

**Thomas A. Ban: Conflict of Interest in Neuropsychopharmacology
Marketing vs. Education
Bulletin - Collated 5**

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Thomas A. Ban: Conflict of Interest in Neuropsychopharmacology: Marketing vs. Education

The term “conflict of interest” is defined in the Webster dictionary as “a conflict between private interests and official responsibilities of a person in a position of trust” (Merriam-Webster 1985). It is used in reference to situations in which fiduciary interest, founded on trust or obligation, is compromised by another interest (Black 1978). If people act contrary to their fiduciary interest they act in “conflict of interest.”

Prior to the 1980s, little attention was paid to “conflict of interest” in science and medicine. At present, authors in most medical journals and speakers, at most medical conferences are required to disclose their financial involvement with the pharmaceutical industry (Krimsky 2006; Lemmens 2008). While receiving funds from industry is a financial motivation, it may or may not lead to an act in conflict of interest.

Neuropsychopharmacology studies the mode of action of psychotropic drugs for obtaining information on the biochemical underpinning of mental pathology in order to develop rational pharmacological treatments (Hollister 1996; Wikler 1957). Psychotropic drugs are the means and the end products of neuropsychopharmacological research. Developed by drug companies and registered by regulatory authorities, the prescription of psychotropic drugs is dependent on interaction between (academic) education and (industrial) marketing. The objectives of marketing (industry) and education (academy) are

in conflict. The objective of marketing is to get a product prescribed in the widest possible population, whereas the objective of education is to guide the judicious and discriminate use of available drugs. Both successful education about the clinical use of psychotropic drugs and neuropsychopharmacological research, are dependent on established therapeutic effects of a drug in a well-defined population, whereas successful marketing is dependent on demonstrated therapeutic efficacy, as defined by regulation, in the widest possible population in which the substance may have an effect in some patients.

Introduction of psychotropic drugs, during the 1950s, focused attention on the pharmacological heterogeneity within psychiatric diagnoses (Ban 1969, 1987). To meet educational and research objectives, there was a need to resolve this heterogeneity by identifying the treatment responsive sub-populations within the diagnostic groups (Ban 1969, 1987, 2007; Freyhan 1959; Klein 1973, 2008). This did not happen (Ban 2008; Klein 2008). Instead, in keeping with marketing interests, the randomized clinical trial was adopted for the demonstration of efficacy in a diagnostically defined but pharmacologically heterogeneous population. Efficacy is a statistical concept relevant to the population rather than to the individual patient. Statistically significant efficacy of a drug indicates that the study population as a whole responds differently to a particular substance than to an inactive placebo with an arbitrarily defined statistical probability to qualify for a significant difference (Ban 1964, 2006; Hamilton 1961). It implies that there is a treatment responsive sub-population in the diagnostic group, but it does not identify the treatment responsive subpopulation (Ban 2006).

Introduction of the first neuroleptics, in the mid-1950s, coincided with the publication of Karl Leonhard's monograph on the *Classification of Endogenous Psychoses* (Ban 2006; Leonhard 1957). In Leonhard's (1957) classification, schizophrenia was split into two major classes of disease, referred to as "systematic schizophrenia" and "unsystematic schizophrenia," with several forms and sub-forms in which moderate to marked responsiveness to neuroleptics varied from less than 1 in 4 patients (in the "systematic hebephrenias"), to more than 4 in 5 patients (in "affect-laden paraphrenia"), one of the three forms of "unsystematic schizophrenia" (Astrup 1859; Fish 1964). The differences in responsiveness were not restricted to therapeutic effects but were present also in susceptibility to adverse effects (Ban 1990). Findings of an international survey carried out in the 1980s showed that the prevalence of tardive dyskinesia was over 20% in the treatment refractory subpopulation in Leonhard's classification and below 5% in the

treatment responsive one (Guy, Ban and Wilson 1985, 1986). Adoption of Leonhard's classification of "schizophrenias" would have been in-keeping with educational needs by providing at least orientation points for prescribing neuroleptics more discriminately in patients with schizophrenia. It would have also provided neuropsychopharmacological research a pharmacologically sufficiently homogeneous population to study the mode of action of neuroleptics in order to get information about the biochemical underpinning of "affect-laden paraphrenia." Again, this did not happen. Instead, a dopamine hypothesis of "schizophrenia" and not of "affect-laden paraphrenia" was formulated; and a series of new "haloperidol type" of potent dopamine receptor blocker neuroleptics gradually replaced generic "chlorpromazine-type of neuroleptics" in the entire schizophrenic population, including the subpopulation in which in Fish's study, they had virtually no beneficial effect (Carlsson and Lindqvist 1963; Snyder 1975; Van Rossum 1966). Since "haloperidol-type of neuroleptics" have stronger affinity to dopamine than to serotonin receptors, whereas "chlorpromazine type of neuroleptics" have stronger affinity to serotonin than to dopamine receptors, it led to severe extrapyramidal signs in many patients with a high prevalence of tardive dyskinesia (Gyermek 1955; Gyermek, Lázár and Csák 1956; Lambert, Perrin, Revol et al. 1959). Then, to undo the harm, prescription practices were reversed, and again, in keeping with marketing interests, a series of new "clozapine-type of neuroleptics," which similar to chlorpromazine-type of neuroleptics have stronger affinity to serotonin than to dopamine receptors, gradually replaced *generic* haloperidol-type of neuroleptics in the entire schizophrenic population including the subpopulation in which more than 4 in 5 patients responded to them (Ban 2004; Ban and Ucha Udabe 2006; Meltzer, Matsubara and Lee 1989). The net result was a shift from neurological to metabolic side effects. Both shifts, the shift from "chlorpromazine-type of neuroleptics" to "haloperidol-type of neuroleptics" and from "haloperidol-type of neuroleptics" to "clozapine-type of neuroleptics," were led by academics. A full circle was closed, half a century passed without a single clinically more effective or selective neuroleptic than chlorpromazine for the treatment of schizophrenia.

