the commentary explaining why RCTs do not constitute sound evidence that ECT does not work — as the recent review by Read et al. contends [31].

Those who do not understand the essential and central role of causality in science are not justified in calling themselves scientists.

Wijkstra et al. in their review of the treatment of psychotic depression concluded; 'Antidepressant monotherapy (and adding an antipsychotic if that fails) both appear to be appropriate… However, clinically the balance between risks and benefits may suggest the [AD only] should be preferred'.

## The stultifying hegemony of guidelines

As John Milton had the Lady say to Comus (wicked son of Bacchus):

> This juggler would think to charm my judgment, as mine eyes,
> obtruding false rules pranked in reason's garb

Also apposite, and more recent, but more prosaic:

> Rules are for the obedience of fools and the guidance of the wise

How well Milton reflects that EBM acts as the juggler of evidence, producing its misleading guidelines: they have less science behind them than is generally recognised — they certainly do 'obtrude false rules pranked in reason's garb.'

### *Failure to use MAOIs*

The stultifying hegemony of guidelines produces a self-fulfilling syllogistic fallacy, a superficial self-satisfied circular reasoning, whereby nobody uses MAOIs, because they're not in the guidelines, therefore is no evidence that they work, as they are not in the guidelines … That is absurdly and unthinkingly recursive: it illustrates one of the various shortcomings of guidelines, which most people feel obliged to abide by — to avoid dispute, trouble, and litigation.

> The MAOI syllogism fallacy
>
> We do not use MAOIs because they're not in the guidelines, there is no evidence they work because nobody uses them, therefore they are not in the guidelines

Humpty Dumpty (attrib.)

The concern about low dopamine is doubly so in older people who have lower dopamine reserves; some may have prodromal Parkinson's disease [32, 33] — think of it like an old battery that cannot hold its charge so that a minimal power demand makes it go flat quickly. Dopamine antagonists drain away the charge and leave the battery flat, producing iatrogenic Parkinson's to boot.

If you have noticed that one of the authors of the Wijkstra paper was Nolen, then you might realise it is strange that it does not mention MAOIs. Nolen was the man who cured the professor in the 'patient story' on my website — the Dutch psychopharmacology professor who was stridently against MAOIs and was cured by Nolen of his psychotic depression using tranylcypromine.

I regard the overuse of antipsychotics to treat depression as one of the stupidest and most shameful exercises engaged in by psychiatrists. They are the most horribly misused drugs. It is not difficult to see why people are stridently anti-psychiatry when psychiatrists do such senseless things.

Thus, a misconceived semantic association ('psychotic') has influenced thinking and practice in the absence of any good underlying scientific rationale, pharmacological justification, or firm evidence — that is not good science, if it can be called science at all.

Lastly, I wish to emphasise that apart from my publication below I have seen (see this 'Patient story') and treated many patients with severe agitated and psychotic depression with tranylcypromine alone, with frequent success — indeed, I cannot remember a single patient who went on to have ECT because of drug treatment failure, but I do recall several who failed ECT and then recovered with MAOI treatment. I have seen many patients (about 10) over the years who have failed to respond to ECT, or relapsed soon after having had it, who have remitted and stayed well on tranylcypromine — the MAOIs are the main anti-depressants we have that substantially elevate dopamine. To this day I remain mystified that no-one in the current era has properly investigated MAOIs, such as TCP, for psychotic depression.

The accumulated positive clinical experience of hundreds of severely and psychotically depressed patients is referenced in the commentary on the history of MAOIs

MAOIs were used for psychotic depression, although not 'trialled' by methods and standards that are currently, if erroneously, believed to be satisfactory — I have discussed elsewhere the details of why RCTs are not a satisfactory or appropriate methodology to assess this question, any more than they are appropriate to establish the efficacy of ECT.

