Controversies
October 13, 2016

# Barry Blackwell: Corporate Corruption in the Psychopharmaceutical Industry:

## Mark S. Kramer's commentary

## Innovation, propaganda, and jail time

### 1. INTRODUCTION

> *"Whoever fights monsters should see to it that in the process he does not become a monster. And if you gaze long enough into an abyss, the abyss will gaze back into you."*
>
> Fred (Nietzsche)

As an academic-type, a mid- 2nd generation Biological Psychiatry researcher (both inside and outside of industry) I had been delighted to read Barry Blackwell's essay on corporate corruption/distortion of the psychopharmaceutical industry. Yes, the field of biological psychiatry/psycho-pharmaceuticals has been stagnant for quite some time. The original academic-industrial symbiosis has been corrupted; its science critically harmed. However, for me none of this has removed the potential "Biology' from Psychiatry. Despite failure of neurokinin antagonist antidepressants to commercialize, I trusted that my discovery (voluntarily put into the hands of others) would be a heuristic milestone to help biological psychiatry mature at some point. But now, the notion that biological psychiatry itself might predecease me is unacceptable. Long inspired by the prescient insights/ eccentric methods of a Paracelsus or Bill Evans (pianist), I have just naturally been drawn to off-beat invention, as well as to preserving frameworks in which it may thrive, i.e., biological psychiatry. So, there is a lot of ground to cover here and elsewhere.

There are three main subjects in the title of the Blackwell essay: Corporation, Corruption, and Psycho-pharmaceutical Industry. No matter how these are amalgamated, the overall topic is crucial on at least two counts: 1) safety of patients has been endangered, and 2) the essential body of knowledge of biological psychiatry/psycho-pharmaceuticals has been

steadily debased. Professor Blackwell identifies that we are in a quagmire. On this, he attempts to define its quality, components, boundaries and causes.

Frankly, I'd been most concerned that the sources in the essay may not have been entirely filtered, and that solutions to our mess were only delegated to one reference. So, this commentary will at some point attempt to supplement those areas, in hopes that this topic will be further amplified by minds and hearts much worthier than my own.

1.1. Professor Blackwell's Moment

Barry wrote:

> *"Real innovation in the psychopharmacology industry existed between 1954 and the mid 1970's after which the era of me-too compounds was ushered in by a changing zeitgeist that set the stage for corporate corruption. None of it was the fault or brainchild of the industry but it was an opportunity seized upon."*

With critical scope and balance this passage conveys Professor Blackwell's authenticity as a psychopharmacology pioneer. Buried amongst some of the contagions[i] he extracted from the seven referenced books summarized in his essay, his above passage alone provisionally suggested an antidote for our currently ill-defined quagmire. The latter includes both biological psychiatry and general science. All that has transpired on the 'corruption front' reinforces uncertain public opinion about the efficacy and safety of psycho-pharmaceuticals, and whether biological psychiatry is scientific (Angermeyer et al., 2016; Benkert et al., 1997; "The Current Crisis of Confidence in Antidepressants," 2011). It is evident that I am concerned both with the effects of corruption on patient safety/ science, and its clamorous eclipse of most things ever noble about Biological Psychiatry and general medicine. It is from that perspective that I seek to understand a pioneer's focus on corporate corruption as opposed to other types.

So, what is it that commands Barry's (and our attention) so strongly? It could not just be about the universals of conflict of interest, monopolistic leverage, price gouging, and impunity which helped seed corruption of psychopharmaceuticals. On balance, these are not unusual at all. So, why are so many so concerned? I imagine many are shocked about the present brand of corruption mainly because it hits us between the ears, not the legs. Perhaps it is now that corruption has ransacked mind over matter, that so many cognoscenti experience visceral shock?

Barry observes that the current epoch of biological psychiatry/psycho-pharmaceuticals is characterized by lack of innovation. Though obvious, this becomes quite astute contextually. In the wake of the mega-profits generated by SSRIs, with shareholders pressuring for more of the same, it had been stalled innovation which accelerated scruples of multiple stakeholders into the abyss. The origins of corporate corruption are most easily understood (see "A Decline in Corporate Social Responsibility" en la página 4) So, I pondered, "is it all really that simple?" If not "why is Barry's headline confined to the psychopharmaceuticals' "corporation" as the source of corruption?" In other words, does the problem - - i.e., the quagmire - - outrun the constraints suggested by Barry's title?

In terms of solutions, it would be most practical for us to know where to point fingers of condemnation. Surely, the wily captains of big pharmaceuticals are easily identified targets. Heavily flanked by packs of lawyerly henchmen, they seem all-too-willing to provoke and engage challengers. They and their shareholders have insidiously demoted corporate social responsibility, redefining such devaluation as "good business." Some certainly deserve harsh punishments, beyond fines, for endangering or killing patients. Attempts to confront and flatten their ilk makes for a logical headline; likely satisfying to those who feel they have worked so diligently for the good of medical science and patient care. Yet, because leagues of concerned scientists/clinicians lack deep legal funding, any initial goal of punishing corporate corruption as a means of stemming harms to patients and damage to science is just not immediately practical. Besides, Pharma is politically embedded in for-profit healthcare systems. How many jobs, how much political graft, is the death of a patient worth? To fight pharma is to fight for universal medical ethics. It sounds like an awfully good goal until reality intervenes.

Corporate corruption easily attracts our attention. Yet, the corporate role is more like that of a Siren's song de-chartering proper navigation in our field. To this end, those succumbing to the corporate Sirens are far more numerous, scattered, obsequious, deceitful, and honor-bound than the handful of wily choir directors of big pharmaceutical industry (and their shareholders,) Thus, those who warrant maximum retribution for our mess are right under our noses, i.e., within the academic rank. These are none other than the most disreputable KOLs who happen to be harbored by their complicit academic institutions and professional organizations. With the free will to stay their oaths, and having possibly been capable at one time of frugally creative innovation, it is these academics who laid to waste their *own professional integrity* and that of their field. Focus on Industrial corruption is currently as practically counterproductive, as "the

devil made me do it."

Like a peat bog undergoing archeological core sampling, our quagmire also has a core, i.e., professional ***integrity.*** This, supposedly the best humanity can muster, is now observed to be nothing more than a most delicate, readily soluble, glue. Originating in religious orders, it was not until the late 1600s that the concept of ***professional integrity*** extended to the practice of law and medicine and of course now much further. (Backof & Martin, 1991; Gillon, 1994). I did trust that professional oaths of conduct would support the most-noble endeavors of humanity: preclinical and basic academic science, clinical science, inroads into the biology of mental illness, and development of drugs and devices that really worked as advertised. Shock and outrage are justified given the rapidity with which *professional integrity* has liquefied under tons of money, greed, and influence.

Most readers are likely biological psychiatrists/physician-researchers, and most are troubled by the multi-faceted systemic corruption that is defaming this - - the beloved field of Biological Psychiatry (mostly psychopharmacology, to-date, with apologies to Dr. Max Fink.) This corruption also infects the parent fields: general medicine and science.

The extents of the quagmire are huge. They include far more than Industrial corruption. At an extreme, the quagmire suggests that society/humanity is dysfunctional. As such, the reader is referred to works in which the really "big picture" issue is covered *ad nauseum* by authors in the fields of theology and ethics. These inquire into origins of, and solutions to, human corruption [e.g, Rousseau (Bertram, 2011; Rousseau, 1987). Philosophers and clergy can struggle with this – the fundamental issue - as most of us here are not primarily interested in a discussion on the fall of humanity, original sin etc. In between these extremes, there are some intermediate targets. These can be addressed pragmatically, but only up to a point. Regardless of whether corruption affects data, business, government, politics – corruption (no matter how sophisticated the devious plan) by definition dissipates an ordered process (such as science) into a quagmire.

### 1.2. A Decline in Corporate Social Responsibility

As "corporate corruption" leads the Blackwell headline, a brief synopsis of its modern incarnation seems in order. The nature of the corporation, pharmaceutical or any other, had been redefined by a series of executive presidential orders in the 1980 Reagan years as "Property

for Shareholders." While at Merck and Co, it seemed that Pfizer had been the first of big pharma to align its governance accordingly. Hordes of financial engineers were recruited to put profit first. Corporate Social Responsibility (CSR) had been marginalized. As Pfizer began to overtake each pharma company on "Forbes Best" lists, pharma followed Pfizer's lead. It was just coincidentally that SSRIs were the late 80s- early 90s blockbusters. Despite giving the appearance that biological psychiatry/psycho-pharmaceuticals had been most affected by the ascendency of marketing over science/CSR, in fact all other therapeutic areas had been similarly swept up in this ideological re-alignment. Prior to the upheaval, Pharma governance did balance medical ethics with profitability. Now, Pharma's operations appear to proceed from Financial Engineering → Global Marketing/Business → Acquisitions and Mergers → Legal → Science. The Medical Ethic is avowed in corporate mission statements, but arguably is the last, if any, consideration. Additionally, large medical corporations have become a genus of privileged private government in the USA.

In a letter to George Washington, Thomas Jefferson said, "Of all the mischiefs … none is so afflicting, and fatal to every honest hope, as the corruption of the legislature." (Jefferson, 1792) Corporations do control public debate and public officials. David Vogel presciently opined 20 years ago, "this is a mockery of the principles of pluralist democracy." (Vogel, 1987) To make things right again in psycho-pharmaceutical science, lo - in the corporate healthcare sector - shareholder profits must be ethically conditioned on Corporate Social Responsibility. This requires yet another orchestrated inversion of corporate governance. That, though, is the weighty subject matter of political science; the details are well beyond this commentary (Vogel, 1987). So, let's move on.

### 1.3. This Commentary Goes Beyond Barry's Essay

Sparked by Barry's mention of "early innovation" lots of my first draft presented arguments (and still does) as to why the science of biological psychiatry/psycho-pharmaceuticals had failed very much prior to the intense marketing of fluoxetine and its cousins in the late 1980s and 1990s. (SSRI marketing simply finished the job.) Just as innovation has been stalled, so had adequate pathophysiological elucidation of our drugs' actions in serious psychiatric syndromes.

It is still surprising to see just how much of my commentary is focused on redeeming, protecting, and iteratively speculating on technical issues in the field of biological psychiatry/psycho-pharmaceuticals. It is as if I believe that by exploring and protecting the

science of biological psychiatry, everything will turn out all right. Please know, that I know corruption cannot be stemmed on that basis. Thus, apologies are offered in advance to those who might find that this propensity of mine encumbers fluid thematic development of "corruption and its tributaries."

This commentary on Barry's essay is based upon some modest thoughts (underlined as defined in 1.3.1 The Anatomy of a Quagmire: Glossary. Page 7**¡Error! No se encuentra el origen de la referencia.**), and its length reflects years of pent- up frustration:[ii]

> *"A vast 'conflict-of-interest laden cabal' insidiously infected the fledgling science of bio-psychiatry/psychopharmacology. It is within this 'innovation compromised host', that anti-psychopharmacology opportunists promote their cottage wares. "Except for a period just following its inception, innovation has been severely lacking in biological psychiatry/psycho-pharmaceuticals. Effective drug treatment had only been serendipitously discovered in patients institutionalized in the 1950s. Absent objective bio-markers of disease and diagnosis[iii], it had only been institutionalization of patients which automatically benchmarked severity of illness and afforded superintendent-researchers with high fidelity longitudinal and cross-sectional diagnosis. Subsequent absence of biomarkers of pathophysiology and drug response left the field, including its clinical studies, open to marketing flimflam.*
>
> *As neatly packaged by investigative journalists or by key opinion leader (KOL) experimercialists, articles on clinical psychopharmacology now require pointed reviews that separate fact from propaganda[iv] Through careful exposés and deconstructions the sordid medical ethics that currently corrupt Biological Psychiatry/Science can be rectified piecemeal and perhaps temporarily. On the other hand, sweeping reform might only be realized with jail time for corporate officers and KOLs who put profits ahead of harms to patients and science. When accompanied by parallel authentic scientific innovation, corruption might be put in check while the science is redeemed."*

Throughout this commentary, my focus is upon antidepressants (for some possibly more accurately termed antidepressant/anxiolytics), as "depression" is the indication upon which I last worked and for so many years. Yet, some preliminary digging reveals that antipsychotics – ("schizophrenia"- my first field), and -- to a lesser degree -- anti-manic agents, follow suit.

### 1.3.1. The Anatomy of a Quagmire: Glossary

#### 1.3.1.1. *Conflict-of-Interest-Laden*

When a professional's judgement (action or decision) can be unduly leveraged for personal benefit of any kind (money, advancement, status) their judgement must be taken to be at high risk for bias. In medical matters, such biases impact ethical tenets of the profession's primary mission.

#### 1.3.1.2. *Cabal*

- an immoral (or a-moral) network of private, public service, for-profit and non-profit individuals who serve in Industry marketing, marketing and ghostwriting agencies, government (NIH, FDA, Congress), academia (basic and clinical), as key psychiatric opinion leaders, and science journal magazine editors. The individuals who are volitionally involved include administrators and their reports, and independent entrepreneurs. Some are motivated by money; others to avoid litigation.