The story of antidepressants in the treatment of depression is similar to the story of neuroleptics in the treatment of schizophrenia (Ban 1974, 2001, 2004). At the time of its introduction, imipramine was found to be powerfully effective in 1 of 3 patients with endogenous depression, an umbrella diagnosis that no longer exists (Ban 1974; Klerman and Cole 1965). Endogenous depression included syndromes, which arose, assumedly

from a primary pathology of mood, which, in typical cases, shared common characteristics of sudden onset, episodic course and full remission between episodes (Ban 2000, 2002; Kraepelin, 1896; Leonhard 1957; Schneider 1920). Patients diagnosed with one or another form of endogenous depression, were clearly distinguishable from each other and from the general population (Ban 1987). Today, these “prototype-based diagnoses” are history; they are swallowed up by broad “consensus-based diagnoses” like “major depression” in the classification of the American Psychiatric Association and “depressive episode” in the classification of the World Health Organization, in which incomplete remission occurs in around one-third of all cases (American Psychiatric Association 1994; Keller, Klein, Hirschfeld et al. 1995; Kessler, McGonagle, Zhao et al. 1994; Michalak and Lam 2002; World Health Organization 1992). Consensus-based diagnoses cover up prototype-based diagnoses to the extent that even if a severely ill patient displays all the symptoms of “major depression” or “depressive episode,” one still would not know whether the patient qualifies for “vital depression,” the form of depression that Kuhn maintained, allowed him to discover imipramine’s “antidepressant” effect (Ban 2000; Kuhn 1957, 1986).

The problem is further compounded by the drastic increase of the depressive population in epidemiological surveys in the first 20 years after the introduction of imipramine and other antidepressant drugs. These studies indicate that even the lowest prevalence figures of depression are seven to ten times higher in the “antidepressant era,” i.e., after the introduction of the first antidepressants with demonstrated therapeutic efficacy, than before (Hoenig 1980; Silverman 1968). Prescribing antidepressants to this large population, in which even with an optimal 1 to 3 response rate to the pharmacological action of antidepressants, implies that more patients are exposed to potential side effects than one could expect to benefit from these drugs (Ban 2001, 2006, 2008; Szendi 2004). The shift from “prototype-based diagnoses” of depression to “consensus-based” unitary concepts of “depression,” such as “major depression” in the DSM-III and “depressive episode” in the ICD-10, has perpetuated this state of affairs. It has also precluded the possibility for using old prototype based diagnoses for the identification of the treatment responsive subpopulation within “major depression” or “depressive episode.” Yet, the shift was led by academics.

Clinical development of psychotropic drugs entered a new phase, during the 1980s with the replacement of single-center isolated clinical studies by multi-center, centrally coordinated clinical investigations, designed with power statistics to prevent Type II error,

i.e., missing of a statistically significant difference because of insufficient sample size. These studies are conducted in order to meet regulatory requirements for introducing a compound into clinical use. Yet, the findings of this research provide the evidence base for both, marketing and education, thereby confounding, by the dawn of the 21st century, education in pharmacotherapy with the marketing of psychotropic drugs (Ban 2006).

Today, most “evidence-based” information in education about the use of psychotropic drugs is generated in such multi-center studies. Treatment guidelines prepared by opinion leaders and reports reviewing evidence-based information by task forces are no exceptions. By disqualifying papers from the first thirty years of pharmacotherapy on grounds of methodological shortcomings, one relatively current such report on “Antidepressant medications and other treatments of depressive disorders” justified, on the basis of “a review of evidence,” the preferential prescription of the newest and most expensive antidepressants over the old ones (Baghai, Grunze and Sartorius 2007; Ban 2008).

In the current state of confusion the contrary objective of education to marketing, no longer provides the necessary balance for the optimal use of psychotropic drugs. The blurring of education with marketing has created a situation in which educators in pharmacotherapy may inadvertently pursue activities in conflict with their fiduciary interests. Addressing monetary incentive alone in this confound, an ethical-legal issue, however important it is, distracts attention from the heart of the problem: that until the pharmacological heterogeneity within the diagnostic groups is not resolved pharmacotherapy with psychotropic drugs will inevitably be dominated by marketing interests (Ban 2007).

