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Tranylcypromine (Parnate): A history of an enduring anomaly

> Progress, far from consisting in change, depends on retentiveness ... Those who cannot remember the past are condemned to repeat it
>
> ~ Santayana [1]

Abstract

The history surrounding the use and regulation of MAOIs, exemplified by tranylcypromine, displays the confused and ambivalent attitudes among doctors and regulators to assessing drugs using randomised control trials, as opposed to discovering useful new treatments (which almost always occurs by serendipitously). Inconsistent application of such 'RCT-thinking' has led to varying opinions, recommendations, and usage which has been going in cycles for 60 years. The lessons of history may help us to resolve these inconsistencies. The earliest papers from 1957 and 1958 describing the clinical observations, following the use of these drugs in 500,000 patients with depression, still surpass much of the clinical information in current texts.

Introduction

This commentary (originally entitled 'A brief history', but no longer brief) focusses on two points: first, how MAOIs including **tranylcypromine (TCP, Parnate)** only just made it into the modern era, in the USA, and into the extant armamentarium of drugs [2-4]; second, about how the early non-RCT investigations and experience (involving ~500,000 patients before 1959) still surpass, in usefulness, much of the information currently available. TCP barely made into the modern era, despite still being the most potent antidepressant drug available (as MAOIs were thought to be by those who first used them), particularly for severe endogenous, melancholic, and psychotic depression types (to the extent that those may be valid sub-divisions of severe depression). Despite the lack, until recently [5], of 'gold standard' double-blind-randomized-

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

controlled-trial evidence*, there is much other evidence and experience to strongly support the epithet of 'most potent' for TCP, which I have described elsewhere.

As is often the case with history, it takes decades, and investigations by many authors, to uncover the twists and turns of complex stories. Frequently events that are thought to have first been done, or thought of, by one person, turn out to have been done, or thought of, by different people in other places. There was a brouhaha over the Loomer, Saunders, Kline paper because Kline was subsequently awarded the Lasker prize and Saunders thought he should have a share of it — after legal action he was awarded a share. Loomer spat his dummy because he did not think he had been fully credited as the first author — this was the first, and last paper he ever put his name to: that tells you something about him.

The history of MAOIs has been investigated and reviewed in several 'recent' papers [6-9]. Their pharmacology, efficacy, and interactions have also been reviewed [5, 10-12].

Kline** [13] took the view his was the first use of **iproniazid** in 'depressed' patients. Other contributions came from others including Lurie and Salzer, Delay — the same man who with Deniker, described the first case of neuroleptic malignant syndrome, and Robie. Delay, and Lurie and Salzer, [14, 15] used **isoniazid in 1952** (not iproniazid); those were investigations of depressed patients.

History

Threatened extinction

It is a tragic, and regretable failure of attitude, education, and training, that few psychiatrists use MAOIs. That is despite the high patient satisfaction and perception of superiority over other newer drugs (echoed by many experienced psycho-pharmacologists). Such data as do exist indicate a low level of knowledge and experience of MAOIs amongst psychiatric specialists. Indeed, less than 1% of psychiatric specialists in the western world have **ever** used them for treatment [16-19].

By any analysis of science and logic this is an astonishing and anomalous situation, for which the pharmaceutical industry must shoulder their fair share of the blame. Those who have read my writings about the biases in the science literature produced by the financial power and interests of pharmaceutical companies will appreciate one explanation for that.

The editor of the *British J of Psychiatry*, a 'conservative' publication, has stated [20]:

> 'Most of the good old drugs have been abandoned and their replacements, all drugs still under patent, have been marketed successfully but are no better, and in some ways worse, than their abandoned predecessors.'

Tranylcypromine (Parnate) nearly ceased to be an approved drug, on two or more separate occasions, in the USA; first when cases of hypertension and deaths from subarachnoid haemorrhage occurred because of lack of recognition of the role of tyramine in food (1964). Then second, in 1971, when the **DESI*** initiative**

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* You can read more about the evidence that RCTs are not the gold standard in this commentary.
** I was pleased that Don Kline joined my MAOI group and contributed to it a few times before his death a couple of years ago.
*** For information on DESI see Shorter and Wikipedia:
http://en.wikipedia.org/wiki/Drug_Efficacy_Study_Implementation
DESI and RCTs go 'hand-in-glove', therefore, for a discussion of drug trials and the FDA's role in them see: FDA and Clinical Drug Trials: A Short History

(Drug Efficacy Study Implementation) demanded a reappraisal of drugs in the American market. The details of this fascinating and illuminating story, which should be required reading for psycho-pharmacologists, are explicated in detail by Shorter in his work '*Before Prozac, the troubled history of mood disorders in psychiatry*' [4].