#### 1.3.1.3. *Infected (. . . science)*

weakened, contaminated, corrupted, conditioned unfavorably

#### 1.3.1.4. *Innovation compromised host*

The host - Biological Psychiatry - since its modern inception (~ 80 years ago), has not obtained a replicable, otherwise clear/ objective pathophysiology for its most clearly defined major disease categories, nor for the underlying therapeutic actions of its empirically validated biological treatments. Additionally, innovative psychopharmaceutical drug mechanisms (neuropeptide antidepressants) which for largely incidental reasons have not commercialized are nevertheless regarded by invited reviewers for high profile journals as failed concepts (Griebel & Holsboer, 2012). Such is the stranglehold that non-commercialization now has on science. (The corollary to this is that once the FDA approves anything, marketing then pays, everyone's hand

is out, concepts suddenly become exciting.)

#### 1.3.1.5. *Anti-Psychopharmacology opportunists*

Gifted author/speakers argue *in largely unqualified terms* that 1) psychiatric disease is a myth/fabrication, 2) that the harms of biological treatment exceed benefit, 3) psycho-pharmaceuticals in most classes cause long term brain damage or amplify the original complaints, and/or 4) psychological treatments alone are equal (or in combination with) are superior to biological treatments. It is questionable the extent to which these folks have observed or treated seriously depressed patients (old style) with tricyclic antidepressants. If they had, then their motivations for writing are highly suspect, or their experiences had been quite different from my own.

#### 1.3.1.6. *Cottage wares*

Products which can be manufactured for mass consumption without factories; e.g., blogs, eBooks, newspaper columns, audiobooks, videos, speaking engagements. Drugs and devices, requiring massive capital investments are largely excluded.

## 2. APOCALYPSE: BIOLOGICAL PSYCHIATRY/PSYCHO-PHARMACEUTICALS?

When initially outlining this commentary I mused "If - as Barry says - the academic-industrial complex had <u>not</u> been corrupt during the early period of innovation, then would a fresh period of innovation in mood pharmacology lead the way to 1) a less greedy, less corruptible academic-industrial alliance? and 2) re-invigorate public support for our field? However, I began to understand that innovation alone could not nearly drain this swamp or win over a disillusioned public. Presently, innovation - no matter its scale or virtue - would be simply placed in some tranche, and rolled up into a CDO-squared (whatever is the science-industrial equivalent of a synthetic collateralized debt obligation.)

As Barry says, for many decades Biological Psychiatry has lacked therapeutic innovation. Additionally, we have not durably adduced the actual physical mechanisms by which our serendipitously discovered drugs treat syndromal disordered behavior – when they do. Psychiatry unfortunately continues to plod along as a specialty of exclusion**.** Our diseases are idiopathic. Like all others in this bin they are identified through cross-sectional and longitudinal observation. Even then, diagnosis of seriously aberrant behavior can only be made after specific

physical findings laboratory, histopathological, or medical imaging results are ruled-out for other diseases (estimated at ~ 10% of presentations). Then, unless behaviors are stereotypically anomalous and clearly disabling, diagnosis according to DSM classification may inappropriately medicalize variations in normal behavior.

The known biochemical pharmacology of psycho-pharmaceuticals neither explains their mechanism of action in stereotypical disease phenotypes, nor points the way yet to the pathophysiology of mental diseases. Given the possibility of slipping back into the era of notionally based psychological theories of mental illness, our failure to explain what we already had has not helped the case for Biological Psychiatry. As implied by Barry, this lack of progress provided a breeding ground for unrestrained avarice, or at least some kind of unsanitary space. Nevertheless, despite the vigorous efforts of its detractors, Biological Psychiatry cannot be readily dismissed by absence of evidence. Not only is its basis in antiquity too strong, but so are the precious little clinical data we have.

If for no other reason, truly innovative treatments might save biological psychiatry/psycho-pharmaceutical science from complete extinction via two routes:

1) ***Non-gamed Innovative Drug Development, Manufacturing and Distribution*** can still be completed independently of big pharma. In fact, this is required presently, as many big companies have already jettisoned their psycho-pharmaceutical development programs (and associated marketing arms.) So, even if an academic innovator wanted to partner with a thoroughly corrupt company, the company would not likely bite. (How's that for rejection insensitive euphoria?) Additionally, private equity is generally not bullish on early psycho-pharmaceutical development. If somehow a disruptive psychopharmaceutical innovation could obtain private equity or foundation support, it is likely that, with exceptions, the inventor/originator would need to manage the project straight through to manufacturing, registration, distribution, and public/professionals' awareness. This route is still surprisingly viable.

2) ***Upturn negative public opinion of our field*** by intense no-hype education. This is needed in order to prepare the public for any true innovations. The days of intense popularity of psycho-pharmaceuticals had been driven by unparalleled happy-pill marketing of Prozac/ its cousins, not the intrinsic value of these agents for whatever it is that ails the masses. The "feel good fluff "came to an end along with patent exclusivity. Most of the marginally depressed

patients and those demoralized by society had been given false hope by all the 4 letter acronym "mood drugs." These folks are mad, easy marks for anti-psychopharmacology crusaders.

So, yes. Some disruptive innovations[v] in psycho-pharmaceuticals could be advanced without corruption, but so far likely within these constraints:

1) the market for innovations for indications within the hodgepodge now termed Major Depressive Disorder/ chronic anxiety disorders would need to be cut back 20 fold (as discussed in "2.1.2: How many "real" (i.e., specifically drug responsive) patients exist? Page 16),

2) a non-addictive recreational drug for "demoralization" - - like Aldous Huxley's ideal pleasure drug (SOMA). A so far impossible goal technically, this type of innovation is also inconsistent with current medical practice, but not in terms of societal demand. (Concurrently, without implying causality - it is curious that as SSRI use has declined a bit, use of some street and prescription addictive recreational drugs has risen), and/or

3) a biological agent/ drug/ device that mitigates persuasively bio-marked "psychiatrically expressed sickness behavior", (e.g., cytokine inhibitor based) (Bilbo & Schwarz, 2012; Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Hunsberger et al., 2016; McCusker & Kelley, 2013; Persson et al., 2014; Yarlagadda, Alfson, & Clayton, 2009)

While innovation alone will not likely diminish corporate corruption of medicine, it might still help stop exsanguination of the field. This prepares for a day, if ever, when corporate social responsibility becomes once again balanced with profit. First, for innovation to occur it seems necessary to first square off with all that has happened in the science of biological psychiatry/psycho-pharmaceuticals, i.e., before industry started wailing its siren songs to academicians. A key to this understanding is to appreciate the diminishing effect sizes of our drugs.

2.1. Diminishing Effect Size of antidepressants

> *"If your experiment needs statistics, you ought to have done a better experiment."*
>
> Ernie (Rutherford)

Melancholic depression (vital depression) is the bedrock diagnostic formulation upon which imipramine had been discovered. Imipramine had been discovered without benefit of RDC, DSM, or statistics. The very first outpatient double-blind placebo controlled randomized studies were merely confirmatory.

Permit me to play constructively the licensed fool (noble court jester) for a moment. So, please understand that anti-psychopharmacology crusaders in the room are not permitted to use this material without my permission. In advance, permissions are denied to each and every one of them.

At root, Biological Psychiatry has not reckoned with just how quickly antidepressant effect sizes diminished following initial discovery. After all, the source of most criticism thrown at the science of biological psychiatry is based upon current (post-1980) small effect size of antidepressants in Major Depressive Disorder [MDD.] As generally sampled post-1980, MDD is a mixture of thinned phenotypes which in the 1950s were persuasively antidepressant responsive vital (endogenous melancholic), less persuasively antidepressant responsive "reactive/neurotic", and antidepressant un-responsive "seriously sad inpatients."

Today, after 50+ years of "*MAD MEN"* (Wikipedia, 2007) style marketing of antidepressants turned anxiolytics, many might regard "drug candidate depression" as comprising a huge demographic (e.g., 25 million in the USA alone) and antidepressant treatment resistance up to 50% of that. These data conclusively frame the opening line of most grant applications and most papers about new antidepressants or antidepressant research. It's a tired line: *"– the importance of this research to relieve the huge burden of . . . etc. etc. blah, and blah mas."* The idea that depression has a huge lifetime and point prevalence is so entrenched, that few would bet against its truth. Yet, we tend to forget that these epidemiological estimates are steeped in controversy: foremost - how many of these people with "depression" would correspond to early samples (Kuhn's, or your depressed relative housed in an attic?) Despite psychometric enhancements to the original Stirling County Study, the original Epidemiologic

Catchment Area survey and its successors, these still suffer the limitations of lay interviewing, as well as biased poverty stricken respondents, hoping to receive unwarranted disability checks. Additionally, prolonged sadness has been increasingly medicalized ever since the 1960s. (e.g., Durà-Vilà, Littlewood, & Leavey, 2013; Vilhelmsson, 2014) Based on diminishing effect sizes observed in antidepressant studies over the past decades, scientists are beginning to agree that antidepressants have been oversold/over marketed, and depression profiles and severity have been inflated. If so, it follows that the numbers of patients requiring antidepressants cannot be inferred from epidemiological surveys of depression.

The meta-analyzed carcass of biological psychiatry/psycho-pharmaceuticals is a prime meal for circling vultures. This prompts: how likely is it that most people neither require antidepressants, nor therapy for their "Moods? Fears? Frustrations?" For less than clearly disabling behavior, the chief scientific challenge when evaluating any intervention for efficacy or effectiveness in an idiopathic state, syndrome or condition involves 1) devising appropriate control conditions, and 2) recruiting homogeneous samples. If the behavior is not stereotypical (and it can be added: not demonstrably at odds with survival) – well, good luck! Many a navel has atrophied under these unsolvable requirements.

Our empirical serendipitous discovery of drug efficacy only initially came about through the inpatient population, without statistics. That is a fact. That antidepressant efficacy applies to "inpatient-lite" out-patient samples, or as yet nearly notionally concocted subtypes, remains speculative based on reported effect size of drug therapy in post 1980 depressed subtypes. (*see - endogenous melancholic depression, undifferentiated depression, dysthymia, atypical depression, or minor depression? below*.) Placebo corrected point estimates of efficacy in most recent "inpatient-lite samples" have been reported repeatedly to be either driven by or most apparently in the most disabled of the bunch. Even of those, based on earliest studies, 20-30% of the "ambulatory sickest" would not be expected to respond at all (Brown & Rosdolsky, 2015; Fournier et al., 2010; Khan, Faucett, & Brown, 2014; Mancini, Wade, Perugi, Lenox-Smith, & Schacht, 2014). However, the effect sizes pre-1975 are as good, to much better, than those for any other treatment for idiopathic disease, in any other branch of medicine.

### 2.1.1. Severity, inpatients v. Outpatients, Assay Sensitivity and Stalled Innovation

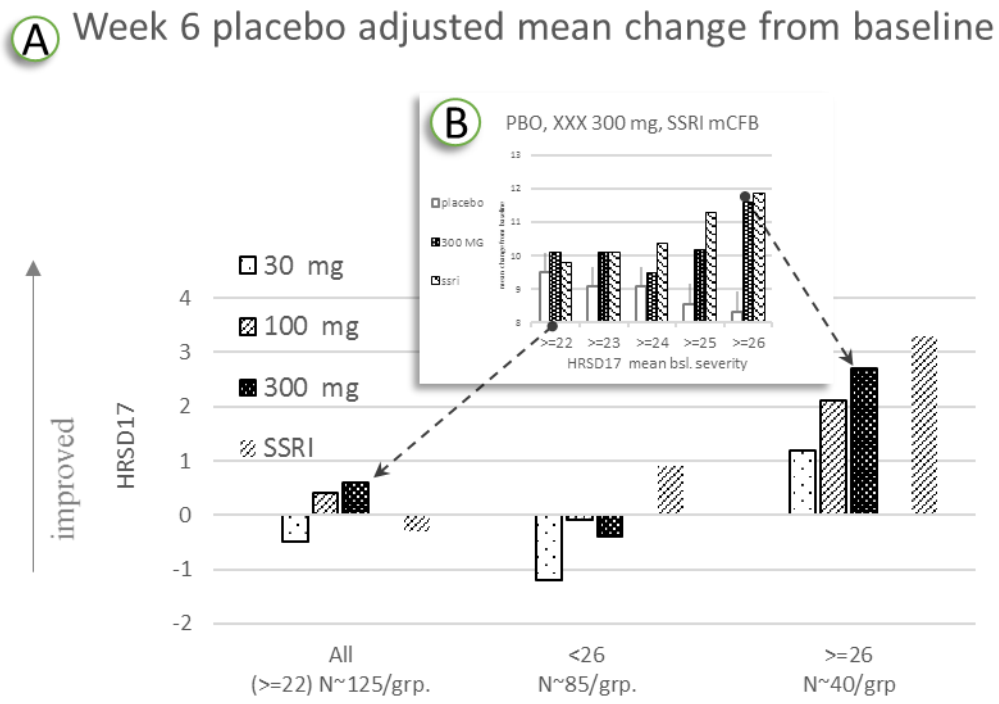
While in industry I struggled with my share of assay insensitive antidepressant trials. Following a strong hunch about a terribly failed ~$8 million dose finding study, I asked statistician colleagues to provide patient level data and a tabular summary of placebo, active control and experimental drug, placebo and adjusted point estimate Hamilton Rating Scale scores at the 6-week endpoint by dose by drug by severity cohort (the latter based upon increasing baseline severity.) Inset A of

Figure 1 based on M. S. Kramer, 2001 depicts a post hoc analysis of a large assay insensitive dose finding SSRI controlled antidepressant study as grossly parsed by patients with HRSD17 baseline scores of $< 26$ and $\geq 26$ points.