Insofar as pharmacotherapy with psychotropic drugs is concerned, the pharmacologically heterogeneous diagnoses have restricted the relevance of pharmacodynamic information generated by neuropharmacological research to the side effect profile of psychotropic drugs. And, insofar as neuropsychopharmacology is concerned, the lack of pharmacologically valid psychiatric diagnoses has deprived neuropharmacological research from clinical feedback to the extent that no clinically more selective or effective pharmacological treatment has developed since the introduction of the first set of therapeutically effective psychotropic drugs in the 1950s.

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December 26, 2013

Barry Blackwell's comment

The picture your essay portrays accurately and elegantly is not so much an ethical "conflict of interest" as a conflict between a homogeneous (specific) approach to drug discovery and clinical treatment versus a heterogeneous (DSM) one. I think it is a mistake to view this as a difference between "education" and "marketing" for the following reasons:

1. You omit all mention of safety and concentrate on efficacy. But the Hippocratic ideal of "First do no harm" surely applies equally to both industry and education and was the foundation of the Kefauver Amendments that set FDA policy. Risk is increased to the extent that large homogeneous populations are used to "prove"

- efficacy and should be of interest to both educators and industry especially since the etiology of a side effect may have nothing to do with the mechanism of therapeutic efficacy.
2. Your thesis demands a narrow definition of who is an educator. As clinical psychopharmacology evolved it moved from asylums, the VA and private practice to academic medical centers - the heart of medical education after the Flexner revolution. And this is where the DSM and double blind methodology flourished precisely because they had a false aura of scientific integrity, serving as an antidote to psychoanalytic ideology. Educators are as much, perhaps more, to blame as is industry for developing and endorsing the tools that led to a heterogeneous approach. The subsequent fact that industry bribed education and its professional associations (APA, ACNP) to support the approach long after its falsehood became clear to a few wise individuals (like yourself) makes any distinction between "education" and "industry" dubious at best.
 3. There is an extent to which making the distinction as you do dilutes the moral implications. So educators are not responsible for what industry does (even as they endorse it) while industry is only trying to make an honest profit (even as it stifles research findings, raises false hopes and kills people). Meanwhile they both foster the heterogeneous approach to clinical efficacy.

In short, I am far less concerned with what I believe to be a weak "straw man" definition of "conflict of interest" than I am about the mutual harm both "educators" and "industry" have brought by endorsing the heterogeneous approach to efficacy while downplaying side effects.

January 30, 2014

Thomas A. Ban's reply to Barry Blackwell's comment

Thank you for your comments. If the recognition that the objectives of marketing (to get a particular product prescribed to the widest possible population) and education (to guide the judicious and discriminate use of drugs) are in conflict would imply approval of

illegal marketing practices, you would be correct that I “dilute moral implications” and provide a ”straw-man definition” for “conflict of interest.” But this is not the case. I consider those practices you condemn, such as bribing, overstating benefits, covering up adverse effects of drugs, etc., just as distasteful, and even criminal, if they violate the law, as probably you do. True, I have not addressed in my essay these well-known concerns because they are quite apparent, already voiced, and rightfully attacked by many, including your-self. Instead, I was trying to focus attention on a less obvious and unrecognized issue. It is the excessive promotion by some educators the prescribing of psychotropic drugs to an artificially enlarged population by the replacement of prototype-based diagnoses by consensus-based diagnoses in which in some diagnoses, e.g., major depression, more patients are exposed to the risk of potential side effects than would expect to benefit from treatment. Pointing fingers at individuals or blaming industry in this situation does not help to resolve the issue. It may even distract attention from the need to develop a methodology that would allow the delineation of pharmacologically more homogeneous diagnostic populations than those currently in use and make possible a more discriminate use of psychotropic drugs

March 13, 2014

Barry Blackwell’s response to Thomas A. Ban’s reply

"The nub of our disagreement lies in your concluding assertion that "pointing fingers at individuals and blaming industry... does not resolve the issue." On this we agree except for the implications. Blame is an impotent strategy if it is accompanied by consequences and sanctions. If the FDA, Law courts and Congress required industry to be honest (and scrupulously scientific) and academic institutions fined or fired faculty who are well funded false prophets then "conflict of interest" would disappear. This is why I called your definition a "straw man" - it leads to no solution."

June 12, 2014

Thomas A. Ban's response to Barry Blackwell's response

My essay is based on the importance of the recognition that there is conflict between marketing with the objective to get a product prescribed to the widest population and education with the objective to prescribe it as discriminately as possible. It would be unfortunate if recognition of this conflict would distract attention from and serve as a cover, “straw man” for unethical conduct because contrary to your contention, the possibility for acting against one’s fiduciary interest in this conflict would not “disappear” by proper legislation and its reinforcement. The negative consequences if educators are acting against their fiduciary interest in this conflict could be reduced by research that would identify discrete, pharmacologically more homogeneous populations than the ones identified in currently used consensus-based diagnoses. Since the negative consequences on neuropsychopharmacology and society are profound if educators act contrary to their fiduciary interest in this conflict, I hope you would agree that concerns for unethical conduct should not suppress the expression of the need to address the conflict between marketing and education.