Some countries, for example Japan, were sufficiently concerned about MAOIs that they never allowed them to be marketed.

> 99% of psychiatric specialists in the western world have never used MAOIs

'A Short History of drug trials': FDA confusion

The quotation heading this FDA article (linked above, on their website) 'Short History of drug trials' encapsulates the dichotomy between serendipitously discovering advances by clinical observation of drug effects, and assessing aspects of their effectiveness using controlled trials:

> 'The function of the controlled clinical trial is not the 'discovery' of a new drug or therapy [correct] ... but 'to separate the relative handful of discoveries which prove to be **true advances in therapy**' [incorrect] Ref 2: Beaver.

In my view that quotation (which appears to be implicitly endorsed by the writer of the article — who is, incidentally, a historian not a scientist) is self-contradictory and misleading; see below.

The first paragraph of the paper has an odd mistake:

> 'The U.S. Food and Drug Administration has evolved as one of the world's foremost institutional authorities for **conducting** and evaluating controlled clinical drug trials.'

That is an erroneous statement: studies of **antidepressants** are done, not by the FDA, but by pharmaceutical companies and teaching centers.

> The FDA do not conduct drug trials

My criticisms of an official body like the FDA, that people assume to be authoritative, necessitate justification.

If the treatment is a **true advance,** and if it is **usefully** more effective than previous treatments, then an RCT is precisely what you do not need (note that I am using the word 'need' precisely; not to mean 'they are useless', but to mean they are not required). A 'true advance' will be obvious, without an RCT — one should emphasise that not performing an RCT does not mean that one is not following the methodologies of science. The famous statistician Sir Austin Bradford Hill said; '*you do not need randomisation and statistics if the difference is substantial*'. Likewise, one does not need a randomised controlled trial to demonstrate the effectiveness of penicillin (or parachutes [21, 22]).

> Randomisation and statistics are not needed if the difference is substantial

When I say, above, that not performing an RCT does not mean that one is not following the methodologies of science, I mean to indicate that scientific and methodological approaches are possible, which do not depend on the somewhat narrow and blinkered approach of RCTs.

In our present era, this FDA angle about RCTs — to the extent that this quotation, by someone on the inside, represents their view or approach — is also

incomplete and misleading, because AD drugs are approved when they have only a few points [HRSD] superiority over a placebo.

> There is not a single drug approved in the last 50 years that has shown more than a trivial difference over comparators or placebo

That, even to a fevered imagination, does not constitute 'a true advance in therapy', nor a 'useful' one. Many observers argue that the differences in these RCTs are not even a clinically meaningful differences, never mind 'true advances in therapy', e.g., see the Lancet '21 AD study' [23]. To include the terms 'true advances in therapy' and 'RCT' in the same sentence is inappropriate — oxymoronic even.

That the FDA went against their own 'rules' in the 1971 decision to keep TCP on the **market*** illustrates this emphatically, because they only allowed its continued marketing because they were persuaded it was effective in severe melancholic depression; **but without clinical trial evidence**.

History: some old papers

In his 1970 book chapter Kline said, of the events described in the 1957 paper [24]; '*it was obvious to us that we were really onto something exciting*'.

However, that is ambiguous because the 17 hospital patients had chronic schizophrenia and the improvement was unremarkable. The nine 'depressed' patients from private practice that were mentioned did not have any detailed description or results reported (until the 1958 paper [25] of which Kline was the sole author) — what exactly was said at the meeting in Syracuse in April 1957 is not known to us now. **Robie's paper from 1958** suggests there was discussion of the spectacular results in melancholia — Robie ran with it enthusiastically — his paper published only a year after that meeting contains a wealth of useful observations that are still informative for most practitioners even now.

