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Editorial: Drug Industry, Psychopharmacology, and Mental Health Care Needs: Where Do We Go From Here?

The pharmaceutical industry has recently been challenged with much public concern, despite its generally impressive success in promoting health care technology over the last decades. Pharmaceutical companies play a central role in new drug development, designing of randomized controlled trials (RCTs) that provide the data required to support efficacy and safety of novel treatments, initiating requests for labeling indications and safety warnings, and influencing consumer patterns of new products by health care providers and the public. As these are for-profit organizations, making huge capital investments that carry substantial risks, market forces and commercial interests must govern decision-making aspects in all these processes, and these may not always overlap with public health benefit. We briefly review the extent of the predicaments that have evolved, and conclude by summarizing unmet needs and outlining some possible directions for change.

The pre-marketing approval average cost for developing a new drug has recently been estimated at over US$800 million (1). The high cost of investment bars government and academia, leaving mostly the pharmaceutical industry to develop drugs for profit, with the consequence that new drug development priorities are largely determined by financial opportunity considerations rather than public health needs. The high cost of investment also translates into a high inducement for marketing, motivating drug development and marketing strategies that have recently attracted much criticism. Offering hope to the large proportion of patients who do not respond well to currently available drugs requires the discovery of novel mechanisms of action. However, the development of new compounds that emulate a known drug's mechanism of action, with some technical improvement (adverse effect profile, duration of action, etc.), tends to be more cost effective, and therefore predominates over investment in compounds with novel mechanisms. This is well exemplified in the field of psychotropic drugs, where the new generation drug revolution beginning in the late 1980s includes almost no novel mechanism agents. Instead, several drug companies have chosen to compete for the development of similar replica agents revolving around few known mechanisms, producing overlap in place of innovation. If public health needs were to guide new drug development, the overwhelming percentage of patients who do not achieve remission with current psychotropic agents, old and renewed (2–4) would have dictated increasing the relative percentage of investment into innovative compounds possessing added or unique efficacy or tolerability.

High cost marketing strategies applied to increase drug product sales have lately been the subject of heated critique. The majority of available evidence-based data on the efficacy and safety of drugs comes from phase III randomized controlled trials (RCTs). The prohibitive cost of conducting large scale RCTs contributes to the fact the majority of available evidence-based data are derived from studies conducted and funded by pharmaceutical companies. Industry-funded drug trials for assessing safety and efficacy are largely designed to comply with federal authority labeling approval requirements, and to affect consuming patterns, rather than to guide clinical practice by addressing real life clinical dilemmas (e.g., such as head-to-head comparisons of long-term safety and efficacy, against available treatment alternatives) as would be mandated by pertinent public health interest. One systematic evaluation reviewed comparative data on the efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder, concluding that although over 46 head-to-head short-term RCTs were examined, the quantity and quality of the evidence was generally found to be inadequate to allow actual quantitative comparisons, illustrating the limited relevance of industry-funded drug trials for guiding real life clinical decision making (5). More recent data suggest a systematic selection bias in antidepressant drug trials chosen for publication from among the many studies reported to the U.S. Food and Drug Administration (FDA) (6). Meta-analysis of both published and unpublished trials submitted