January 22, 2015

Barry Blackwell's response (2) to Thomas A. Ban's response

The difference between us has narrowed not to what the problem is but what to do about it. You express the benevolent but naïve opinion that educators will be educated to stop selling their prestige and opinions to industry by “research that would identify discrete pharmacologically more homogeneous populations.” Both of us hope that long awaited goal can be achieved but this is unlikely if money will still be deployed to bribe susceptible educators with flexible consciences to express opinions for or against a specific product. Greed is embedded in the human genome. Even the most specific of drugs will have properties that can be used to convey advantages of one product over another. Such as onset or duration of action, side effects, cost, ability to measure blood levels etc. These will be embellished by the purchased endorsements of vulnerable educators. The experiment you

propose for educators has already been performed with politicians. There is no sign they can be educated to cease being puppets for the lobbying industry despite the fact that their statements are rigorously judged “true or false” by “PolitiFact.”

March 5, 2015

Thomas A. Ban’s response (2) to Barry Blackwell’s response (2)

Our disagreement, as I see it, is not about “greed” or whether educators sell their “prestige and opinions to industry” because I never questioned that. Our difference is that even if educators don’t sell their “prestige and opinions,” we have created evidence-based data exclusively on the efficacy of psychotropic drugs on enlarged diagnostic populations that by confounding marketing with education serves marketing interests. All I am suggesting is that we should generate evidence-based data by identifying treatment responsive subpopulations with respect to effects of psychotropic drugs, as much as possible, so that even if educators do sell their prestige and opinions, the potential harm from it should be reduced.

March 19, 2015

Jose De Leon’s comment on Thomas A. Ban’s essay and on Barry Blackwell’s comment on it

If one comments on the issue of conflict of interest in neuropsychopharmacology, a very “conflictive” issue, one should acknowledge his/her own conflicts about the issue and of the discussants who are commenting on the issue.

In that spirit of openness, regarding the issue of conflict of interest, I would like to acknowledge that I do not agree with all of David Healy’s writings but I usually recommend his book (*The Creation of Psychopharmacology*. Cambridge, MA: Harvard University Press, 2002) to my residents. One suspects that many

neuropsychopharmacology experts might disagree with my admiration of some of Healy's writings.

Regarding Dr. Blackwell, I have never met him in person but I am very familiar with his book *Discoveries in Biological Psychiatry* (Lippincott 1970), to the point of recently ordering a second copy. I know his claim to fame, the "cheese" effect associated with MAO inhibitors. I am also familiar with one of his letters on lithium prophylaxis (*Br J Psychiatry* 1971; 118: 131-2) in which he made Dr. Schou very unhappy by comparing him with a religious fanatic. In summary, I am neutral (I credit him for the cheese effect, but detract him for criticizing Schou) regarding him besides admiring him as being one of the "elders" who started psychopharmacology.

Regarding Dr. Ban, I am afraid that I am very positively biased in a way that I may have made my words too critical. (If I were to believe in psychoanalysis, which I do not, I would accuse myself suffering from a reactive formation in this comment.) I have never met Dr. Ban in person but I have always admired 1) his involvement in the AMDP English version; 2) his schizophrenia treatment response studies using Leonhard classification; and 3) his crucial role as main CINP historian. In November 2013, Dr. Ban contacted me by e-mail. Since then, we have had several wonderful e-mail and phone conversations. We discovered that among other things, we share a love for 1) the history of psychiatry, 2) descriptive psychopathology, and 3) conceptual issues. Moreover, I have discovered he is a very nice and gentle "elder." He impresses me as more of a "Franciscan monk" than a psychopharmacologist. I am a psychopharmacologist in my 50s; if one conducted a personality study on me and my colleagues in this age group, high mean scores in arrogance and meanness would be expected, making Dr. Ban an absolute statistical outlier.

Unfortunately, Dr. Ban's kind nature complicates his ability to criticize conflict of interest in psychopharmacology. Lenzer and Brownlee's comment in *BMJ* (2008; 337:206-208) titled "Is there an (unbiased) doctor in the house?" described corrupt doctors, using psychiatrists as an example. This is not a good thing to be known for. In this context, having Dr. Ban talk about conflict of interest is probably not a good idea; he would be naturally prone to be too soft. I am afraid that I agree 100% with Dr. Blackwell who may have become a very nice gentleman with age but was less so in the 1970s. As Dr. Blackwell describes, I believe that Dr. Ban missed the point completely in his comment. In that sense, I found Dr. Healy's discussion on conflict of interest was much more illuminating (*Medical partisans? Why doctors need conflicting interests. Aust N Z J Psychiatry* 2012; 46:704-7)

despite that I found some areas somewhat offensive. I have never met Dr. Healy but I suspect current psychopharmacologists deserve someone like him as a critic, instead of somebody as kind as Dr. Ban. I also found Dr. Maj's article illuminating (Financial and non-financial conflicts of interests in psychiatry. *Eur Arch Psychiatry Clin Neurosci*. 2010 Nov; 260 Suppl 2:S147-51).