I cannot resist quoting him extensively:

> I have been astonished to see how many severely or moderately depressed persons can be returned to a normal state of wellbeing on this chemotherapeutic regime, **without resorting to ECT**. ... in other cases Marsilid has maintained an ECT induced remission apparently indefinitely.... During the 19 years that I have been giving ECT for melancholia, there have been many occasions when I have seen what appeared like a miracle as a severely depressed person emerged from despondency after a few treatments. But in the 33 years I have been practicing there has been no experience as satisfying as observing the occasional depressive who emerges from his despondency after a few days on Marsilid. To be sure there are very few that respond so quickly, but it is astounding to see when it does occur! **It demonstrates more convincingly than any statement any researcher can make, what a remarkable chemical this is** and how widespread will be its field of usefulness, once we have acquired the accurate methods of prescribing that are necessary to assure its safe.

The Bailey and Kline papers in 1958 [25, 26] did contain details about the depressed patients he had treated and were equally positive — also containing observations and comments which would be educative for present-day practitioners.

> During the year following the 1957 Syracuse meeting approximately 500,000 patients were treated with iproniazid.

* I thank Professor Shorter, who kindly 'dug out' his old records pertaining to this issue, for drawing this to my attention, because I had failed previously to appreciate this.

I imagine Kline might have had some sort of influence or input on the 1971 FDA decision — as subsequently suggested by Ayd [9]. Either way, it highlights the **ambivalent attitude towards trials as opposed to 'clinical experience'**, something I have written about elsewhere. Note also the bolded quotation about this from Robie, above.

Discussion of this 'historical introduction' by the FDA might seem peripheral to the main point of this commentary; however, it highlights the anomalies in this, and the 1971 decision, insofar as the FDA have equivocated between insisting on RCTs and, prudently — in my opinion — accepting 'clinical' evidence.

However, moving on …

Excessive reliance on RCTs

There is a general lack of appreciation of the limitations of RCTs and their unsuitability for assessing, or generating, certain kinds of evidence. Although clinical opinion appears to have saved tranylcypromine twice during its history of use, I also contend that systemic devaluating of clinical observation and non-RCT scientific methods continues.

We need scientific methodology and objective and well recorded observations and analysis of the data. Science has a many-faceted, more comprehensive, and nuanced repertoire of methodologies and techniques: RCTs, overused and badly used as they are, constitute but one of these many facets of this inventive investigational enterprise.

As I have argued elsewhere, excessive reliance on RCTs has blinded people to the multiplicity of investigational methods in science and made them behave like blinkered horses. One of the powerful driving forces for this 'mono-methodological' approach has been the need for drug companies to have simple, quick, cheap, and easily manipulated trials, to get them over the finishing line for FDA approval of their drug. Unfortunately, that process has a tenuous relationship with good investigational science.

> RCTs may serve well the approval purpose, but they are not suitable strategies to address many of the other important scientific questions that investigators should be addressing

Back to the history

Under pressure from the FDA [related to the hypertension issues], and despite protest from SKF (Smith Kline and French Laboratories, as it then was, now part of GSK), TCP was withdrawn from the US market in **Feb 1964** [2, 27], but returned in **June of that year**, after revising the labelling (this was pre-DESI).

Then, in 1971, the FDA considered again withdrawing TCP after DESI determined it was probably ineffective. Professor Shorter kindly provided me with the notice in the 'Federal Register' that recounts these events. This indicates that they accepted the opinion that TCP was so effective in serious depression that they decided to let it stay on the market despite lack of 'RCT' evidence.

> Whoever persuaded them to adopt that view — which went against their ethos at that time of acquiring more power, influence, and control — deserves our enduring gratitude; Ayd indicated it may have been Kline and Schiele [28, 29].

The timing, and the consequences of the FDA's nascent DESI program, conspired to produce the anomaly of tranylcypromine being specifically disapproved of (when re-introduced in late 1964) for precisely what it was, and still is, usefully effective for; that is to say, severe melancholic depression with or

without delusions — exactly the sort of depression that would typically be considered suitable for ECT.

The enduring irony is that the first papers (1957/8) described MAOIs as 'obviating the need for ECT'.

> Yet, 50 years on, most patients who are sent for ECT have not been given an MAOI first — talk about slow learners.

For completeness we should note the results from Pagnin et al [30], who assessed the results of **RCTs of ECT vs MAOIs** — included studies were from over 50 years ago [31-35] they concluded:

> As compared with MAOIs, the ECT showed a significant greater efficacy and the likelihood of a positive response with ECT was approximately 6 greater than with MAOIs.

Quite apart from the obvious comment that RCTs constitute a limited investigational methodology, one would also note that since such a large proportion of patients receiving ECT relapse within a few months, studies such as the above which have not followed the patients up for six or 12 months are of lesser value. The MAOI used was phenelzine to a maximum dose of 60 mg. None of the patients in these reports received tranylcypromine.