Dose response for the experimental drug placebo corrected point estimates SSRI benchmarking) in the highest baseline severity cohort examined in Display A. Inset B provides evidence that the data in the Display A are not cherry picked or random. Rather, mean change from baseline for placebo decreases, and both the experimental drug and the SSRI control response increase as a function of increasing baseline severity cohort, albeit post hoc. This implies that only~ 30% of the enrolled sample contributed to the signal. This finding is further lightly supported: 1) the formulation of experimental drug that patients received in this large multi arm DBRPCT provided exposure of about 25% less than a previous formulation (that numerically beat the SSRI), and 2) following my lead, the same phenomenon (citing ACNP, 2002) was then published a decade later (a rare type of analysis at the individual large study level) by another scientific team in Industry (Ratti et al., 2011).

*Figure 1 Anatomy of a large assay insensitive antidepressant study*

*KEY: Phase IIB Compound XXX 30-300 mg, an SSRI 20 mg, vs. placebo. Placebo adjusted mean change from baseline to week 6 by HSRD17 baseline severity, (group baselines within 0.1 HRSD units of each other, 10 mg dose not shown) A= placebo corrected; B inset= unadjusted mean scores (Y axis truncated)*



Nevertheless, despite post-hoc comparability of antidepressant efficacy in this dataset with that typical of 1999, why aren't the large 1950s placebo corrected antidepressant point estimates observed? Following are some of the factors which have compromised our clinical studies.

#### 2.1.1.1. *Inclusion/Exclusion Criteria and pragmatic realities*

My view is that the further out studies are conducted from deinstitutionalization, the more we lose the ability to identify and enroll the most drug responsive patients. This view is descriptively supported by the manner by which gross identifiers of patients enrolled in pre-1970 differ from those enrolled in modern antidepressant studies. The latter studies generally are not required to enroll patients on the basis of their vegetative signs and symptoms, or endogenous (vital) quality. The other grossly disparate contribution of outpatient studies is that patients who are a danger to themselves or others, who are grossly agitated or retarded, and who are incapable of getting to appointments regularly are mainly excluded (the latter, de facto.) These are the realities of severity and disability proscribed by formal exclusion criteria as well as a pragmatism which precludes or biases investigators against enrolling patients most appropriate for antidepressant treatment.

#### 2.1.1.2. *Psychometric bridging*

Despite hundreds of reports which claim our ability to bridge old and the new patient phenotypes, we are incapable of demonstrating that psychometric guarantors of validity, kappa for rating scales, and checklist DSM diagnosis have faithfully substituted for the original comprehensive clinical judgements made by seasoned PI superintendents and their apprentices. The field tried in earnest. But without the biomarker of persuasive response of an individual patient to psychopharmacological challenge-withdrawal etc., psychometric substitution for clinical wisdom is pie in the sky. This is not just a biased opinion. The speculation is at least supported by dwindling effect size over time. If the reader can propose other explanatory variables that haven't been tested, that would be welcome. However, this really isn't needed as simple descriptive data indicate that our current "depressed" are far from the phenotype upon which our initial drug discoveries were based.

The illustration above, plus the narratives and quantitative examples presented below, strongly suggest a need to re-assess meta-analyses of antidepressants, antipsychotics (and with a lesser urgency - anti-manic agents) which are based only upon post-1980 FDA database of

DBRPCTs. Initial inspection of available individual ~pre -1975 studies and their reviews, suggest that placebo effects, and in some cases placebo corrected point estimates, vary directly and inversely (respectively), with year of study conduct (i.e., most strongly from year of the very first discovery of the class-indication through the present.) This proposition seems most supported for antidepressants, followed by antipsychotics. (Alphs, Benedetti, Fleischhacker, & Kane, 2012; Kemp et al., 2010; Sysko & Walsh, 2007) That this happened prior to SSRI marketing is significant.

To keep one's eye on the ball, means to refocus on the science, not the corporation and its marketers.

As Barry says, corruption is rampant, and as opined, innovation is required in tandem as we attempt to fight it. Here is why. Through all of this chaos, **Biological Psychiatry is undergoing death by meta-analysis**. I personally know, as few here will, that many promising concepts for biological psychiatry/psycho-pharmaceuticals have been drawered because of nothing more than faulty signal detection, parsimonious trial design, coupled with inadequate exposure of drugs that did not require optimization (driven by exorbitant manufacturing cost, fear of dose-related safety litigation, and misunderstandings about receptor specificity and selectivity in disease),

2.1.2. How many "real" (i.e., specifically drug responsive) patients exist?

To make clear what follows, can we agree to assume that current weak signals of antidepressant efficacy in acute studies are mainly driven by high placebo expectation plus a measly proportion of seriously ill "inpatient-lites" enrolled; that the latter are a mixture of old endogenous (vital), "reactive?" and "unspecified" If so, from that we can estimate the epidemiology and availability of most of the patients who embody the originally described biological signal of drug effect. These would have been the inpatients prior to deinstitutionalization of the 1970s. More than any ECA style epidemiological estimate, major depression (the type that provides large effects with drug treatment) can be extrapolated from inpatient demographics of the 1950s. This idea is conditioned on the loss of effect size following the first several outpatient studies, whose subjects were even then enrolled based on diluted inpatient phenotyping. The epidemiological data on inpatients and total population by year were extracted from Torrey. (Torrey, 1997) If all of the above seems even mildly reasonable and if

what follows below is acceptable, then we are provided with a testable initial explanation as to why innovation faltered so deftly in biological psychiatry/psycho-pharmaceuticals, and why corruption may have filled its vacuum with such rapidity.

So, let's run the numbers. In the USA alone in 1955, the inpatient sample upon which antidepressants would have been discovered and would have been approved (had efficacy data been required back then), would have been in no more than 15% (Major Depressive Disorder: unipolar depressed, depressed bipolar and severe "reactive") of our ~80,000 inpatients at the time, i.e., this would amount to only ~13,000 known major depressives in the 1950s mold. Had deinstitutionalization not occurred, then presently (as corrected for population growth in the USA) the sample would be ~24,000 (about 10 fold less than would be required technically for an orphan approval status of a new antidepressant.) This means that drug appropriate major Depressive Disorder might merely be an orphan drug development indication -- (Yes, you read that correctly!) --, the definition of "orphan" is clearly defined by Sharma, Jacob, Tandon, & Kumar, 2010. This is also striking, as then drug appropriate depression would be about 1-2 orders of magnitude less than today's epidemiological claim of medically (antidepressant worthy) depression.

Thus, based on the response of this type of patient receiving imipramine in earliest studies - of all such patients in the USA – only a total of ~ 9000 will respond within weeks in all or none fashion (~40%); another ~ 9000 with significant clinical improvement (~35%); ~5000 (20%) with no response at all – in all of the USA. (Similar computations for other countries may differ.)

Some may be boiling at this point. The natural response is to poke as many holes in the pot as possible. Is this or is this not an exaggerated representation of what befell affective disorder Biological Psychiatry? (Note Bipolar is included within the above calculations.)

One could argue that there is still an "imipramine" or "SSRI" responsive "inpatient-lite" phenotype floating around in present DBRPCTs; it's possible. If so, my guess is it might be atypical depression. But this might require stimulant or MAOI probes to detect, not TCAs or the 4 letter Sxxxs. (Stewart, McGrath, Quitkin, & Klein, 2009)

To bring it all home (at least to my neighborhood) in terms of the practical epidemiology of assay drug responsive depression, if these 24,000 patients were equally distributed among our

20 largest cities there would be an average of only ~1200 assay sensitive depressed patients per city. About 200 of these would be disqualified, being inpatients, from today's big pharma studies. Even if the remaining 1000 outpatients could be identified as being "authentically depressed" they could not be the same as our 50s benchmarks when studied in outpatient studies: they could not be a suicide risk, a threat to the community or themselves, and most would be able to care for themselves (even if barely). Greater than 50% of these "once inpatients of old" are now scattered onto subway grates, cardboard and church shelters, if not recurrently jailed. Many of these would also be excluded because of concurrent medical comorbidities, not using birth control and other reasons. (Preskorn, Malcuso, & Trivedi, 2015). However, Preskorn, et al, commenting on one of the most wasteful studies in NIMH history, STAR*D, perpetuate a most troubling myth. With some deference, it is as they say - - that 5 times the number of "depressed" would have to be screened to meet inclusion exclusion criteria for a double-blind placebo controlled randomized controlled trial powered on 2.5 HRSD17 placebo corrected point estimates at alpha .05 and powered at 80%. Yet, these fine colleagues miss the point that 20 fold more of today's "depressed patients" would need to be screened to enroll a DBRPCT powered on, and to achieve, the 6-7 placebo corrected point estimates characteristic of imipramine. Would anybody care to estimate the time and cost to enroll and safely manage such a study? I can. Such screening is in no way attempted in any study today, and it is never accomplished in any NIMH study of modern vintage. (Even small ones in ersatz patients are not usually funded for replication.) STAR*D merely studied depressed patients who are prescribed antidepressants as marketed – meaning that baseline severity ratings are bogus/modern/inflated. Additionally, countries that still have healthy inpatient accommodations cannot be said to be housing Kuhn's population. Those who practice in countries with socialized medicine should educate me, if not so. If so, that's where the studies need to be done.

As in all such defined outpatients today, study statistical noise overwhelms signal. The fruitlessness of then trying to find bio-markers in this chaos makes ignorance look awfully good. And for the STAR*D study of mostly medicalized normals, taxes upon those on lightly supplemented social security incomes were plundered. That is demoralizing, but hardly depressing.

As discerned from the materials and methods sections of the first reported outpatient antidepressant double-blind placebo controlled randomized trials of the 1950s, these were performed by physicians who followed the enrollees from inpatient to outpatient status and

possibly back again (Ball & Kiloh, 1959; Thiery, 1965) Many investigators had to be aware of most of their patients' inpatient longitudinal records.

Thus, unlike today, the very first studies of imipramine assessed drug efficacy in the outpatient setting enrolling well characterized patients - - also with important subtext: the feasibly of treating carefully selected previously hospitalized patients on an outpatient basis. At the outset of these studies, it was not the notion that every bon-ton outpatient with depression would be expected to wildly benefit from an antidepressant. Actually, far from it. Great care was taken in the first studies. And their results were just as Kuhn had observed on an inpatient basis un-blinded.

One underemphasized casualty associated with the promise of biological psychiatry/psycho-pharmaceuticals (and that having been high jacked to justify partly deinstitutionalization in the 70s), is that our most objective benchmarks for severity and diagnosis – hospitalization and cogent longitudinal history - began to be replaced by soft surrogates. Yet, surprisingly drug efficacy in the first outpatient DBPCRTs looked very promising. However, in the aftermath of de-institutionalization these early signals likely provided only a false hope for durable generalization.

After 5-10 years of soft surrogates, and as DSM became little more than word anchored checklists divorced from multi-dimensional in-habitat expert clinical observation, our field's research became diluted first with a "form fruste" type of inpatient-outpatient; later to be joined by frankly symptomatic volunteers.[vi] Even in the very first DBRPCTs we could see that 20% were not responsive, 40% responded dramatically likely in switch like fashion, and < 40% were just improved. We could also likely agree that at the outset there had already been differences in response rates between what our pioneers termed endogenous vs. reactive (neurotic/ characterological, chronic and milder) depression (Ball & Kiloh, 1959; Kiloh & Ball, 1961; Thiery, 1965). [It may seem that I rely too heavily on these papers, but be assured that there are > 20 – not exactly Cochrane material – but which nevertheless consistently support the point. Those that do not, when included in the authors' to-date unpublished meta-analyses (available upon request in raw form) still do (Maxwell, 1981; Undurraga, Tondo, Schalkwijk, Vieta, & Baldessarini, 2013).]

The alarm of faltering effect size did persuasively sound in the 1960s. It had not been heeded as adroitly as it could have been when it did. After all, early clinical researchers could

not be too prickly, as industrial sponsors were always ready to pack up their bags and run. It is now easy to understand why back then the crazed drive, political and media gymnastics of chaps like Nathan Kline had been required just to live another day. This is all to say that lack of innovation as a breeding ground for corruption began early-on with dilution of phenotypes in clinical science. This likely occurred under the political pressures which Biological Psychiatry needed to vigorously fight a fashionable, baselessly prosaic, protracted and publicly unaffordable psychoanalysis. Thus, the early battles of biological psychiatry were being waged on the backdrop of government and corporate impatience, not corporate corruption.