March 20, 2014

Barry Blackwell's reply to Jose de Leon's comment

I enjoyed and appreciated Professor Jose de Leon's perceptive and (mostly) generous comments in response to my own concerning Tom Ban's posting on "Conflict of Interest in Neuropsychopharmacology." In doing so he declared his own "conflicts of interest" towards Tom and I based on his prior knowledge of our accomplishments.

Jose expresses some ambivalence about my credibility based on a letter I wrote to the *British Journal of Psychiatry* 43 years ago questioning Dr. Schou's credibility in regard to his previous research on lithium prophylaxis. We seem to have a court full of credibility issues!

The origin of that controversy stems from 1968 (46 years ago) when I had just completed residency training at the Maudsley Hospital and was working as a research fellow with Professor Michael Shepherd. We published an article (I was first author) in the *Lancet* *Prophylactic Lithium: Another Therapeutic Myth?* [*Lancet* 1968 (1) 968-971]. This article did two things; it provided a rigorously critical analysis of Schou's study methodology (for which the Maudsley was renowned under Sir Aubrey Lewis) and it employed the same methodology to show that imipramine could produce similar results.

In 2012, (54 years later), I published my memoir, *Bits and Pieces of a Psychiatrist's Life*, in which I devote 14 pages (215-229) to the topic, "Learning from Lithium." In it I state: "We reached the wrong conclusion for all the right reasons" (p.220). By this I meant that more than a half century of clinical practice has clearly proven Schou's claim was accurate and a great boon to the profession and our bipolar patients. What is also true however is that the scientific method Schou chose was seriously flawed for a variety of reasons discussed in the original *Lancet* article and it failed to distinguish lithium from

imipramine – controversies about trial design and outcomes in bipolar disorder that continued for several decades.

I challenge Professor de Leon to resurrect and carefully read our original 1968 article, review the subsequent research and also read the appropriate section in my 2012 memoir before submitting his own contribution to the “Controversies” section of inhn.org on the subject of Prophylactic Lithium. I am confident from the tenor of his current comments that he is a fair-minded scientist and that doing so will eradicate any doubts he still has in assessing my own motives in the lithium controversy. I will be happy to provide him with a free (autographed) copy of my book.

April 24, 2014

Thomas A. Ban’s reply to Jose de Leon’s comment

Thank you for your comment. If conflict of interest issues could be restricted to financially motivated actions contrary to fiduciary interest, i.e., to the legal-ethical definition of the concept, I would agree with you to leave it to those currently involved with them. But this is not the case and my essay addresses a “conflict of interest” issue that has not been addressed to date in so far as I know. It is the “conflict of interest” that arises from the “conflict” between “marketing” with the objective to get a particular psychotropic product prescribed for the widest possible population and “education” with the objective to provide a guide for the judicious and discriminate use of psychotropic drugs. Introduction of psychotropic drugs during the 1950s, focused attention on the pharmacological heterogeneity within psychiatric diagnoses. To meet educational and also research objectives in neuropsychopharmacology, there was a need to resolve this heterogeneity. Yet, in keeping with marketing interests, the randomized clinical trial was adopted for the demonstration of therapeutic efficacy in pharmacologically heterogeneous diagnostic populations. There has been virtually no effort for well over half a century to develop a clinical methodology for identifying the treatment responsive subpopulations. Compromising the objective of education for marketing interests interfered with the development of neuropsychopharmacology. It also encouraged the indiscriminate use of

psychotropic drugs. Addressing "conflict of interest" issues which qualify for the legal-ethical definition of the concept may assist in capturing crooks, whereas addressing conflict of interest issues which arise from the conflict between marketing and education by adopting or developing a methodology that would provide pharmacologically more homogeneous diagnostic populations than current consensus-based classifications may open the path for the development of more selective and thereby more effective psychotropic drugs.

December 11, 2014

Samuel Gershon's comment on the exchange between Thomas A. Ban and Barry Blackwell

I agree, but in addition, Pharma is in control of everything from telling the patient, based on information they give them about what medication to ask for. Then, when the doctor prescribes that drug, another force acting on the market, an ill-advised community advisory group, comes into force and gives ill advice, which is unhelpful. I have been asked about two such cases in the last 10 days.

February 26, 2015

Thomas A. Ban's reply to Samuel Gershon's comment

Pharma's control on prescribing is made possible by international trade agreements which guarantee companies exclusive property of information on drugs (under patent protection) they are developing. The potential negative effects of industrial control of data, however, could be reduced by research that would generate information on subpopulations within diagnoses in which the different psychotropic drugs are effective. Even the current negative role of "patient advisory groups" might be reduced by the availability of such information.