I regard it as one of the greatest failures of psychiatry in the last five decades that no trial of TCP has been performed in melancholic depression, especially compared to ECT, or to prevent post ECT relapse, which is common (approximately 50% of cases within six months).

Cost, inconvenience, cognitive problems, negative patient and doctor preference, relapse rates, and other problems indicate that a trial of an MAOI before ECT is preferable, as indeed patient reports strongly indicate.

As Atchley commented over 50 years ago in relation to the 1964 commotion:

> It is easy to criticize, but one must realize that the new Drug Amendments of 1962 and the regulations they have engendered have thrust tremendous administrative responsibilities on an agency [FDA] which is inadequately staffed and which has been compelled to recruit personnel who have not yet had time to become adequately experienced.'

Until its brief removal in 1964, tranylcypromine had been widely recognised as being effective in severe melancholic depression, even when ECT had failed [4, 24, 26, 28, 36-38].

TCP was only re-admitted to the American fold of approved drugs after further 'studies' [2] and with restrictive conditions and sterner warnings [27]. As far as I can surmise these studies were never published, presumably because they were [FDA?] reconsiderations of pre-existing material (6 months would have been insufficient time to do further trials). It is pertinent to observe that the FDA may have bitten off more than they could chew vis-à-vis DESI. Contemporaneous comments suggest they had to recruit rapidly a lot of staff who were therefore inexperienced and would have struggled to do an adequate analysis [27].

Moreover, history should note, as subsequent generations of practitioners should note, that the newly appointed medical director of the FDA, Joseph F. Sadusk, warned that **unless physicians meet this responsibility [their professional obligation to be fully aware of the facts] then useful therapeutic agents might not be available in the future simply because they produce adverse side effects**.

It is also to Sadusk's credit that he took advice and allowed TCP to remain on the market.

Beahrs commented [27]:

> Doctors, when they have the facts—can be trusted to utilize hazardous substances in the best interests of the patient. **It would be well for the FDA to bear this in mind** and to use its regulatory power with discretion in any area in which a significant segment of the medical profession agrees that a drug, even though potentially hazardous and having a certain risk in its use, can be used effectively to the best interests of the patient'.

One of these (odd) re-approval conditions (in 1964) was to include the **specific contra-indication of its use in melancholic depression**, which was contradicted by the decision in 1971, and for which there is no scientific or RCT evidence.

Note, as recently as 2003 and 2008 the indication of melancholic depression was in the USA PI, having seemingly come and gone from intervening versions of the FDA-approved material in the PDR, **where it was approved for 'severe depression melancholia'** (box 2, no. 1284) — the interpretation of the evidence had changed [3, 39].

Again, it seems now not to be approved for severe melancholic depression: but it is hard to be clear who is saying what, about what, and to whom, or even when or where, or why.

There are many anomalies and inconsistencies in various editions of the PIs issued [note that these PIs are approved by the FDA, EMA et cetera), in different jurisdictions and at different times, about the types of depression it is, or is not, supposed to be good or bad for — also note that **all of them have inaccurate and erroneous information about ST**.

The British did not over-dramatize these 1964 events and they neither withdrew TCP from the market, nor placed restrictions on it. Incidentally, when I say over-dramatize, I am not being anti-American; indeed, it was a JAMA editorial, by an American, who used the words 'hysterical' and 'ill-advised' in the context of TCP withdrawal with further adverse comments about the American response to the issue [2].

It is difficult to intuit what knowledge base and confusion of reasoning processes might have generated these jumbled notions

I think the above snippet owes something to my unconscious remembrance of this quotation from Charles Babbage, the father of computing:

> On two occasions I have been asked, — 'Pray, Mr. Babbage, if you put into the machine wrong figures, will the right answers come out?' ... I am not able rightly to apprehend the kind of confusion of ideas that could provoke such a question.
>
> ~ Charles Babbage, Passages from the Life of a Philosopher.

Exactly what caused this is mostly lost in the archives and the mists of time. I consulted the eminent psychiatric historian, Professor Edward Shorter, who was unable to further disentangle the muddle of (mis)information on the subject.

The AMA 'Council on Drugs'

The AMA 'Council on Drugs' summary of 1964, outlined in JAMA [2], is an example of 'experts' asserting their 'authority': their monograph was poorly researched. The incorrect information in it is still having an adverse influence on practice.