Thus, not being spoon fed the above realties, mid-2nd generation Biological Psychiatry researchers such as myself accepted a 2-3-point HRSD placebo corrected point estimate as truth of a "good" antidepressant effect. Yet, it would take enormous suffering for me to understand as a professional what had really happened in our field and exactly how astonishingly early it had occurred. With a strongly forgiving heart, I know for sure that most of our clinical research after 1975 or so had been generally misguided because, except for isolated work, it could not protect the purity of the only thing we had. Our field had been depleted of its only truths, and I'm pretty sure it occurred early on and at least in many instances for political purposes, academic career advancement, and to keep pharma engaged. Once deinstitutionalization took place, few academicians could readily track, define, and consistently recruit the index samples. Effect sizes therefore continued to slip.

### 2.1.3. Non-endogenous melancholic depression, undifferentiated depression, dysthymia, atypical depression, or minor depression?

Much of the above argues that today's diminished placebo corrected signal in industrial antidepressant studies is directly related to decreasing enrollment of macroscopically disabled patients. Arguably, when relative baseline severity is co-varied this effect is easily observed in post-hoc analyses of large failed studies; lacking that approach then meta-analyses of placebo corrected point estimates by year, beginning with the very first reported placebo controlled studies, are suitable.

In earliest uncontrolled studies of drug efficacy, patients had been diagnosed according to an amalgam of psychoanalytic formulation and Kraepelian empiricism. This required repeated observations within, and between recurrent episodes (when warranted): each evaluation of the

patient's pattern of signs and symptoms (i.e., syndrome) was only to be a scene in the patient's "clinical movie." If faithfully recorded, as well as integrated, then the patient's entire "movie" constituted the diagnosis. This is important, because our initial discovery of psychopharmaceuticals is forever tied (at least until biomarked) to this essentially universal quasi-empirical framework of clinical observation. Therefore, it had been a huge error when the terms "endogenous" and reactive (neurotic) had been jettisoned from DSM in terms of drug discovery. The jettisoning was rationalized only after dilution of the phenotype.

While either endogenous and reactive (neurotic) can be relativistic, Kraepelian labeling becomes feasibly reliable when both (i.e., Kraepelian and Psychoanalytic) diagnostic frameworks are used in tandem. It is remembered that Roland Kuhn and many others of that period used psychoanalytic formulation to identify "reactive/neurotic" depression. The latter category on its own is murky, whether understood by psychoanalytic formulation or empirical descriptors. However, "reactive" as a subtype becomes far less probable when stereotypical endogenous serious melancholic depression comparatively presents. This is important for empirical research, as the crude (but effective) metrics of imipramine response (full, some, and none) in earliest identified endogenous severe melancholic depressive subjects are clear, as are those pertaining to "reactive/neurotic" depression (confounding by side effects is discussed en la página 35**¡Error! No se encuentra el origen de la referencia.**). "Reactive" depression is a hodge-podge category which might have been labeled today as "minor depressive disorder"[vii], "atypical depression" or "dysthymic disorder" had all of those even persisted into DSM-V!

Attempting to summarize this section compactly: "minor depressive disorder" no longer exists, "atypical depression" (in its alleged spectacular response to MAOIs and psychostimulants is more than intriguing) is likely a *key syndrome* that might be validated biologically as distinct from melancholic type depression or any other), "Undifferentiated depression" is likely a cross sectional sampling artifact of recurrent melancholic depression, and mild "dysthymia" is likely everything wrong with post-1980 outpatients entering antidepressant studies.

Dysthymic disorder is now termed Persistent Depressive Disorder (Dysthymia) in DSM V. In my view, this is the diagnosis that fallaciously made outpatient antidepressant treatment a superstar. It is also most closely aligned with reactive/ neurotic/ or characterological depression which in 1960 antidepressant parlance might have qualified as "reactive." (The type of patient, as already described, did not exhibit the persuasive response upon receiving imipramine that

disabling endogenous melancholic depression did.) We are left wondering the extent to which serious atypical depression might have been labeled "reactive" in the earliest studies. If so, their placebo corrected dichotomous point estimates were only about 50% less than the endogenous melancholic depressives' response to imipramine (Kiloh & Ball, 1961; Thiery, 1965) Reviews highlight the controversial aspects of trial design and discordant drug treatment effects that still plague some (dysthymia and minor) of these ersatz diagnoses (Rapaport & Maddux, 2002) "Dysthymia" more than any other opens the avenue to medicalization of normal behavior, whereas lack of intense focus on atypical depression had been a grave heuristic error.

Had Kuhn's sample been resurrected sedulously and now biomarked we might not be having this conversation.

2.1.4. The everyman's bio-marker

If you've read the above and have said to yourself, "Kramer is demented, having trashed almost all of our promising gray zones in depression diagnosis", I might have agreed save one detail: DBRPCTs of the minor/chronic or atypical forms have not generally defined the enrollees according to preliminary "drug response" screening.

What is preliminary "drug response" screening?

This, a hugely iterative n=1 crossover Response-Withdrawal-(Rechallenge)-Re-response (RWR) paradigm, defines a registry of patients who can then be randomized to a typical DBRPCT in which for example fMRI correlates, dexamethasone suppression, inflammation indices can be studied. This is in line with L-DOPA neurological challenge (*Thank you Barney Carroll!)* To date, biomarker or genetic studies have been attempted, but not replicated in subtypes. It is evident that patient selection is sub-standard in most of these studies, as can be readily inferred from the trifling ratio of those screened to those enrolled. This "RWR" approach, if used, would likely be just as maligned as most enrichment strategies already are. However, for all the 'hems and haws' we really are not at the stage of assessing real life efficacy with effective drugs in the appropriate populations – i.e., effectiveness. Even then, means for assessing objective compliance monitoring must be solved. Yet, I argue that "RWR" is a humble and ethical approach – one already tried by a few, an is consistent with the very little we know. It can advance our understanding of MAOI / stimulant treatment of something labeled "atypical" a step further. But few will likely conform to this unpretentious idea given its Ludditic nature.

Also there is a pragmatic aspect: unless recruitment is engineered in the form of a precise parallel single rater processing network, there is no individual grant that will permit 5 years to recruit authentic imipramine responsive melancholic vs. MAO-I responsive subjects with atypical depression. However, that could be a teaching moment for NIMH.

## 3. THE CABAL'S FINAL INFECTION OF BIO-PSYCHIATRY/ PSYCHO-PHARMACOLOGY.

### 3.1. Prologue: Damages to The Double Blind Randomized Placebo Controlled Study

Barry bemoans the corruption and intellectual havoc that the cabal (big pharma, KOLs, hallowed academia, the FDA, and a bought congress) have wrought on patients, Biological Psychiatry, and general medicine. Even though already 14 years out of industry, I too am still reeling from the cabal's late stage corruption of our most promising research tool – the double-blind placebo controlled randomized control study.

Most damage to the DBRPCT had already been done by the 1970s, way before 60 minutes discovered Irving Kirsch, and before he discovered the attention that a "ditty of a meta-analysis" could reap.[viii] The harms to the DBRPCT have been considerable, as have been the consequences: 1) increased costs of the DBRPCT [section 3.2], 2) over-the-top tabloid style criticism of biological psychiatry/psycho-pharmaceuticals in journals, [section 3.3] 3) and the advent of RDoC [section 3.4.]

About thirty years following demonstration of Streptomycin's efficacy and safety in Hill's randomized controlled design study in 1948, that design matured into the double-blind placebo controlled randomized control trial - the gold standard for clinical research and drug approval (Collier, 2009.) After the 1962 Harrison-Kefauver amendment, it had become obligatory for drugs not previously grandfathered-in to be studied in a controlled study design. Fortunately, the TCAs and MAO-Is had been studied in DBRPCTs in the 50s and 60s, and were thus deemed efficacious "by committee review." By 1978 the design and its statistics had become the FDA's gold standard for approval.

At the onset of my research training (mid 1970s), my mentors had fully adopted the double-blind placebo controlled parallel group randomized trial design for psychosis and depression research. It had been exciting to read the initial data that supported RDC/DSM-III, IV. These promised replicable diagnostic screening; that internal, inter-rater and retest reliability of rating scales might allow almost anybody to quantitate severity/disability and drug effects.

After all, Spitzer and colleagues had reported very robust 'kappas' for diagnosis and rating with the Schedule for Affective Disorders and Schizophrenia; then Williams with the SCID (Spitzer, Endicott, & Robins, 1978; Williams et al., 1988.) Did cram-courses and scripts transform research technicians into well-studied master differential diagnosticians and raters of drug effects?

Perhaps it was because I had great interest in biostatistics that I'd been kappa-duped to think that structured scripts might permit lay people to assess and rate depression with similar élan as those with decades of seasoned clinical acumen. Who was I to argue with kappas? Yet, in the 1990s, I began to question whether "expert vs. non-expert" validity (concurrent, criterion-related, convergent, or discriminate) of the HRSD/MADRS/Beck had changed over the long haul, e.g., by generation? (I know that it is a nearly impossible question to address adequately, if at all.) Instead we do have data which are interpreted to demonstrate improvements in inter-rater reliability with advancing publication year (from 1960 through 2008.) Lest we be fooled, it seems that this tightening had been accompanied by an increase in variability only at the lower end of mean HRSD severity ( see Trajković et al., 2011.) With antidepressant effect size diminishing so rapidly, and given industry-impelled gradual boosts of numerical gameable severity for enrollment, it is no wonder that our antidepressant studies fail so often. On that, I have the bittersweet distinction to have been the first author ever to report that ~50% of antidepressant registration studies are assay insensitive or negative (M. Kramer & K. Ghosh, 1999.)

### 3.1.1. Drug Discovery and the Hegemony of Biostatistics

Philosophically, medicine's dependency upon biostatistics (beyond confirmatory), our early loss of antidepressant signal (inpatient toward outpatient samples) plus the cabal's final poaching of the DBRPCT (KOL supported marketing of efficacy of *forme frustes* for the original syndromes) have all been detrimental to innovation in Biological Psychiatry as well as other fields of medicine. It doesn't take advanced mathematical modeling to understand that new anticancer drugs or biologicals (with their harms downplayed) do not restore overall survival to expected life span. These banes on society and most patients are minor discoveries, thus far with minor heuristic import, despite elegant bio-marking. In that context it is worthwhile celebrating that the discovery of antidepressants didn't require statistics, except as confirmatory.

Arguably, when a skilled clinician opines that the effect of a treatment is uncertain, the effect is likely minor, i.e., at least it is far from universal in the sample studied. Statistics are not needed at all, except maybe as a tool for generating hypotheses. Publishing initial uncertainty is a waste of time. With the possibility of a Type II, there is only the need to keep at "it" – for how long depends on the nature of the underlying theoretical framework -- tweaking variables of all sorts. In this regard, prosaic rating scales and pre-powering of studies are oversold. Clinical outcomes with any treatment need to be bluntly functional, based on observable changes in chief complaints. I am still surprised with all the bellyaching that this has not been routinely enacted for industry antidepressant research (e.g., actual quantification of sleep time, psychomotor activity etc. easily done with a FITBIT™)

When an "a-ha" type of certainty accompanies a treatment, even when obtained under non-blind non-controlled conditions, the effect is likely major, worthy of replication, and deserves bio-statistical confirmation. Arguably, this is an economical way forward in science, but is conditioned on multiple replications and tons of humility. From this standpoint, hegemony of biostatistics paralyzes early clinical discovery. Even when effects are large, dread of the Type I error has enabled biostatistics to scientifically and legally shift from confirmatory towards obligatory – way too early in the game.

It had been perhaps one too many eager experts in academia, plus industrial parsimony, by which the so-called Phase Ib study (e.g., in 5 -10 well-chosen patients) had been discontinued by most of the psycho-pharmaceutical industry by ~1995. This process had likely been initiated beginning in about 1980 by an amalgamation of sloppy expert opinion with subsequently overpowered Phase IIA studies, carelessly and rapidly enrolled. This had been a perfect storm, but not yet due to blatant corruption by industry. Shockingly, it ushered in an era of bio-statistical hegemony. Today, instead of fixing the fundamental problem, dilution of samples, we engage in endless missives from the side show barkers: bio-statistical estimation of "truth", i.e., frequentist vs. Bayesian, confidence intervals vs. threshold probability (p-values), the rules of meta-analysis. Compared with the big picture, this is just sophisticated mind candy.

Reminisce that the clinical effects of imipramine (and MAO-Is) were initially large, easy to spot in mostly easily earmarked small numbers of inpatients, were independently replicated, and questionably only required as book-keeping statistical characterization. Yet, today statistical analyses are required to discern clinically meager group-wise antidepressant effects.

To do so, ~5 fold greater patients are required now than that in the 50s/early 60s. Additionally, current > 50% failed studies of psycho-pharmaceuticals have already been one factor causing parsimonious big pharma to exit the field at least for now (e.g. Klein & Glick, 2014.) This may be considered a good thing by some. However, this is not so good for science or humanity - considering the unctuous alternatives of RDoC, alternative medicine's hokum placebo effects, or any new or old psychodynamic or Albert Ellis cognitive therapy, or new behavioral theories or techniques waiting in the wings.