March 26, 2015

Donald F. Klein's comment on the exchange between Thomas A. Ban and Barry Blackwell

The discussion between Ban and Blackwell misses crucial current issues. "Conflict of interest" rose to public interest when it became apparent that Pharma publications were regularly more outcome positive than independent studies. This led to the suspicion of bias but with no way to prove it, since data were sacrosanct. Therefore suspicion was diverted onto the basically problematic, ad hominem approach of authors declaring income sources. This miscarried repair diverted from the basic issue "Is there really data bias?"

This issue can only be met by independent data analysis at the patient level. If a therapeutic claim is made, shouldn't the data supporting that claim be available for independent analysis? Otherwise, peer review is helpless since it only has data summaries and inferential statistics and implicit trust in their relevance and accuracy.

That is exactly the highly charged debate going on with regard to the initially forward looking policies of the European Medicines Agency. Their web site yields worthwhile, detailed access to the EMA positions.

However, the move to demand public access to patient level data is now stymied in court by firms claiming that such disclosure causes economic loss. The European Ombudsman has already declared that public health issues trump questionable economic losses. Recently, it looks like EMA is backtracking. Still ambiguous re decisions but the concerns of Pharma may prove decisive. Stay tuned.

Ira Glick and I have also addressed these issues in our paper, Klein DF, Glick ID: "Conflict of interest, journal review, and publication policy," published in *Neuropsychopharmacology*. 2008 Dec; 33 (13): 3023-6. My point is that both Ban and Blackwell could have improved their rather abstract discussions by reference to the current legal and judicial struggle for and against open access, as well as citing the various activist groups.

July 10, 2014

Barry Blackwell's reply to Donald F. Klein's comment

I agree with Don Klein's point concerning Pharma's current stranglehold on data and the consequent absence of independent peer review to which he and Ira Glick have drawn attention.

This is certainly the contemporary focus of concern but both Tom Ban and my comments were embedded in a more historical and fundamental analysis of conflict of interest. My own focus which, while it may appear "rather abstract," goes to the roots of a problem that involves far more than industry and its latest maneuvers. It includes trial study clinicians who relinquish their data for analysis and publication in return for money without critical oversight; academics who provide paid for endorsements of industry claims; professional and advocacy organizations that accept funding for meetings or organizational support in return for access to the public and spurious legitimacy; practicing physicians of all stripes who accept lavish dinners, golf outings and office paraphernalia in return for prescribing a company's products; journal editors who publish flawed articles and print dubious advertising claims; Presidents and Department Chairs of prestigious universities who accept million dollar grants to support faculty stipends and research with the naiveté of a Robin Hood robbing the rich to help the poor; the FDA and Congress for turning a blind eye to flawed products and over the top television advertising to the public which drown out bad news with distracting visual images. In its broadest sense conflict of interest is about how greed and money suborn scientific integrity.

Contemporary opinions about "conflict of interest" continue to debate its meaning and implications as recently as the current issue of JAMA, *Potential Conflicts of Interest for Academic Medical Center Leaders* (JAMA 2014; 312(5): 558. My sentiments echo those of Arnold Relman, long time former editor of the New England Journal of Medicine, expressed in his final letter to JAMA, submitted a few short sad weeks before his death. "Academic medical centers and pharmaceutical companies are quite different social functions. The companies are obligated to maximize profit for its owners and shareholders. In contrast, AMC's have a moral commitment to serve the public interest before their own. No individual can simultaneously serve as a leader in both these institutions without compromising obligations to one or both."

While these caveats are directed to leaders at the apex of the most involved and prestigious organizations, my own concerns, expressed above, cover a wider range.

September 11, 2014

Thomas A. Ban's reply to Donald F. Klein's comment

I appreciate and share your concern about lack of “open access” (transparency) of data generated in clinical (and all other) research with psychotropic drugs. Yet the lack of open access is primarily a legal issue, as the proprietary nature of that information is protected by the law. It should not distract attention from the inherent conflict between marketing and education and the need for psychiatric research to identify pharmacologically more homogeneous populations than the populations identified by current consensus-based diagnoses

February 5, 2015

Donald F. Klein's further comment on the exchange between Thomas A. Ban and Barry Blackwell

Barry Blackwell and Tom Ban share my concerns about lack of open access to data generated in clinical research. However, Tom suggests “lack of open access” is a local legal issue, properly a sub-issue within the larger issues of marketing vs education.

Barry argues that current Pharma practices irretrievably blur the distinction between unbiased data and education, since what passes for education is actually tendentiously distorted data.

I accentuate that “local legal issues” are not inviolable dicta. Rather, the nexus of opposing social and economic interests, fought out in the political arena. Politically modifiable, interest based, legality is so neglected that even appropriately broadening conceptual issues, e.g., “marketing vs education,” may still displace enlightenment from concrete conflicts. Worse, it may deflect from the organized, active political groups that, hopefully, lead to legal change.