to the FDA during licensing suggests that, compared with placebo, the new-generation antidepressants do not produce clinically significant improvements in patients who initially have moderate or even very severe depression, but show significant beneficial effects only in the most severely depressed patients (7). It follows that published drug efficacy reports have apparently provided an inflated effect size, misinforming clinical decision making. Such phase III clinical trials are generally tailored to demonstrate the short-term efficacy and safety of a new intervention under ideal clinical conditions in comparison with no treatment (placebo) for the purpose of satisfying regulatory requirements for drug approval and marketing. In contrast, phase IV studies are designed with the pragmatic aim of comparing long-term effectiveness between available treatment options under real-life clinical conditions for the purpose of guiding treatment decisions. A large-scale phase IV research initiative prompted by the National Institute of Mental Health (NIMH) found a highly representative real-life clinical sample of depressed outpatients to exhibit low antidepressant response rates and a long time to remission for a generic prototype selective serotonin reuptake inhibitor (SSRI) (8), suggesting that previously published data in the sizable short-term industry-based literature indeed do not generalize well to actual clinical populations. Similar recent phase IV initiatives could not demonstrate superior effectiveness and tolerability for second- compared with first-generation antipsychotic drugs in the treatment of schizophrenia, with the majority of patients reporting early discontinuation of their assigned treatment, in large part owing to inefficacy or intolerable side effects (3, 4). Consequently, doubts have been raised whether the US $11.5 billion annual expenditure on the plethora of newer antipsychotics is justified in terms of concomitant gains for public health (9). In a similar vein, safety issues have been less than adequately addressed in several industry funded articles and reports. The highly publicized case of rofecoxib (Vioxx) litigation against Merck & Co. Inc. has been resolved after the company agreed to pay US $4.85 billion to settle litigations of drug-induced myocardial infarct and ischemic stroke in return for not having to admit causation or fault (10). Two recent articles published in The *Journal of the American Medical Association* (JAMA) by expert consultants involved in the litigation against Merck suggested the company may have systematically engaged in inappropriately influencing the publication and reporting of scientific articles relating to rofecoxib (11) and that published articles and analyses submitted to the FDA depicted a risk-benefit profile of the drug more favorable than that revealed in internal company analyses of the trial data (12). Another worrying example is current litigation against Eli Lilly for allegedly withholding information about olanzapine (Zyprexa)'s propensity to induce diabetes (13). Yet another highly publicized and long debated example is the lack of adequate assessment of suicidality in second-generation antidepressant phase III drug trials. Pharmaceutical companies have been criticized for not including formal assessments of adverse suicidal tendencies during antidepressant phase III trials, for pre-selection of non-representative patient samples by actively excluding subjects reporting prior suicidal tendencies, and for hiding suicide reports during drug trials. Post hoc meta-analyses found children and adolescents starting treatment with several newer antidepressants had a 4% risk of developing short-term suicidal ideation or behavior (e.g., there were no actual suicide cases), compared with 2% in those receiving placebo, leading the FDA to require black box warning on juvenile prescriptions in 2004 (14). Re-analyses are limited, however, in having had to reconstruct a post hoc proxy to assess "suicidality" (15), which may not translate well to actual suicidal risk. The warning was later extended in 2007 so that all antidepressant medications now carry an expanded black-box warning incorporating information about an increased short-term risk of suicidal symptoms for patients up to 24 years of age (16). The warning was extended based on additional evidence extracted from nearly 100,000 participants in 372 antidepressant RCTs, for a trend for increased risk of suicidality in the 18–24 age group that did not reach statistical significance, and despite the fact that such risk was substantially lower in antidepressant trials for other indications (e.g., obesity, smoking cessation and insomnia), indicating that such a risk is likely confounded by the indication (e.g., depression) (17), as had been previously suggested (18). The revised warning further clarifies that there is no evidence of an increased risk for

adults 25 years or older, that the risk is decreased for adults 65 years of age or older, and that "depression and other serious psychiatric disorders are themselves associated with increases in the risk of suicide." These developments have led to critical media coverage and growing public mistrust, with pursuant dramatic reductions in juvenile antidepressant prescriptions following 2004. Recent studies provide divergent data on the impact of the reduction in antidepressant treatment rates on suicide rates, with early data from the U.S. and the Netherlands (19) and Canada (20) reporting an increase in suicide rates followed the 2004 warning. In contrast, studies in the U.K. did not find such increase in suicides among minors despite a 40% decrease in antidepressant prescriptions (21, 22). As noted by one commentator, sustained antidepressant use among depressed patients is so infrequent that locating any effect on the risk for suicide in the general population would be surprising, given U.S. data showing that only half of depressed adults and a quarter of adolescents initiate antidepressant treatment, nearly half of all adults who start treatment discontinue after just a few weeks, and only 3% of adolescents dying by suicide in New York City had toxicology data showing recent use of antidepressants (23). To this, one should add the generally lower efficacy of antidepressants among minors (24, 25). Despite this lower efficacy, benefits of antidepressants in the pediatric population clearly outweigh risks related to suicidal ideation/suicide attempt across both anxiety and depressive indications (26).