Again: out of all covariates assayed to explain the decrease in assay sensitivity of the antidepressant DBRPCT, the most likely owe to the easy dilution of DSM diagnosis and severity of illness. (Alexander, Fava, & Gomeni, 2009; Khin, Chen, Yang, Yang, & Laughren, 2011) Why? Because big pharma is run on competitive milestones, the speed with which enrollment is expected encourages gaming of diagnosis and severity. One author put this into a straightforward essay. (Rosen, 2012) Lacking enrollment of the real McCoy, why would we ever expect mainly symptomatic volunteers to exhibit low placebo responses, and specific drug effects? By this I am not saying that all industrial psycho-pharmacology investigators are corrupt. However, 15-20% must be in some manner. It only requires 10-15% professional patients to derail a well powered trial into one which misses its already meager endpoint (analysis on request.) Whereas 30-50 per arm had been sufficient to detect a strong antidepressant signal prior to 1965 and occasionally later (Amsterdam, Case, Csanalosi, Singer, & Rickels, 1986), today's dilution of diagnosis (essentially enrolling pretty sad "medicalized normals") requires 150 or more patients per arm, in order to obtain as little as 1.5 HRSD placebo corrected point estimates, and huge placebo effects. This has not deterred the FDA from approving on this basis.

This axiom – "less is more" - applies to sample selection for clinical experiments in our field. Lacking historical and clinical context, statisticians dutifully remind us that precisely because the earliest outpatient studies of imipramine enrolled small numbers that their robustly positive results probably comprised Type I errors. By contrast, most of our statistician friends would agree that when "small numbers" faithfully represented the limit of the entire local sample, that these might closely correspond to the population mean derived from <u>all</u> similar localities. Thus, the burden of statistical truth rests with multiple replications of local experiments, not an increase of N in any given experiment. On that note, I'd like to see tons more scholarly work on the value of replication (e.g., (Moonesinghe, Khoury, & Janssens, 2007)) than "why all science/neuroscience is bull-pucky" (e.g, Button et al., 2013; Ioannidis,

2008; Zaloccusky, 2013)

I've already illustrated the effects of sample dilution in this regard (Figure 1 Anatomy of a large assay insensitive antidepressant study, page 14.) When P.I.s are required by Industry to enroll more patients than actually exist per geographic area/ unit time they dilute signals of drug effect and assay insensitivity. This is no better illustrated than by statistician Frank Liu, a trustworthy colleague (Liu et al., 2008). The ~2003-2004 studies he analyzed, obviously the $NK_1RA$ negative phase III studies of Merck (likely including a failed study that Keller et al, also happened to be left out of the publication) were huge (> 600 patients each), required > 150 per arm just to detect statistically significant placebo corrected point estimates of HRSD17 mostly (> 2 to < 2.5) for SSRI active controls. In these multicenter studies, statistical significance and size of signal generally greatly diminished midway into enrollment.[ix]

Consistent with the theme of "innovation is required in tandem with efforts at anti-corruption", it would be foolish to think that the fatal infection of our DBRPCTs would prevent future treatment discoveries in Biological Psychiatry. Yet, to think otherwise would imply that scientists have discerned other ways of getting there. Often it had been the lone researcher/ chemist and his staff to be among the first to taste our future psychopharmaceuticals and to appreciate their non-specific neurological effects. However, given the trivial effect sizes of these drugs 60 years later, as well as absence of gross neurological "tells" in some of our newest molecules in normal people, discovery of their specific actions could only have been discerned as 'drug attributable' in well-known patients, those with markedly abnormal stereotypical behaviors.

### 3.1.2. Loss of Inpatient Benchmark

As mentioned above, and as amplified here it had been crucial that drug discovery occurred through inpatients. This was by virtue of the two main standards at that time the inpatient setting afforded: 1) huge severity of dysfunction had been assured, and 2) constrained scope (homogeneity) of independent variables. The former though qualitative, is far from speculative. After all, inpatients included those with recent suicide attempts/ strong ideation, significant socially threatening agitation, and grade 4 performance status (all consistent with Severe Melancholia). Also, there had been no need for timely arrival at outpatient appointments. The latter standard, constrained scope: diagnosis could be constructed ideographically for each

inpatient - both longitudinally (based on hospital records and the personal experience of superintendent physicians), as well as through direct observation of the patient (in session and in his interactions – social and solitary - in the habitat.) Eating, sleeping, toileting, libidinous, emotional, and problem solving/cognitive behaviors were directly observable and daily 24/7. None of this excluded psychodynamic formulation of disabling probable or borderline "neurosis." Thus, it is no mystery as to why the very first inpatient DBRPCTs exhibited superb assay sensitivity and large effect sizes. Kuhn's potential bias deserves scrutiny. However, the very first double-blind placebo controlled randomized control trials, confirmed his integrity – at least in terms of his observations.

The inpatient research setting worked so well in detecting a chemical's relatively specific therapeutic effects, that these results were used politically in the 1970s to close the asylums (which provided the "secret sauce" of discovery.) Compare the presence of each of the above inpatient research conditions to the same elements as they exist in today's for-profit CRO guided research. Even at the very beginning of outpatient research the most characteristic "tells of melancholia" had been muted by study design. It was at about this time – say early 60s - that the cabal was informally organizing, Industry began to increasingly depend on academia and public units for ideas and testing.

Industry had to have very well understood the potential of outpatient sales at the outset. State and federal politicians had to be listening attentively given the screeching of anti-psychiatry sociologists and other activists. Their yelps provided the soundtrack which played behind the "burden of financing asylums" that were criticized as beastly, anyway. Those politically astute earliest leaders of Biological Psychiatry must have already entered inner political circles in the 50s and 60s.

It was at about this time – say early 60s that the cabal was informally organizing, Industry began to increasingly depend on academia and public units for ideas and testing. Was Biological Psychiatry fighting for its own funding and media battles against the psychoanalytic lobby at the time? Industry had to have very well understood the potential of outpatient sales at the outset. State and federal politicians had to be watching attentively given the screeching of anti-psychiatry sociologists and other activists. Their yelps provided the soundtrack which played behind the "burden of financing asylums" that were criticized as beastly, anyway. Those politically astute earliest leaders of Biological Psychiatry must have already entered inner

political circles in the 50s and 60s. Via the 1962 H-K amendment by 1966 the National Academy of Sciences/National Research Council (NAC/NRC) evaluated efficacy of old drugs and had already declared that early antipsychotics, lithium, as well as amitriptyline and imipramine were effective agents.

So far, at this point in the account, harms to the DBPCRT had not been voluntarily malicious/ the result of much corruption. Speculatively, any that occurred were likely the consequence of increasing separation of researchers from their ring-side inpatient clinical seats. After all, by the mid-1970s asylums had not yet closed, and marketing of psychopharmaceuticals had not yet considerably impacted outpatient selection for most DBRPCTs (NNTs were still about 4-5).

In the mid-60s pre-SSRI era however, previously defined phenotypic samples of drug response became blurred. Outpatient general physicians could not make subtle nosological distinctions, but could be swayed by the stream of increasingly sexy amitriptyline ads in major medical journals. Not to beat on dearly departed Dr. Ayd, even before amitriptyline, Merck bought and distributed 50,000 copies of Dr. Ayd's "Recognizing the Depressed Patient" to local medical docs, and this practice likely began to dilute diagnosis. This distribution of literature may have happily contributed to the de-stigmatization of depression. It certainly increased sales of amitriptyline; these helped those of imipramine. If it had not been for Frank, as the story goes, Merck would not have developed amitriptyline for depression. Buried in an old file cabinet at Merck, I found the monograph to be accurate for the times, and laudably lacking all signs of gloss. So much for good intentions.

So, via Dr. Ayd's book one can already discern a faint distant image of "Mount Science and Sales." Today, with its asymptotic incline and thick slime, almost all climbers are poised for a long slide down the Mount. (Psycho-pharmaceuticals is already in full glide.)

In the tricyclic era, local and federal politics of deinstitutionalization were boiling, the FDA must have been aware of need to offset social burdens with deinstitutionalization and it had already been hiring statisticians. In my view it was deinstitutionalization beginning about 1972, (coinciding with Federal Supplementary Security Income and Disability and legal rulings preventing States from using patients as free labor for asylum upkeep) by which we lost our best benchmark of potentially big clinical outcomes, at least for the drugs upon which we'd already stumbled.

3.2. Increasing cost of psychopharmacology clinical research

Compared with the 1970s, up to three studies must now be performed today just to achieve proof of concept. Because of signal dilution, the number of patients required for a statistically significant result has doubled to tripled. The per patient cost has risen by at least two-fold. Thus, the cost of proof of concept and dose finding may be 5 fold greater than yesteryear. Despite the FDA's willingness to approve on the basis of 2 positives, few companies are currently in favor of running up to 3 fold the number of phase III studies to succeed, nor to grapple with the way those might look in the FOI database. The high costs have paved the way for costly trial add-ons. These, with unproven predictive validity are a) for dose finding (PET receptor occupancy) b) surrogate fMRI markers, c) IVRT and similar doo-dads to fix assay insensitivity. Most of the pioneering investigators have sold their practices, or have passed on, and most clinical research is now conducted by Contract Research Organizations. Signals continue to deteriorate.

These days most clinical psycho-pharmaceutical research is also financed through private investor groups. These are now eventually teamed with the remaining distribution and marketing arms of big pharma, but with ever decreasing pairings. Curiously, investors groups do not want to pay for active control arms. It is no wonder industry has left the scene, or is behind closed doors redefining it. They are, actually doing the latter. But that is another story for another time.

3.3. Open hunting season on Biological Psychiatry

This I feel is very important to cover. It is something which may also weigh on others here. I am really frustrated, embarrassed by, and hopping angry with the constant barrage on the clinical science of Adult Biological Psychiatry. I have said more than once elsewhere that for every deconstruction and legal action levied against the corrupt cabal, it is the unadulterated, unbiased, scientific accomplishments alone of biological psychiatry which deserve a huge hug. This is not yet happening.

It's not just a matter of self-respect and legacy. It has something to do more deeply with my sense of humanity: the suffering witnessed and absorbed from the horrendously psychiatrically ill patients that I've treated and monitored. They deserve so much more than a tear down of this field. A vital question which will remain for me after this manuscript and the next are finished is already percolating: "shall I gracefully exit from any continuing efforts to

innovate in Biological Psychiatry science, or shall I just become a part of an anti-corruption cabal, or shall I focus entirely on other areas of research while returning again to the arts?" If I ask this kind of question, will not the potential $4^{th\ +}$ generation researcher, with even more options, also ask it?

The anti-psychopharmacology crusaders, those who do not flatly refuse the concept of psychiatric disease, focus primarily upon the numerically small effect size of our drugs (specifically antidepressants) accompanied by large responses to placebo.

Barry writes that his essay reveals, "the brazen scope and toxic brew of brass-knuckled and subversive tactics deployed by the psychopharmacological industry to infiltrate and corrupt every nook and cranny of our discipline." Well yes. As much as we might wish/ pray that industry (and its stockholders) would be a lot more altruistic, they are by nature these days an a-moral beast - at least once marketing of product begins.

I readily admit my fondness for the elegant writing styles of the 7 authors Barry cites, but I am highly suspect of some, and their motivations. As others have opined, their works, however, must be taken as a wake-up call to Biological Psychiatry. Otherwise, to me some merely represent the tip of a blatant and growing network of anti-psychiatry opportunists – i.e., investigative reporters, psychologists, book authors, blogger paparazzi, gleefully whiling away their hours selling their memes/ cottage wares.[x]

The biologically oriented psychiatrists among them are terrific authors, but their messages are derivative of those of Szasz (well worth the reads) and Laing, two pioneering artists of shock and awe anti-psychiatry who had pretty good personal reasons for their positions. In all of this trashing of psychiatry and Biological Psychiatry my view is *"It is one thing to renew a failing field through destructive renovation, but quite another to demolish its structures to reposition its nearly dead real estate."*

After the very first DBRPCTs of the 1960s, through the present, odds ratios of drug to placebo point estimates of efficacy have greatly diminished. The ORs observed in earliest RCTs were large and these, without influence of KOL marketing, supported the uncontrolled and early controlled clinical observations of pioneers Roland Kuhn, John Cade, Mogens Schou, Colonel Paraire, Henri Laborit, Pierre Deniker, and Heinz Lehmann (Ban, 2007; Brown & Rosdolsky, 2015; Shorter, 2009)

As stated previously, those who ought to know may not appreciate that the greatest decrease in effect sizes occurred in the early 1960s i.e., within a few years of the first robustly positive RCTs and their replications [see Table 1 (M. S. Kramer, 2016)] My conclusions are based upon the studies I selected for example, but should not be considered biased as they are supported quantitatively by previous authors (KLERMAN & COLE, 1965; Li, Frye, & Shelton, 2012; Undurraga et al., 2013)