July 2, 2015

Thomas A. Ban's reply to Donald F. Klein's further comment

We certainly agree that “local legal issues are not inviolable dicta” and that “opposing social and economic interests” should be “fought out in the political arena.” The difference between our positions is that you believe that fight in the political arena should be given top priority in conflict of interest issues in neuropsychopharmacology, whereas I argue that the fight in the political arena should not distract attention from the need for identifying treatment responsive populations within diagnostic categories and delineating the therapeutic profile of psychotropic drugs. Addressing the same issue in 2006, I wrote: “Blaming industry for withholding information; chastising governments for allowing the release of semi-finished products: and slanting academic psychiatry for confounding education with marketing, have little impact... There is no political solution for any of these issues, but all three issues would be resolved by the identification of the treatment-responsive form(s) of illness within the diagnostic categories and the delineation of the therapeutic profile of psychotropic drugs.”

Reference:

Ban TA. Academic psychiatry and the pharmaceutical industry. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2006; 30: 429-41.

July 16, 2015

Donald F. Klein's response to Thomas A. Ban's reply

I believe there is more agreement than disagreement here. All agree that transparency is needed. I believe that requires access to patient level data as the EMA has held. Tom emphasizes that there are major legal problems in gaining such access. Therefore, as scientists, our focus should be on developing more homogeneous diagnostic sub-groups that will allow a better understanding of pharmacological interaction with

pathophysiology. This leads to better specificity of prescription and accuracy of prognosis. Certainly I agree, but must simply point out that such scientific development and legal/economic modification are not mutually exclusive goals.

My emphasis is that the current parallel group, placebo controlled, extensive design actually is problematic, since it gets in the way of improving homogeneity by confounding response due to specific drug benefit with improvement due to non-specific factors, e.g., "spontaneous" remission, anti-demoralization, etc.

The approach that may lead to more homogeneity in medication response is the "intensive" approach, basically double blind placebo substitution in apparent medication responders. This was previously discussed in the INHN comments on Bech's Clinical Psychometrics.

September 17, 2015

Thomas A. Ban's response to Donald F. Klein's response

Thank you for your response. I certainly agree with your statement that "the current parallel group, placebo controlled, extensive design actually is problematic, since it gets in the way of improving homogeneity." In fact, your statement corresponds completely with my view expressed in the essay that opened this exchange. It reads: "Introduction of psychotropic drugs, during the 1950s, focused attention on the pharmacological heterogeneity within psychiatric diagnoses. To meet educational and research objectives, there was a need to resolve this heterogeneity by identifying the treatment responsive subpopulations within the diagnostic groups. This did not happen. Instead, in keeping with marketing interests, the randomized clinical trial was adopted for the demonstration of efficacy in a diagnostically defined but pharmacologically heterogeneous population."

Undoubtedly, by using an "intensive research design," i.e., a "double-blind placebo substitution in apparent medication responders," as you suggest, would be one way of improving homogeneity, but this is a different issue that is beyond the scope of this

exchange on Conflict of Interest in Neuropsychopharmacology: Marketing vs. and Education.

September 22, 2016

Ernst J. Franzek's final comment

As a clinician and researcher who is particularly interested in improvement of disturbed mental states of individual patients I am very happy with Tom Ban's clear statement about the conflict of interest.

Within the schizophrenic spectrum there is one subgroup, affect laden paraphrenia as described by Leonhard, which responds best to neuroleptic treatment of any kind. Within the depressive spectrum, the best responders to antidepressive treatment of any kind suffer from pure Melancholia, also described as vital depression. From the clinically point of view there is not really a benefit of the "new" drugs compared to "old" drugs.

The replacement of single-center isolated clinical studies by multi-centers, centrally coordinated investigations took away the clinical observation of experienced psychiatrists and offers an elusive security of a better effectiveness of new psychotropic drugs.

Treatment with psychotropic drugs has become widely accepted and developed to a big business in mental health care. On the other hand, a careful education in skillful pharmacotherapy almost vanished. I completely agree with Tom Ban that the contrary objective of education to marketing no longer provides the necessary balance for the optimal use of psychotropic drugs. Indeed it prevents interest and education of young psychiatrists in differentiated psychopathology as one of the basic skills of clinical psychiatry.

My suggestion is that the way out of this dead end could be by going back to the clinical roots and by abandoning the need of multicenter studies with high statistical power, but lack of clinical relevance in individual patients.

February 9, 2017

Edward Shorter's final comment

Tom Ban opens this stimulating exchange with a shot across the bow: "No clinically effective pharmacological treatment has been developed since the introduction of the first set of therapeutically effective psychotropic drugs in the 1950s." So true.

Barry Blackwell replies to this, then Ban emphasizes the cardinal role of what others have called the "Key Opinion Leaders," or "KOLs," basically academics who have sold out to industry for handsome monetary rewards. Indeed, says Ban, the KOLs have helped enlarge the clinical population with a given diagnosis so greatly that many patients enrolled in trials don't have the disorder in question at all, but will get all of the agent's side effects while reaping none of the benefits.

Don Klein weighs in: The real issue is whether academic bias in favor of Pharma has produced a series of unduly favorable trials. The pathway to answering this question: We need public access to patient-level trial data.

Barry Blackwell replies to Klein: No, the whole enterprise has been corrupted by Pharma. Academic medical centers have a fiduciary duty to serve the public interest rather than industry. Such centers often fail in this duty.