They did not cite or discuss then-current and important pharmacology research data, or indicate they were aware of it: here is a selection of some of the papers that they might have consulted, if they had been aware of that then-current research [40-51]. They did not cite these papers, and it is clear they had an

incomplete understanding of the implications of them (if they had even seen them).

Incidentally, that uncited research was done by eminent pharmacologists, one of whom was no less than the Lasker-prize-winning Bernard Brodie, whose laboratory produced Nobel prize winners.

It is fair to say that the AMA 'Council on Drugs' summary of 1964, represents poor scholarship

The 'Council on drugs' missed an opportunity to develop an understanding of the mechanisms of these forms of toxicity and the difference between the tyramine reaction and serotonin toxicity — a regrettable failure that has echoed down the decades — and which justifies the disappointment that I have expressed about the profession. They are still failing to make this distinction, see my material and papers on ST.

The fact that 'eminent' people produced an important report yet were unaware of research from eminent pharmacologists requires no further comment.

This 'AMA Council on drugs' report is one of the sources of, among other misconceptions, the idea that: 'Tranylcypromine should not be administered to any patient … with cardiovascular disease [or] hypertension', and that it is 'incompatible with general anaesthesia', and various other, either dubious or groundless, assertions which still seriously mis-inform clinical practice [2].

More historical background

As a member and minor contributor to the excellent material on the website of the 'International Network for the History of Neuropsycho-pharmacology', and as the convenor of the **International MAOI expert group**, I have had extensive interactions with the generation of doctors, a decade or two ahead of me, now in their 80s and 90s, some of whom have made contributions in this arena. One may unprejudicially observe that many of them had training strongly influenced by psychoanalytic ideas, with psychopharmacology taking a back seat. This helps one to understand why some old material is out of step with what, even then, would have been 'informed opinion' in pharmacology.

Lest I be thought unduly anti-American, I should add that England was probably no better: when I was preparing for my specialist exams in the late 1970s it would have been possible to pass providing you knew about Freud, Melanie Klein, and suchlike perverse notions; but there was no need to know the difference between diazepam and chlorpromazine beyond the fact that one of them was green coloured and the other red — which I am sure analysts regarded as significant.

Indeed, I remember one example question from a then-recent exam paper was; '*Masturbation causes insanity; discuss*'

When I saw that I was filled with a sense of dismay and incredulity, admixed with hilarity — perhaps there is a long compound German word that describes that mixed feeling. No wonder I nearly gave up psychiatry! I have told the story of how I almost entered the wine trade elsewhere.

It was therefore no surprise to me to find, in the original admission notes of one patient from the back-wards of Bexley 'asylum' [dating from the 1950s] that I reviewed [around 1977], the introductory descriptive statement, written in beautiful copperplate hand-writing;

> This patient suffers from the dull morbid apathy associated with continual masturbation

History of Product information (PI)

It is also apt to note that the PI current in 2013 for Parnate from GSK continues to be a litany of mistakes, misunderstanding and misinformation (like many other standard sources on MAOIs). A number of these mistakes are sufficiently serious that, were similar errors to be committed by a physician in the care of a patient, they would probably qualify as medical malpractice. It is astonishing to me that such an error-ridden document can appear as an official representation of what is correct/advised vis-à-vis MAOIs/Parnate: it leaves me in a state of speechless bemusement — it belies the claim put forward that these documents represent state of the art scientific information [52].

Since those comments represent robust criticisms, I should state that as an authority on serotonin toxicity it is my firm opinion that the information in the PIs is both poor in general, and incorrect in detail. Those are serious errors and omissions with implications of life-threatening clinical relevance.

> Those serious errors are no trivial matter

American College of Neuropsychopharmacology report

One still commonly encounters people who think that it is dangerous to combine TCAs with MAOIs: most standard texts still reproduce this mistaken view. Historically, one should note that the American College of Neuropsychopharmacology accepted a report about this way back in the 1980 [53], adopted in 1980, which I have discussed in detail elsewhere. It concluded that the concerns about such interactions were an overreaction based on 'myth'. The authors, White & Simpson, cite Ayd (1977), who has called the lethal reputation and 'official' prohibition of the MAOI-tricyclic combinations:

> Ayd (1977), one of the several myths or unscientific generalizations that plague contemporary psychopharmacotherapy

However, Ayd, knowledgeable and eminent as he was, then gave detailed lengthy restrictions in his guidelines for its combined use (i.e., MAOI + TCA), such as exclusion of psychotic, endogenous, or bipolar depressed patients [54]. White & Simpson appear to endorse the dubiously founded idea that the order in which the drugs are given is relevant *'particularly if the tricyclic is added to treatment with an MAOI begun a week or more prior*'. I disagree with that because my extensive experience of hundreds of cases (where I have done precisely that) categorically contradicts it — besides which, I cannot see a pharmacological argument which would support the proposition that the order in which they are given would make a crucial difference.