*Table 1 placebo corrected efficacy of antidepressants over time*

| *investigator/paper*<br>year | *Kuhn*<br>~1954 | *Ball and Kiloh*<br>1959-1961 | | *MRC**<br>1965 | *Maxwell*<br>1975 data | *All*<br>post 1980 |
|---|---|---|---|---|---|---|
| N | ~100 | ~30/ARM | ~30/ARM | 60/ ARM | ~600 /arm | multi 1000s |
| drugs | imipramine | imipramine | imipramine | imipramine | | all classes |
| design | OPEN | DBRPCT | | DBRPCT | META, DBRPCT | META-ANALYSES |
| treatment setting | IN | OUT | | OUT | BOTH | OUT |
| patient type | severe endogenous melancholic | severe endogenous melancholic | severe reactive | mixture (endogenous melancholic + > 50% reactive)<br>< 50% severe<br>diurnal variation not needed | all comers | mixed |
| exclusions | none | suicidal ideation and extreme agitation | | → same | none | medical comorbidity and those typical of industry studies |
| years of marketing | 0 | 1 | | 6 | 16 | > 25 |
| odds ratio (IMI:PL ) | 12.59 [a] | 10.48 | 5.78 | 3.14 | 3.82 | < 1.6 |
| NNT | 2 | 2 | 3 | 4 | 3 | > 7 |

[a] Uses Ball control group

With few exceptions **modern** meta-analyses of antidepressant efficacy rely on the FDA post- 1980 database. Most agree that when publication bias is taken into account (E. H. Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008), and depending on the selection of studies, placebo corrected point estimates of HRSD antidepressant effects (and Standardized Mean Differences, too) are often ~ < 2, / ~0.2-0.4 With qualifications, the anti-psychopharmacology position - - that antidepressant efficacy is quantitatively trifling -- is reasonable, on condition that pre-1975 studies are omitted from the analyses. When they are not, detractors primarily employ the results of a few studies to indicate that our early discoveries were nothing more than biased and bogus. (e.g., 1965 MRC.) However, detractors have not yet studiously dissected these pre-1975 studies, and have thus ignored their greatest strengths. In fact, the studies wonderfully discriminated drug from placebo in the aggregate. Large placebo corrected HRSD estimates > 7 as well as effect sizes hovering around 0.7-0.8 are present (Maxwell, 1981; Undurraga et al., 2013)

For example, by 1965 the Medical Research Council conducted a DBRPCT on the comparative efficacy and safety of placebo, imipramine, phenelzine, and ECT (This is the study upon which some detractors rest their case against antidepressant Biological Psychiatry.) Yet, the MRC study is notable for its confounded crossover design and for its dependent outcome measures. The latter outcomes markedly differ between its un-validated 5-point depression scale as compared with its nascent global impression ratings. When the quantitative scale is taken as un-validated for detecting drug effects then: 1) the percentages of patients who were markedly improved upon receiving imipramine monotherapy were strikingly greater than those receiving placebo monotherapy at the predefined 4 week endpoint (excuse the p values: Chi-square 7.35 n=58 $p < 0.007$; 24 weeks, $p < 0.05$;[xi] 2) the outcomes on the unnamed un-validated five point depression scale did not detect treatment effects, 3) all were outpatients; < 50% illness of spontaneous origin (endogenous) < 50% were considered severely depressed, on entry the present duration of illness had already been 4-5 months, and by 1965 imipramine had already been marketed to outpatient physicians for 6 years by Ciba-Geigy. The un-confounded short term imipramine data are displayed in Table IV of the MRC publication.

Many have tried to draw the attention of Montcrieff, Kirsch, Whitaker and many others with data-driven arguments on the above and other studies. This has not been evenly received by them. The agenda of anti-psychopharmacology crusaders is now a well-rehearsed, fashionable,

and modular. It has attracted sizable audiences. For every challenge they have a modular response.

For example, when confronted with data supporting early large placebo corrected point estimates of antidepressants ES, they say the DBRPCT studies were un-blinded by side effects. Really? Well - it turns out that SSRI and TCA side effects overlap nicely with signs and symptoms of anxiety and depression. If the incidence of dry mouth, nausea, and constipation averages > 20% on imipramine and ~10% on placebo in an individual patient, how is the rater to know the assignment of an individual patient even if they wanted to game a study? By that logic why wouldn't the study be biased against the drug arm? In fact, in testing an $NK_1RA$ antidepressant (known for its placebo like adverse experience profile) a positive placebo controlled study in as carefully selected melancholic depressives as can be found in the noise at even academic centers revealed that those patients with drug attributable fatigue (albeit mild and transient on L-759,274) were rated as less improved than those receiving L-759,274 without that adverse experience (M. S. Kramer et al., 2004) Balanced support is also derived from reviewing those "active placebo" (low dose atropine or barbiturate) vs. antidepressant studies in which imipramine grandly beat the active placebo. [See: e.g., (Undurraga et al., 2013). ] Detractors will then say that atropine and barbiturates are antidepressants. Cherries can be picked by two or more.

### 3.4. RDoC as Proxy for The DBRPCT?

Just beneath RDoC lurks a massive, I would think generally unwanted, conceptual shift for psychiatry. At first DSM will coexist with it. One motivation for RDoC, not yet seen explicitly stated, might be the hope that it will mature enough to fix the broken DBRPCT. The keys to RDoC's pitiful repair is to neither depend on fallible/ corrupt clinicians or real idiopathic patients of old. For me the missing element to fixing the DBRPCT is the elusive biomarker. For others it is RDoC. My conundrum with RDoC is "bio-mark exactly what to what?" And when I begin to put together all "that?" which is "what?", there appears in me suddenly a state of "terminal irrelevancy."

Poetically: will my BOLD signals of *"terminal irrelevancy"* be mapped to those parts of brain which code "sinking" and "feeling" and "disappearing horizon" and "last" and "supper" and "nausea" and "gagging?" Will contrasting pixels on the fMRI signify a paralyzing

emotional state? Will it gibe with "water "(in the para-hypothalamic angiotensin region), "paralysis of aquatic memory region" (in the hippocampal hypothalamic tract), "degeneration of accommodation" (in midbrain peri-cranial nerve III), and "nausea" and "vomiting" (posterior nucleus solitarius (medullary tract to IVth ventricle vomiting center?) Will I be diagnosed as RDoC "Terminal feelings of Irrelevancy?" What procedure, drugs, or biologicals will be deployed for my state? How will they choose the target? Or will a multi-BOLD-targeting monoclonal antibody be produced on demand by a Keurig style machine in the lobby? Will it only take $10,000 pharma debit cards or will cash do? And after all that, will they be astute enough to behold that the short term treatment is very low dose "Compazine plus Ondansetron." - uh – total cost = $10.

I've never seen anything of practical value come from data-mining in psychiatric science, other than in cleaning up contrast in brain imaging. The idea of starting with a hot new drug mechanism, developing its biomarkers, using adaptive trial technology to win on either the conventional diagnosis, or alternately a new RDoC biomarked subsample construct (e.g., fMRI activated/deactivated circuitry of this or that) seems to be intellectual malfeasance. Time might tell, but I don't think there is enough left for me. RDoC - despite being concordant with this era's technology (high throughput chemistry, protein targeting, functional genomic networks and detection of something or other by BOLD signals) – is notional.

RDoC simply cannot be the answer for now for practical reasons alone, as it must rely extensively on data-mining. That field will not be far enough along in any reasonable timeframe to handle mega-data uncertainty. Most importantly for Biological Psychiatry, datamining cannot yet manage the non-linear influence of "fine scales" of data, (e.g., regulatory protein interactions) with macroscale behavior (both together are termed "multiscale analysis.") Thus, RDoC appears to be a naïve wish to automate the wealth of earliest clinical observation and insight that we've had all along, now dying off. (RDoC must be related to the field of A.I. in some manner.) If that is it, then maybe there is some hope.

The two potential likely unintended virtues of RDoC are 1) that it may engage a few very creative souls who would not have been otherwise in the field; from them may sprout an "a-ha" or two, and 2) to create persuasively biomarked constructs for which biological agents might abrogate a conscribed domain of signs and symptoms. These would be those which may reside in a syndrome of abnormal behavior (a DSM diagnosis), but one not touched by existing

treatments (e.g., cognitive dysfunction of schizophrenia.) This seems to me more like magic shrapnel than a magic bullet. Yet, with all candor, I do feel like an old Luddite - a lone ranger inclined most of the time now to savor history more than trailblazing.

## 4. Specific Recitations Barry Draws From His 7 References that command Sharp Dismissal

It would require many years to critique adequately each of the books Barry cites. Most of the books are great, and some of the seven books annoy the heck out of me.

The positive: The views and styles of the Abramson and the Peterson works have inspired me to take some pragmatic actions; much more than would be typical of my disposition. This is because they speak to my conscience. They've spent most of their capital on putting patients first. Lemons and Waring is useful as a roadmap to potential legal solutions. The mixed: I found David Healy's old book, "the Antidepressant Era" indispensable while tackling the science (my "from pain to endogenous anxiety/depression hypothesis") and transformation of neurokinin receptor antagonists from potential analgesics to antidepressants. For this I have acknowledged his keen scholarship. However, aside from his recent indispensable efforts at data transparency, I am quite disappointed that I cannot fathom the constructive value in most of his subsequent philosophical and some scientific positions. Perhaps this reflects my late blooming tendency in all things - including becoming a proper curmudgeon. Or maybe someday I might be able to convey to him, if he is ever open to it, the wholesome ecstasy in just one drop of creative experience in Industry. This is what I felt 18/7 as I worked shoulder to shoulder with the most brilliant and dedicated scientists in the world, save a few duds, who also wished to bring forth my dream – never intended to be a magic bullet, but just a novel heuristic to help make inroads into solving our primary puzzles.

The terrible: There are certain passages that Barry extracts from his seven references which require some counterpoint, and may have been unintentionally dignified. They are examined below.

### 4.1. Our drugs prolong mental illness through brain damage?

Barry recites this credo from a particular sect of anti-psychopharmacology crusader in his essay:

*". . . Instead of healing a broken brain they inflict unspecified harm that creates chronicity."*

I feel strongly that this notion should not be dignified. In an informal exchange with our e-mail chat group, I mentioned I had been *". . . very concerned that this alone will be the unintended headline of Barry's instructive essay; a headline that is impossible to balance. The clinical valence that authors give data pertaining to this claim are all over the map [re BDNF, dendritic atrophy/ sprouting, reversibility of volumetric change, etc.] Clinical data from the Netherlands etc. conflate severe withdrawal sequelae with authentic increase in relapse/recurrence and permanent brain changes. I can understand the horror of this were it truly an indicator of causality rather than association."*

The idea of drug induced structural brain damage with antidepressants is notional as is the concept of antidepressant induced tardive dysphoria (El-Mallakh, Gao, & Jeannie Roberts, 2011) Change in brain structures, mainly atrophy of certain hippocampus and related regions, appears to be associated with depression and stress, but not with past history of antidepressant treatment (Cole et al., 2011; Opel et al., 2014.) Preclinically, antidepressant administration is associated with neurogenesis. Balanced reviews of preclinical and clinical neurogenesis in depression are available (e.g., Malberg, 2004; Tang, Helmeste, & Leonard, 2012.)

Neurogenesis in depression is an important area that could bring us one step closer to the pathophysiology of authentic depression. As synaptic clefts appear to be widened in depression, decreasing or reset of apical dendritic distance is likely a desirable thing for the depressed. Yet, instead of advancing such hope, those who sell fear turn this around as a potential harm. As of now, all evidence from long term studies or in human brain regions (co-varied for disease severity, duration, comorbidity, region in depressed age and gender matched controls) is opposed to antidepressant induced deleterious structural changes to human brain. Yet, it still applies that antidepressants do perturb a series of neurochemical systems. So, unless patients are seriously disabled, antidepressants should be a last line of treatment, but not withheld inordinately.

With regard to antidepressant use, if it is ever replicated that potential long term undesirable structural CNS changes are drug attributable, then this would warrant much more conservative practice guidelines than presently, especially for today's ersatz patients. However, for the sake of the authentically depressed, this must not become the headline (unless surely

warranted.) For even that, risk benefit must be assessed. Last time I looked depression and schizophrenia were deadly idiopathic diseases.

Beneficial or not, brain changes or none, the general medical principle is to treat at the lowest effective dose for the shortest time. Dilution of effect size had already occurred by the time that Keller and others studied longitudinal outcomes in depression. Based on these studies guidelines have been published which indicate as qualified that antidepressants may need to be administered chronically to prevent recurrence and relapse. I wondered from the outset why these findings would be incorporated into practice guidelines (even as qualified?)

The need for chronic prophylaxis of chronic or recurrent serious depression or recurrent mania is clear for patients who understand the risk of no drug treatment and perhaps only after a clinical pattern has been established in the individual patient. In view of the heterogeneity of "depressed" subjects in ~ post 1985 longitudinal analyses of recurrence/ relapse, how or why should Keller be used to dictate guidelines? What in the heck did they study anyway? There is no pleasure in saying this, but the further out applied antidepressant research findings are from the original discovery, the less they likely mean for the individual "patient." There are no validated physics-style formulas to guide treatment. Each candidate for drug therapy is an n of 1, and in this sense some of the medically conservative positions of Alan Frances make sense: patients opting for antidepressant therapy require the undivided attention of an up-to-date expert who attempts to understand the whole person. This is not a soft (touchy-feely) position. It is pragmatic. It is the only means by which the ideogram can be conceived correctly.