Ban replies to Jose de Leon, who has meanwhile signed in. Ban reiterates his main point: There is a conflict between the needs of a marketing department and the duties of the industry and of the academy to educate the public. One might add that failure to educate the public properly about the role of reuptake in the efficacy of the SSRIs (probably very small) illustrates this conflict.

Then Ban hammers home the point that RCTs were designed to show efficacy in clinically heterogeneous populations. This does indeed suggest that marketing needs are in conflict with underlying science ("education").

Blackwell shoots back with doubts about the prospects of academics agreeing to help make clinical populations homogeneous.

I have one critical remark: This fast-moving and thoughtful exchange ignores that the greatest barrier to achieving clinically homogeneous trial populations is not sell-out academics, but the DSM. Such diagnostic constructs as "major depression" are hopelessly heterogeneous, but it occurs to few academics to unpack this unitary "depression" (or unitary "schizophrenia") in order to study drug effectiveness properly. The DSM diagnoses

are taken as gospel in other words and constitute a huge obstacle to drug discovery on the grounds that "You can't discover drugs for diseases that don't exist." Why are most academics so resistant to rejigging the DSM diagnoses? Just sell-outs? Respect for authority that goes back to the awe-stricken reception of Emil Kraepelin's textbook? Difficulty of getting grants to study diagnoses outside of the DSM framework? Whatever the reason, the unwillingness of academic psychiatry to challenge the DSM is really quite striking.

Don Klein starts to wind things up: Hey, we should wage a political struggle to get Pharma under control and gain access to patient-level trial data, rather than just fretting about heterogeneity.

Ban replies, no, the real struggle is intellectual: to define treatment-responsive subgroups.

The protagonists end by agreeing, "Let's dump the current model of conducting RCTs."

April 6, 2017

Thomas A. Ban's final reply to Ernst Franzek's and Edward Shorter's final comments

We received two final comments on the collated document of this project, which includes the transcript of the essay and the exchange that followed its posting: one comment from Ernst Franzek and another from Edward (Ned) Shorter. It is my privilege to answer both before the final collated document is converted into an Educational E-Book.

Ernst Franzek's comments are focused on the original essay. He recognizes the contrary objectives of marketing and education. To establish a proper balance between them, he emphasizes the need for teaching "differentiated psychopathology" in the training of psychiatrists in order to open up the possibility to identify subpopulations within consensus-based diagnoses responsive to one or another pharmacological treatments. Ernst notes that "replacement of single-center isolated clinical studies by multi-centers, centrally coordinated investigations" deprived these studies of the clinical observations of

experienced psychiatrists” and suggests “to go back to the clinical roots by abandoning multicenter studies with high statistical power, but lack of clinical relevance insofar as individual patients are concerned.” Whether one would need to revert to single center studies to get clinical relevance of findings is a moot question. It would probably be more important to understand that in conditions for which other treatments are available, the demonstration of therapeutic efficacy of a substance without identification of the treatment responsive subpopulations or demonstration of advantages in terms of side effects is exclusive to marketing interests.

In contrast to Franzek’s final comment in which clinical, educational and research issues relevant to conflict of interest between marketing and education are discussed, Edward Shorter in his final comments provides a fast moving overview of the exchange. It reads like a drama with direct quotations from the participants that culminates in a finale in which all the divergent views are reconciled. It is unfortunate that in this elegant presentation the essence of this exchange is missed. Thus, Ned writes: “I have one critical remark: This fast-moving and thoughtful exchange ignores that the greatest barrier to achieving clinically homogeneous trial populations is not sell-out academics but the DSM. Such diagnostic constructs as ‘major depression’ are hopelessly heterogeneous, but it occurs to few academics to unpack this unitary ‘depression’ (or unitary ‘schizophrenia’) in order to study drug effectiveness properly.”

After reading Ned’s comment, one wonders what we did wrong since the central point of this exchange is exactly what, in his perception, is missing from this exchange.

To ascertain that there is no misunderstanding, a direct quotation from the original text reads: “In the current state of confusion, the contrary objective of education to marketing no longer provides the necessary balance for the optimal use of psychotropic drugs. The blurring of education with marketing has created a situation in which educators in pharmacotherapy may inadvertently pursue activities in conflict with their fiduciary interests. Addressing monetary incentive alone in this confound, an ethical-legal issue, however important it is, distracts attention from the heart of the problem: that until the pharmacological heterogeneity within the diagnostic groups is not resolved pharmacotherapy with psychotropic drugs will inevitably be dominated by marketing interests.

"Insofar as pharmacotherapy with psychotropic drugs is concerned, the pharmacologically heterogeneous diagnoses have restricted the relevance of pharmacodynamic information generated by neuropharmacological research to the side effect profile of psychotropic drugs. And, insofar as neuropsychopharmacology is concerned, the lack of pharmacologically valid psychiatric diagnoses has deprived neuropharmacological research from clinical feedback to the extent that no clinically more selective or effective pharmacological treatment has developed since the introduction of the first set of therapeutically effective psychotropic drugs in the 1950s."

June 15, 2017