Most people have forgotten that tranylcypromine was accepted as being effective for psychotic depression, before it was temporarily removed from the American market in 1964 because of the hysteria about the 'cheese reaction'. You can read about how the FDA 'DESI' initiative flexed its muscles at that time by only allowing TCP back on the market for atypical depression, and stating specifically that it was contra-indicated for psychotic and melancholic depression: that story of DESI is contained in another of my commentaries:

https://www.psychotropical.com/65-tranylcypromine-parnate-a-brief-history/

Thus, as Milton wrote all those years ago, as if he knew we would have RCTs and EBM beguiling our judgment, '… obtruding false rules pranked in reason's garb.'

That sums it up, poetically and memorably.

One final observation is this, as noted in the parallel commentary about ECT: many experienced clinicians would state forcefully that ECT most definitely works, even though the RCT evidence is poor; however, the same is not the case

when it comes to discussing MAOIs. It may be that this is simply because more doctors have experience of people getting better with ECT, but they hardly ever use MAOIs, so they have not seen it with their own eyes.

## *Psychotic depression and 'multi-aminergic' treatment strategies*

P K Gillman

Originally published in British Journal of Psychiatry (in response to Wijkstra, J., Lijmer, J., Balk, F. J., et al (2006) 'Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis'. e-letter.

To the Editor,

"The resurgence of the suggestion that neuroleptic drugs should be used for treatment of psychotic, or refractory, depression is important because of the potential for worsening the illness; i.e. by lowering dopamine when it may need to be raised. A previous meta-analytic study (Parker, Roy, et al, 1992) found a significant effect size only for the superiority of ECT over TCAs, but not TCAs + neuroleptic over TCAs, or MAOIs. The Wijkstra et al. study (2006) substantiates the case against the usefulness of neuroleptics in psychotic depression. However, neither study was able to distinguish between 5-HT and NA (SNRI), vs. mono-aminergic, treatment strategies. It is both curious and disappointing that more attempts have not been made to simultaneously augment multiple mono-amine pathways, for two reasons: 1) major depression probably involves changes in NA, 5HT and DA. 2) the SNRI clomipramine is of superior efficacy for severe depression (DUAG, 1986).

Any results which suggest the superiority of SNRI over mono- aminergic strategies, like standard TCAs (which increase NA, but affect 5HT and DA little, except for clomipramine), are thus of considerable importance. See Gillman (2006) for an in depth analysis of the issue of which TCAs exhibit clinically relevant SNRI potency.

I therefore report my analysis of 21 consecutive cases of psychotic depression, treated using SNRI strategies. Nineteen of the 21 (90%) recovered fully without either neuroleptics or ECT. Only unequivocal clinical data indicating delusions were used to justify the diagnosis of psychotic depression. All patients were adjudged to be fully recovered because they were able to leave hospital and resume their normal functioning and responsibilities without significant functional impairment or symptoms. All were treated, and all followed up for a minimum of 2 years, by the author and remained well: except those few patients who did not maintain the same maximal dose throughout follow-up. All those showed signs of early relapse but recovered on restitution of the maximal dose.

Ten (of 21) cases had had no previous treatment in the index episode. Two had received bilateral ECT in the index episode prior to referral; 2 had bilateral ECT given by the author. Of the total of 21, 15 received clomipramine alone, 3 tranylcypromine alone, 2 sertraline + nortriptyline, 1 ECT (recovered). Three of the 4 ECT cases relapsed rapidly, but all 3 remitted with drug treatment.

Prudic's (1990) results showed that about 85% of psychotic depressives respond to ECT, but 60% relapse within 1 year: leading them to sum up: 'The implication is that 20% of medication resistant patients respond (to ECT) and maintain gains for 1 year'. So, as Wijkstra et al. note, the fact that 'many clinicians assume that ECT is more effective than pharmacotherapy' is especially unfortunate. I hope my experience will encourage others to try 'multi-aminergic' strategies including MAOIs and sertraline + nortriptyline.