For antipsychotics, the story is quite different. For this, we ethically broadcast the possibility of irreversible neurological sequelae. The verdict is not quite in on 2$^{nd}$ generation antipsychotics, except to say that many who have scrutinized the data, including me, are not impressed. Their neurological AEs, now joined by metabolic AE safety, are an issue. Short term efficacy looks similar to 1$^{st}$ generation data. Compliance may be improved in patients receiving 2$^{nd}$ generation. Use in the elderly and children requires extreme evaluation of risk/ benefit. However, none of that makes the psychiatrist a candidate for a Nuremberg trial, as Whitaker implies.

4.2. The Cabal created a modern plague – says Robert Whitaker

Authors like Whitaker are stunning. They rarely lie, but are masters of omission,

selective emphasis, and well, spinning a story. They know the exact step in thematic development to feign balance. But this is only after they have calmly unsheathed sword and have jabbed with unrealistic intellect. Yet, I am not sure how Whitaker could possibly seduce (if he did) one as worldly, as distinguished, as Barry who acts inadvertently as a publicist for Whitaker. Barry extracts from Whitaker's "epidemic or "plague":

> *"The best attempt to quantify this problem [of corruption], described in the title as an "epidemic", is by Robert Whitaker, also characterized in his* ***best seller*** *as "a modern plague." Using data from SSI and SSDI recipients he graphs a fourfold increase between 1987 and 2007 involving both children and adults."*

This is not nearly so devious as Whitaker makes it sound. The fourfold increase is due to the initially reported safety improvements of fluoxetine (and its cousins) over tricyclic antidepressants, de-stigmatization of mental illness coincident with fluoxetine, and lastly tremendous synergistic marketing of depression plus anxiety when pharma gained expanded I. P protection with anxiety disorder indications for the expiring drugs. During a similar period, numbers of benzodiazepine prescriptions only remained stable with population growth. (Ilyas et al., 2012) What this all means I am not exactly sure. It seems irrelevant because new antidepressant sales are now down, and projected to continue their dramatically fall over the next 5 years. So, maybe the public has found something else to smooth over life? Use of recreational drugs is up. We may be looking at the future of drug development re buprenorphine analogues etc. (of course, these are high expected to be dose-related recreational, despite the safety cap.[xii])

4.3. Blockbuster drugs from the evil empire

> *. . . Blockbuster drugs are growing 10-20% worldwide, often with markups of several thousand percent. . .*

This needs an update.

From a scientific medical perspective, happily, latest antidepressants - those with little but nominal derivative pharmacology to offer, are now far from blockbusters. Is 3rd party payer wisdom prevailing? Is the traditional lobbying mechanism "pooping out?" Certainly politicians who take campaign contributions as pay for play in health care are parasitic bottom feeders who

deserve jail time.

*About mark ups:*

The mark ups are remarkable here in the USA, yet not at all in some highly socialized medicine or just plain poor countries. Surely, price gouging is not needed to recoup R and D, small molecule manufacturing, and/or ordinary overhead expenditures. So why are prices so high? Is it only greed and monopolistic behavior? Is it fair that one country would be price gouged and another not for the same product? Does it seem reasonable that a company who houses its business in the USA can charge the government for its medication but can legally avoid mega billions in tax through tax inversion or relocating headquarters to offshore tax havens?

Speaking not as an apologist, but as one who just does not know: The budgets required to defend intellectual property or worst case unwarranted class action suits, to build factories to comply with green regulations, or the huge manufacturing costs of biologicals have not yet been disclosed.

Some big pharma SEC reports disclose at least a portion of the huge legal funds that are allocated. It is impossible to tell whether these are for defense or strategic intimidation of small fish. In terms of allocations for product liability defense, it's hard to say sometimes whether the litigation against the company is warranted.

- Litigation and judgements were warranted for example in 1974, when HG Robbins went belly up shortly after defending the Dalkon Shield intrauterine devices. As far as I know no jail time occurred. The company hid detrimental safety data and marketed aggressively anyway.

- Pfizer paid $ 1/3 billion to settle lawsuits over a drug for menopause symptoms that allegedly caused blood clots and was accused of hiding cancer risks for the drug.

- Unless you believe, in yet another case, that GSK paid off the FDA and an advisory panel, GSK may have unfairly lost 4 billion in sales and litigation on an anti-diabetes drug whose risk of heart attack was no greater in the end than Metformin.

- Vioxx (2008): Merck paid $4.85 billion to settle a reported 50,000 claims. This episode is beyond complex. I leave the issue to legal scholars, because even now there is conflicting information about the sequence of scientific findings, exactly how, by whom, and when they were interpreted, FDA adjudications, etc. I have heard that certain cheeky marketing e-mails were pivotal to the findings of many courts.

Because legal expenses can be casually factored into the bottom lines by huge health care companies, only jail-time for executives and advisory boards might change unethical behavior as warranted.

4.4. Industry studies are limited, FDA rules for approval do not guide practice

Barry extracts:

> *". . . This usually means a small carefully selected, sometimes unrepresentative, sample for as little as six weeks, barely enough time to judge only common side effects. Just two such trials are required. As early as 1956 this was described in the first psychopharmacology text (Cole 1956) as "scientific myopia" (Zubin, 1956) but that standard remains in place today. "*

Jonathan Cole was likely spot-on in 1956, as back then patients were so close to the original substrate of discovery that big pharma could have done more to dissect subtypes and longitudinal practice guidelines. Even then, Cole's vision needed to be funded; perhaps his statement on "scientific myopia" had been directed towards industry? It certainly had not been directed at the FDA as Harris-Kefauver had not yet appeared. Today, Jonathan almost has his wish granted. It is noted that most antidepressant dossiers include one-year open label safety and efficacy ratings in > 100 patients receiving NMEs. Although the PIs only had an open label data for a year, no PI (or natural grouping thereof) in my experience ever penned idiographs on these

"patients." Nothing ever prevented investigators' groups from publishing observational anecdotal compilations. If objective, I doubt whether these – as hypothesis generating - would be effectively litigated/censured by pharma.

Also, additional patient material, at great expense to pharma, is often available. Though not mandatory, regulatory submissions have included 24 to 150 wks. relapse-prevention studies. see: (Glue, Donovan, Kolluri, & Emir, 2010) This is to say, that there had been opportunities galore for clinical academic PIs to collectively accumulate and report clinical knowledge. But this did not happen. When did research become such a soulless mill for them?

Dr. Cole might have relished new FDA commissioner Cardiff. I remember reading somewhere that he opined that antidepressant dossiers should include 1-2 order > patients per study! Without biomarkers, this is the epitome of misunderstanding. Actually there is preliminary evidence that smaller (e.g., 70/arm) antidepressant studies in well-chosen patients in a limited number of sites will exhibit far more signal than now seen in 150 / arm.

## 5. On Award Winning Styles Of Investigative Reporting

Can you imagine just how difficult it must be to earn a reasonable living as an anti-psychiatry investigative reporter? I almost can, as there are parallels between the mechanics of all they do, with those trying to secure a passable living in the arts. Most lack steady income, and unless independently wealthy, supported by another, even if at the top of their game will suffer from cyclo-deposit-thymia – i.e., periods of feast and then famine. Firstly, professional writers and musicians generally start their careers with extra-ordinary native talent. Secondly, to be working with ease under pressure, native talent must be compulsively polished for a time just so that "absolute perfection" can be authentically downgraded as asymptotic luster, not a goal. Thirdly, such refined talent requires a vehicle/ product that might satisfy audience need. Fourthly, before launching any product it requires a ton of smart publicity. Lastly, some momentum must be maintained in between product launches. This is accomplished by any number of low cost techniques of media publicity (special events, public speaking, marketing a cause, staging a debate, taking a stand on a controversial subject.) The polarity of the resulting publicity is irrelevant as long as it is managed.

Robert Whitaker knows all this. Evidence abounds that he works diligently at all of this, too. Exactly when will he face litigation from industry or a patient group outside of MIA? Yet, I

have also wondered whether his script is just a well-rehearsed show, or whether it reflects closely held beliefs. If not the former, then is he is writing on behalf of some seriously troubling personal event he, a friend, or family member suffered at the hands of a biologically oriented psychiatrist or two? If so, the dialogues may change.

As may be the case for some of the other authors Barry cites, Robert Whitaker is a clear well-researched writer who is remarkably biased in his interpretations. From a safe distance, I've watched as some of my colleagues, the best of minds, tangoed with him. Finally, they had no recourse except to deliver exactly what he must have craved, attention - even if in the form of *ad hominem* attacks.

Whitaker addresses important issues, but in doing so trashes the efficacy and safety of psycho-pharmaceuticals, ECT, seizure therapies, and psychosurgery (not that I would defend psychosurgery.) He positions his negative interpretations of inconclusive or non-replicated data alongside the brief horrendous period of forced sterilization of psychiatric inpatients, and then emphasizes how unfair the hegemony of physicians' prescribing privileges. He repeatedly uses the fallacies of incomplete evidence, low hanging fruit, and anti-psychiatry "quote-mining" from patients who do not prefer e.g. antipsychotics. He misidentifies honest dosing issues as malicious practice, and suggests that Nuremburg trials should be staged for bona fide medical physician researchers who have probed neurochemical systems with psychostimulants in schizophrenic patients. How can this not be the work of a 'smart' unethical self-promoting author?

I would agree that he identifies gamed phase IV pharma techniques of study design that minimize efficacy and safety of competing drugs. He seems to favor moral treatment (who doesn't?), but peculiarly sans medication. He ascribes malicious intent when the biochemical pharmacology of a medication is invoked as the mechanism of action in the disease. Yet, he wants us to take this as evidence that these are not idiopathic diseases when in serious form.

Over the years, pharmacologists have developed biochemical pharmacology screens (now hundreds of targets)– but these are certainly not exhaustive. Not knowing the exact mechanism of our drugs does not imply devious marketing, except if companies are still marketing on mechanisms that have been disproven (i.e., chemical imbalance.) What is the difference whether SSRIs work through serotonin or primarily through calcium transport? (Kripes! I get it.

But it's not "Nuremberg here we come!") To then lay it on about the drugs not being cures, only band aids; moreover, inflicting nothing but harm is - - - uh, show business?

It is only because Barry promoted him, and that he is right about KOL conflict of interest, over-marketing, and other issues mentioned herein (all of which unfortunately currently lack decent solutions) that he is given a fleeting place at this table.

For Biological Psychiatry, Whitaker and his ilk do not present testable hypotheses for our unknowns. Instead, they use scientific unknowns as weapons of reproach against conscientious researchers. We already know the financial engineers/marketers are oblivious and immune to Whitaker and Co. So then what is the response of seniors in biological psychiatry to both the Whitakers and the pharma marketers; how is that message to be presented to the public?

I suppose my greatest objection is that Whitaker's self-promotion is based on blaming psychiatrists about antipsychotic induced tardive dyskinesia as if it were a plague. Yes, I wish we had better drugs and understood much more. Yet, TD is a potentially severe, well-characterized, and labeled side effect. It's potential suggests that clinicians treat with antipsychotics at the lowest possible dose for the shortest time – when possible and warranted. It is arguably a reasonable risk for selected patients with schizophrenia. (On balance, antipsychotics reduce mortality and morbidity including suicide (clozapine) in the treatment of schizophrenia: for controversial aspects see (Aguilar & Siris, 2007; Healy et al., 2006; T. Turner, 2006; Ward, Ishak, Proskorovsky, & Caro, 2006.)

With religion steadily losing its embrace, medicalization or "alternative healing" of demoralizing states (normal behavior) is now likely the rule, as is rise in recreational street and diverted prescription drug. (Bishop, Yardley, & Lewith, 2006; Twenge et al., 2015) Plainly, people have their "moods" and life has always been intermittently tough.

"Entirely-insolvable/ completely-menacing issues of our lives" soften and disappear with even slight endogenous positive change in mood, insight independently. Various authors have speculated on why this may occur. (Federmeier, Kirson, Moreno, & Kutas, 2001; Ganio et al., 2011; Schnurr, 1989; Subramaniam & Vinogradov, 2013) Despite this ready observation - as interesting as it is easily forgotten - it should be enough to encourage continued investigations into "normal neuro-science" –perhaps only nominally "neuro." [xiii]

Some detractors of Biological Psychiatry opine that psycho-pharmaceuticals could not possibly be capable of imparting those subtle insights afforded by psychological therapies. However, this notion runs counter to common experience. After all, psychological insights can accompany slight changes in mood (Ashby, Isen, & Turken, 1999; Isen, Johnson, Mertz, & Robinson, 1985) and physical activity, irrespective of whether these are endogenous, associated with slight activation of activity or decrease in avoidance.) on mental, emotional, physical clarity and overall well-being, suggest that CBT, IPT, etc. should be disregarded as essential. (Bartholomew, Morrison, & Ciccolo, 2005; Biddle & Mutrie, 2007; Richards et al., 2016; Ybarra & Winkielman, 2012) Perhaps many things can be solved by a daily walk in the park or whimsically: listening to the lyrics of "When You're Smiling" (Wikipedia, 2006)

Just as drug therapy may be superfluous for the vast majority of those epidemiologically earmarked as mentally ill, so might the notion that therapy is required to live a normal life. Despite encouraging initial meta-analyses on the efficacy of CBT and other non- psycho-pharmaceutical therapy for a range of anxiety-depression complaints, it appears that effect size is waning. Given the difficulty of validating their control groups, it seems to me that cognitive, emotional, or behavioral therapies are oversold (Boot, Simons, Stothart, & Stutts, 2013; Johnsen & Friborg, 2015; Kazdin, 2014; Zhu et al., 2014) The wonders of a talk with a good friend, a change of scene, taking a chance, or just sitting quietly/ reflectively are vastly under-rated "therapies" reimbursed by birthright. Actually, I have long thought that studies of combo CBT and antidepressants in less than seriously suffering folks are more promotional than not; especially when birthright therapies are nearly freely available. Some wine, a talk with a friend, and a walk in the park daily. How to control the study? Are confidence intervals really required? When people require more than patience, and when an uncomfortable mood does not remit, or is cyclic, and growing in intensity, well - - then maybe external help is needed. Until non-medical therapy controls can be adequately validated, then patients and friends alike must be at least supported with a great deal of attention, compassion, and sometimes well-timed tough love. I'm not prone to label all that as therapy, or anything other than being a decent person. Personally, I've never prescribed or administered any medicine without wishing to embody all that.