My extensive experience of refereeing and analysing case reports in relation to ST [55] would indicate to me that the explanation for the [often poorly] reported problems (remember that most of the opinions expressed above were a result of case reports, not controlled experiments) is that people have failed to observe the rule of good pharmacological practice which is '*start low and go slow*'. Also, it can be a serious mistake to mix too many different drugs together, especially in above-usual doses — this is often done with little or no understanding of pharmaco-kinetic interactions.

> The White & Simpson report was adopted as ACNP policy in 1980 — yet most practicing psychiatrists do not know about it and most texts have failed to reference it

This story represents a masterclass in the art of failing to learn from history and failing to study the pharmacological science underlying therapeutics in psychiatry. Such persistent and pervasive failures are nowhere better illustrated than in the story of serotonin toxicity.

This shows how chance events, twists of history, and commercial influence can change both people's perception of reality and their clinical practice.

The hysterical over-reaction to TCP's disadvantages, real and perceived, have led many to over-emotively express these as dangers. Such attitudes and opinions contributed to it being abjured by almost everyone, or at best being relegated to 'last resort' status, with a skull & crossbones on the label. Indeed, as indicated by the above references, most practitioners simply did not use it at all. I remember that most of the patients referred to our specialist unit in the 1970s, for consideration of the genuinely last-resort treatment of stereotactic tractotomy for intractable depression, had not been treated within an MAOI prior to referral.

If you do not use it, then it does not work; if you use it only for 'atypical depression' [whatever that is], then that is all it works for.

Incidentally, I say 'whatever that is' because it is an imprecisely defined notion that has been floating around for 60 years [56, 57] still with no clear definition or agreement on what it is, or whether it constitutes a valid diagnosis, or if it is stable over time and responsive to a particular type of treatment [58-60]. It seems to me that if this notion was introduced 60 years ago and people are still discussing whether it is valid, then we already have the answer.

Clinical and patient experience

Suffice it to say, in this context, that surveys of the opinions of patients who have suffered dreadful long-standing severe depression, and who have had many different sorts of drugs (and ECT, ketamine etc), show conclusively that they-themselves express a strong opinion that MAOIs, especially tranylcypromine, have given them more improvement (and often with less side effects) than any other treatment, including ECT [61, 62].

That accords with my experience and that of the many colleagues in the 'International MAOI expert group': I have frequently seen long-standing remission induced by MAOIs, especially tranylcypromine (Parnate), in patients who have failed to benefit from ECT, and in those who have been continuously ill for 10 years or more, despite multiple attempts at treatment; for instance see Kaths story: I have published a brief summary of my retrospective audit of treatment of psychotic depression with TCP [63], and see also 'The professor's story'. There is much other information in other sections of the website concerning this question of effectiveness.

I have become progressively less hopeful, not only about psychiatrists' knowledgeable use of drugs, but also less hopeful about the available means to (re)educate them — because of the persistently pervasive negative influence of drug company money in medical education. I therefore view positively the influence of the Internet, which is empowering non-medical people by enabling them to make decisions for themselves, especially when their medical attendants' knowledge and objectivity have been perverted.

Anyone who encounters a patronising proscriptive practitioner, who is not open to evidence and discussion of the risk-benefit analysis and who says: 'we don't use those drugs any more, they are dangerous' (words like those have been reported to me by numerous patients and correspondents), can now, if they so choose, pro-actively re-define the doctor-patient relationship and direct their own treatment. That is empowerment, that is true democracy. What is even more positive is that such consumer attitudes, pressure, and actions are becoming an important driving force for changing doctors' prescribing behaviour. That is

because consumer pressure is the most important counterbalancing force to the disproportionate influence of pharmaceutical companies' self-serving and financially motivated misdirection of doctors' knowledge and prescribing habits.

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