Danish University Antidepressant Group (1986) Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. Psychopharmacology, 90, 131-138.

Gillman, P. K. (2006) A Review of Serotonin Toxicity Data: Implications for the Mechanisms of Antidepressant Drug Action. Biological Psychiatry, [Feb 3; Epub ahead of print].

Parker, G., Roy, K., Hadzi-Pavlovic, D., et al (1992) Psychotic (delusional) Depression: a meta-analysis of Physical Treatments. Journal of Affective Disorders, 24, 17 -24.

Prudic, J., Sackeim, H. A. & Devanand, D. P. (1990) Medication Resistance & Clinical response to Electroconvulsive Therapy. Psychiatry Research, 31, 287 - 296.

Wijkstra, J., Lijmer, J., Balk, F. J., et al (2006) Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis. British Journal of Psychiatry, 188, 410-415.

References

1.Smith, GC and Pell, JP, Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ, 2003. 327(7429): p. 1459-61.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14684649

2.Wijkstra, J, Lijmer, J, Balk, FJ, Geddes, JR, et al., Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis. Br J Psychiatry, 2006. 188: p. 410-415.

3.Treadway, MT, Bossaller, NA, Shelton, RC, and Zald, DH, Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J. Abnorm. Psychol., 2012. 121(3): p. 553-8.

http://www.ncbi.nlm.nih.gov/pubmed/22775583

4.Calabrese, JR, Fava, M, Garibaldi, G, Grunze, H, et al., Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. J Affect Disord, 2014. 168: p. 439-51.

http://www.ncbi.nlm.nih.gov/pubmed/25113957

5.Whitton, E, Treadway, MT, and Pizzagalli, DA, Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. Current opinion in psychiatry, 2015. 28(1): p. 7.

6.Wijkstra, J, Lijmer, J, Burger, H, Cipriani, A, et al., Pharmacological treatment for psychotic depression. Cochrane Database Syst Rev, 2015. 7: p. CD004044."

**References**

1. Wijkstra, J., C.D. Schubart, and W.A. Nolen, *Treatment of unipolar psychotic depression: the use of evidence in practice guidelines.* World J Biol Psychiatry, 2009. **10**(4 Pt 2): p. 409-15.

2. Gillman, P.K., *Psychotic depression and 'multi-aminergic' treatment strategies.* British Journal of Psychiatry, 2006: p. http://bjp.rcpsych.org/cgi/eletters/188/5/410.

3. Ashcroft, R.E., *Current epistemological problems in evidence based medicine.* J Med Ethics, 2004. **30**(2): p. 131-5.

4. Greenland, S., J. Pearl, and J.M. Robins, *Causal diagrams for epidemiologic research.* Epidemiology, 1999. **10**(1): p. 37-48.

5. Pearl, J., M. Glymour, and N.P. Jewell, *Causal inference in statistics: A primer*. 2016: John Wiley & Sons.

6. Pearl, J., *On the Interpretation of do(x).* Journal of Causal Inference., 2019: p. Feb.

7. Solomon, M., *Just a paradigm: evidence-based medicine in epistemological context.* European Journal for Philosophy of Science, 2011. **1**(3): p. 451.

8. Berwick, D.M., *Broadening the view of evidence-based medicine.* Qual Saf Health Care, 2005. **14**(5): p. 315-6.

9. Rawlins, M., *De testimonio: on the evidence for decisions about the use of therapeutic interventions.* Lancet, 2008. **372**(9656): p. 2152-61.

10. Pearl, J., *Reasoning with cause and effect.* AI Magazine, 2002. **23**(1): p. 95-95.

11. Storm, L., P.E. Tressoldi, and L. Di Risio, *Meta-analysis of free-response studies, 1992-2008: assessing the noise reduction model in parapsychology.* Psychol Bull, 2010. **136**(4): p. 471-85.