## 6. PAPER TIGER

In my view, summarized in *Table 2*, the clean-up of our corruption must start with that which is most at hand, yet proceeding as possible to "pie in the sky":

Table 2 Best laid plans

| Staging | Targeted Component | What | Initiated by | Effector groups |
|---|---|---|---|---|
| Immediate | Academia | Critique of experimercial publications and anti-psychopharmacology crusader propaganda | Individual insightful scientists or by journal club | An enjoyable journal club can be formed of likeminded great retired scientists contributing to reviews |
| | | Censure, Humiliation of KOLs:<br><br>With each fact based Congressional Inquiry or law suit, KOLs violating their professional integrity must be expelled from their professional societies with recommendation to their University for sanctions or approbation | Petition by an emeritus group of 1st to 3rd generation retired Biological Psychiatry pioneers [EG] | ACNP, ECNP, American Psychiatric Association, Society of Biological Psychiatry, World Psychiatric Association, British Neuropsychiatry, etc. |
| | | KOL loss of academic standing at their universities | EG | To be joined by legal firm's TBD |
| | | Document communications with journal editors refusing to retract distorted and harmful data | EG drawing on Whistleblower related legal discovery | To be joined by legal firm's TBD |
| Intermediate | Industry | Petition Congress and DOJ to enforce served jail time for corrupt titans of Industry who have been merely fined. | Anyone with gonads | Legal/Political |
| In any timeframe | All three branches of Government, as well as Global Business | Inversion of "Corporations as Property." | Humanity | Legal/Political |

As one said, it might sound good, but details are needed and volunteers are currently lacking. Seeds for each element of action within the above paper tiger have nevertheless been important to plant. There is evidence that activities have already begun.

As to the inveiglers: their deeply private self-mortification and confessionals though required, are inadequate. There are after all laxly enforced regulation in place to curtail

marketing of fraudulent data. However, fines are useless and must be augmented with **jail time**. This is what a few of us are investigating. The marketing memo in all cases leads to the executive committee, its Board of Advisors, and the CEO. This is a slippery slope which may encourage legal ambulance chasing for a time. Is this a necessary evil that must be invoked to combat brazen unaccountable unconscionable behaviors of the healthcare industry and academia?

Also, there is a need for upstanding retired professionals to form a union of concerned scientists whose mission would be to formulate the principles upon which an intellectually cogent - media friendly - front could counter publicly disseminated anti-psychiatry anti-psychopharmacology cottage industry propaganda. This would require a strong interface with media and a panel of on- call speakers to defend the past science of biological psychiatry, temper public expectations, and to point the way forward without hype.

Part and parcel to all of the above, prescribing privileges for active pharmaceutical formulations must be limited to those with complete medical education, lest the financial engineering demons infect any other sector of mental health, such as psychology, or non-medically credentialed medical investigative reporters. (Of course, that is the least of all reasons.) On this note, if words matter as much as non-medical investigative reporter/ authors feel they do, then perhaps the Whitakers' of the world should be held accountable for theirs. What they dispense on blogs and in their books might be considered in some courts as the equivalent of medical malpractice. I think this just might be where "free speech" and "murder of a patient" would intersect given the perfect legal storm.

## 7. CONCLUSIONS

As partly based on Barry's essay, augmented with my own experiences as a biological psychiatry/psycho-pharmaceuticals scientist, my positions are: 1) until financial engineering overwhelmed science in big Pharma, "real" innovation (drugs that worked and were as safe as possible) in psycho-pharmaceuticals had invariably been the primary goal of industry when working closely with academia, 2) with repeated failure to achieve that goal, the cousins of fluoxetine became filler to achieve healthy stockholder dividend and continued investments, 3) marketing money infected medical ethics and indirectly medicalized normal behavior, 4) the clinical trial became unreliable as an ultimate adjudicator of basic science and preclinical

predictive validity, and 5) all this had been accomplished by a cabal consisting of academia, big pharma, the FDA, NIH, publishing, and paid KOLs.

The corruption of Biological Psychiatry has occurred in parallel with that of medicine. It had been lack of scientific innovation in this fledgling field, coupled with endless pharmaceutical company financial engineering plus marketing of recycled concepts that provided a breeding ground for the corruption that we only now with outrage begin to grasp.

Yet, the cause of the despicable corruption, **as distinguished from its temptation**, rests only with medical professionals - - individuals in our ranks who have betrayed their professional oaths of integrity. Far from being held to the highest of all standards, these are academically oriented physicians who, if not leaders of their professional societies, continue to be sanctioned by them with not only impunity, but at times with honor.

All of the above is pie in the sky in the absence of a sizable legal defense fund to counter nuisance retaliation/ litigation from industry. Efforts of this magnitude alone can indirectly crimp industry payola to Congress. Even then this would require a legal reworking of the concept of "corporation" at the level of the Supreme Court in the USA. It is hard to believe that this could not be accomplished as both the top 1% and remaining bottom understand that the scientific basis of their medical care must not be gamed. On second thought, those who've made it to extreme power are likely infected with the narcissistic notion of "let them eat cake!" Sometimes words matter, though. So we try to be optimistic stewards.

As one amongst us said to me: "those horses have already left the barn." Yes. Deep down, I feel discouraged. A part of me still yearns for that rush of discovery I experienced while in Industry. Sure my "ego" had been gratified. But know, that never a day had gone by when I did not worry about unintentionally harming "my" patients. There were many false alarms and many sleepless nights. My work filled me with the hope of repaying the privilege of my education, kindness of my mentors, and perhaps a reason why I'd been born..

Surprisingly, my own solution to our quagmire, before I even knew there was one, had arisen because of wishing to address medically a serious sickness in my family. I would not then have known this would be at the interface of immunology and psychiatry. This required enduring bitter-sweet changes in operation style: working without a staff, learning two new fields of medicine, combining low expectations with persistence, moderation of Type I error phobia,

separating as much as possible from self-aggrandizement, as well as firm vanquishing of all competing profit motives. In my current experience, sponsorship - beyond self - can and been acquired through non-profits, a remarkably affordable basement lab/office, and slow but pragmatically effective clinical research. All this by a very small band of doer dreamers. For this I am grateful for the astonishing synchronicities that have brought me to this moment.

I am sad to say that most of what I've written in the body of this chapter indicts humanity. In closing, please relish with remorse the following from the movie the Big Short:

> *". . . from a good idea turned an atomic bomb of fraud and stupidity. We live in an era of fraud – not just in banking . . . but in government education food religion – everything - even baseball. What bothers me is not that fraud is not nice or that fraud is mean, it is that in 15,000 years fraud has been short sighted and never has worked. Eventually people get caught – things go south. When the hell did we forget all this? I really thought we were better than this. The fact that we are not, does not make me feel all right and superior. It makes me sad. It is not fun to witness pompous arrogant dumb people be so wildly wrong as they are. I know at the end of the day that average people are going to have to pay for this, because they always do."*
>
> Michael Baum (the fictional name of real life money manager Steve Eisman, played in the movie "the Big Short" by Steve Carrell.) He profited from corruption by taking short positions.

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[i] Some of these authors posture themselves as revolutionary. Some suffer from *argumentum ad numeram*, an appeal to mob mentality directed against the medical institution and its paternalism. Each of the most demeaning authors has decided that their works are less damaging than those who they accuse therein of wrongdoing. Just as there is trumped up science by press conference, there is trumped-down medicine by investigative journalists

[ii] See bio-sketch on INHN to understand the history. This informs my comments.

[iii] For example, with biomarkers, the primary cabal and its secondary opportunists would ordinarily be under external limits that might temporarily redirect them to paths of societal virtue. Yet even this should not be expected, as seen with $12000/ month bio-marked anticancer biologicals. Thus, pharma marketing gets to keep its cake and eat it too. The large print: Of patients with positive biomarker XYZ cancer response is overall response rates are 66 %. The fine print: Overall anticancer response is observed in 23% of patients with XYZ cancer, irrespective of biomarker status. Overall survival is not greatly impacted.

[iv] In this I have come to respect the efforts of Professor Barney Carroll, a substantial pioneer-contributor to the science of psychopharmacology, who has elegantly taken on scientific propaganda paper by paper. Yet, perhaps out of fear of being identified as apologist, few with exceptions, e.g. Klein, 2000– have attempted to confront sensation seeking investigative reporters or cloaked anti-psychopharmacology authors.

[v] Innovations we need: ("small thing": pathophysiology of all major categories of "mental illness"), biomarkers starting with known effective drugs in tightly controlled samples of authentic patients, rapid and durable antidepressant, low harm rapidly acting antipsychotic, effective anti-neurodegeneration, anti-sickness (cytokine) syndromes, non-addictive analgesics, better anti-cycling agents, a less cumbersome lithium, bullet proof controls for talking therapy research, an rapidly effective treatment for disabling obsessive compulsive syndromes, eating disorders, chronic pain-depression treatment, completely effective alcohol anti-addiction strategy, intensive treatment discovery in children and adolescents, treatment of borderline and other severely disabling personality disorders, and many more. Start anywhere economically.

[vi] Professional Patients and Deception In Clinical Research Trials, see http://www.forbes.com/sites/medidata/2015/10/19/professional-patients-and-deception-in-clinical-research-trials/#5cfc5b324cea or Devine EG, Waters ME, Putnam M, Surprise C, O'Malley K, Richambault C, Fishman RL, Knapp CM, Patterson EH, Sarid-Segal O, Streeter C, Colanari L, Ciraulo DA. Concealment and fabrication by experienced research subjects. Clin Trials.2013;10(6):935-48.

[vii] Despite 1) authors in 2002 suggesting ways to improve clinical trial designs in it to detect antidepressant effects, 2) the NIMH launching in 2003 a 4-year study of St. John's Wort to treat it, 3) a 2011 meta-analysis declaring antidepressants as clearly ineffective treatment for it: you'd think that in 2013 the DSM-5 would at least recognize "minor depression." (Barbui, Cipriani, Patel, Ayuso-Mateos, & van Ommeren, 2011; Diagnostic and Statistical Manual of Mental Disorders, 2013, "Treatment for Minor Depression," 2003; Rapaport & Maddux, 2002) But no, it no longer exists.

[viii] His data-driven anti-psychopharmacology made him a favorite target for defenders of the biological psychiatry flame. Being myself at times in show business, I can relate to Kirsch. Most do not know that Irving had been nominated for a Grammy award as Best Comedy Recording in 1974. This he accomplished by distorting recordings of Richard Nixon's speeches and press conferences during the Watergate hearings (according to Wikipedia, anyway.

[ix] In meta-analysis, these studies in ~2500 patients, when properly weighted, were negative outliers, among 5 positive studies in > 2500 patients (3 prior and 2+ thereafter at 70 -125 per arm) in which high dose NK1RAs clinically and statistically separated from placebo with Hedge's G ~ 0.5 - (M. S. Kramer, 2016b)

[x] Whoops! Psychologists are likely offended, now. I don't want any part of your dollar, but I do not believe your controls. Maybe someday I'd want to really take it on as a project as I think there is a way forward. However, biological psychiatry is much more important for me just now. That is all.

[xi] Computed by the author. NNT are offered in lieu of confidence intervals.

[xii] Recreational anesthetics are also now being administered IV as unapproved allegedly rapidly acting specific antidepressants for treatment resistant depression. But, ketamine has street value (as a recreational drug it is termed “special K” or “ket”.) Until proven otherwise, are physicians are just running ketamine den’s for ket admirers? We are waiting to observe, if ever, whether its metabolite, (2S,6S;2R,6R)-HNK proves to be an antidepressant without the rush. If so, and if durable, that might be quite a breakthrough.

[xiii] With regard to normal and abnormal behavioral states, glia and vasculature may count as much - or more - than circuitry in what we’ve been trying to understand and achieve for decades. This is a speculation that I’ve held for 50 years; I am delighted that reports are just now appearing which are investigating this area.

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