12. Bierman, D.J., J.P. Spottiswoode, and A. Bijl, *Testing for Questionable Research Practices in a Meta-Analysis: An Example from Experimental Parapsychology.* PLoS One, 2016. **11**(5): p. e0153049.

13. Kennedy, J., *Can parapsychology move beyond the controversies of retrospective meta-analyses.* Journal of Parapsychology, 2013. **77**(1): p. 21-37.

14. Ioannidis, J.P.A., *The Proposal to Lower P Value Thresholds to .005.* JAMA, 2018. **319**(14): p. 1429-1430.

15. Wasserstein, R.L. and N.A. Lazar, *The ASA statement on p-values: context, process, and purpose*. 2016, Taylor & Francis.

16. Greenland, S., et al., *Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations.* Eur J Epidemiol, 2016. **31**(4): p. 337-50.

17. Matthews, R., R. Wasserstein, and D. Spiegelhalter, *The ASA's p-value statement, one year on.* Significance, 2017. **14**(2): p. 38-41.

18. Halsey, L.G., *The reign of the p-value is over: what alternative analyses could we employ to fill the power vacuum?* Biol Lett, 2019. **15**(5): p. 20190174.

19. Fisher, R.A., *Presidential address to the first Indian statistical congress.* Sankhya, 1938. **4**(14): p. e7.

20. Ioannidis, J.P.A., *Cochrane crisis: Secrecy, intolerance and evidence-based values.* Eur J Clin Invest, 2019. **49**(3): p. e13058.

21. Laborit, H., *[The potentialization phenomenon of general anesthetics.].* Presse Medicale, 1950. **58**(23): p. 416.

22. Laborit, H., *[Complements to utilization of synthetic antihistaminics in anesthesia.].* Acta Anaesthesiologica Belgica, 1950. **1**(1): p. 42-3.

23. Laborit, H., P. Huguenard, and R. Alluaume, *[A new vegetative stabilizer; 4560 R.P..].* Presse Med, 1952. **60**(10): p. 206-8.

24. Tundo, A., R. de Filippis, and L. Proietti, *Pharmacologic approaches to treatment resistant depression: Evidences and personal experience.* World J Psychiatry, 2015. **5**(3): p. 330-41.

25. Anderson, I.M., A. Sarsfield, and P.M. Haddad, *Efficacy, safety and tolerability of quetiapine augmentation in treatment resistant depression: an open-label, pilot study.* J Affect Disord, 2009. **117**(1-2): p. 116-9.

26. Amodeo, K., R.B. Schneider, and I. Hegeman Richard, *Call to caution with the use of atypical antipsychotics for treatment of depression in older adults.* Geriatrics, 2016. **1**(4): p. 33.

27. Wijkstra, J., et al., *Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis.* British Journal of Psychiatry, 2006. **188**: p. 410-415.

28. Parker, G., et al., *Psychotic (delusional) Depression: a meta-analysis of Physical Treatments.* Journal of Affective Disorders, 1992. **24**: p. 17 -24.

29. Mulder, R., et al., *Treating depression with adjunctive antipsychotics.* Bipolar Disord, 2018. **20 Suppl 2**: p. 17-24.

30. Simons, P., et al., *Antipsychotic augmentation for major depressive disorder: A review of clinical practice guidelines.* Int J Law Psychiatry, 2017. **55**: p. 64-71.

31. Read, J., I. Kirsch, and L. Mcgrath, *Electroconvulsive Therapy for Depression: A Review of the Quality of ECT vs Sham ECT Trials and Meta-Analyses.* Ethical Human Psychology and Psychiatry, 2019. **21**: p. 64-103.

32. Askins Bailey, T. and S. Panjwani, *Atypical Antipsychotics in Late-Life and Treatment-Resistant Depression.* The Consultant Pharmacist®, 2018. **33**(2): p. 83-88.

33. Peters, R., *Ageing and the brain.* Postgrad Med J, 2006. **82**(964): p. 84-8.