Strikingly, however, the hundreds of industry-funded, high-cost, large prospective placebo-controlled antidepressant studies cannot be used to guide clinical practice despite enrolling several dozens of thousands of patients, as these studies were largely designed to circumvent rather than address the treatment of suicidal depressed patients. To address this, NIMH was prompted to sponsor studies of large representative patient samples that despite inherent methodological shortcomings related to their retrospective observational design, and demonstrated that antidepressant treatment in real life is correlated with reductions in suicides and suicide attempts in the weeks and months following antidepressant treatment initiation (27, 28).

This coincides with epidemiological data repeatedly reporting that despite the generally low fraction of depressed patients who receive adequate treatment, increments in second generation antidepressant prescription rates are correlated with decrements in population suicide rates (29 — 32). In conclusion, it appears that while idiosyncratic effects among rare vulnerable individuals cannot be ruled out (33), antidepressant-induced "suicidality" among younger individuals does not generally appear to translate into an increased risk of serious suicide attempts or completed suicides, and that treatment of depression is vital for reducing suicide rates even among minors (26, 34).

The overall concern is that industry practices producing selective data designed to satisfy labeling requirements and marketing, may expose patients to drug trials that do not aid clinical practice and damage public trust and may in fact hinder the appropriate utilization of much needed drugs. Despite the high cost of performing drug evaluation trials, the requirement for public health interest input into their design appears mandatory. This is evident not only from the above demonstration of how reliance on industry generated evidence may have underserved the clinical practice of the field for years regarding efficacy for newer drugs (3, 4, 6, 7). The other side of the same problem is that there is no commercial interest in generating safety and efficacy evaluations for older drugs that are still in wide use after their patent period has expired. One example is the recent awareness of limited if any efficacy (35) and increased mortality (36) related to the off-label use of antipsychotic agents for behavioral and psychotic symptoms among elderly dementia patients. It was not until evaluations initiated by drug companies interested in introducing an additional labeled indication for new generation antipsychotic drugs, revealed increased mortality in short term placebo-controlled trials (37), that the FDA released a black box warning on all antipsychotic agents, stressing that evidence based data on the older antipsychotics is lacking (38). This prompted NIMH to sponsor retrospective research revealing that a similar adverse propensity afflicts the use of old generation antipsychotics (39) that have been inadvertently prescribed for this indication since their introduction half a century ago, without appropriate evidence-based studies to guide such practice. Another illus-

tration is provided by the widely used mood stabilizer lithium, for which mostly limited retrospective data are available to guide clinical practice regarding serious adverse effects such as irreversible long-term renal impairment (40), despite being in clinical use since the 1940s. Rare long-term efficacy studies demonstrating significant reductions in rates of attempted and completed suicides for clozapine prophylaxis in schizophrenia (41) and lithium prophylaxis in bipolar disorder (42), against respective newer generation comparator drugs, further serve to illustrate the vital need for performing long-term phase IV studies designed to address pertinent clinical issues.

Barbui and Cipriani (43) have recently reviewed common pitfalls that plagued phase III clinical trials, including deficient statistical power, use of placebo arms in disorders where active comparator treatments are available, use of inappropriate dose regimens, employment of multiple comparison strategies to identify differences, use of composite outcome measures rarely employed in practice, and a short-term follow-up period. They argue that since phase III trials are designed and funded to comply with regulatory approval requirerments, the only way to overcome these long criticized shortcomings is by altering regulatory requirements by the FDA and the European Medicines Agency (EMEA), the European Union corrolary regulating drug approval and marketing. They further emphasize the importance of increasing support for comparative phase IV clinical trials designed to answer longer term real world clinical management questions, as well as for pharmacoepidemiological studies (or "medicine-based evidence") that investigate how and why drugs are actually prescribed under prevailing medical practice and actually used in real life (e.g., many times not in accordance with strictly labeled indications), and monitoring outcomes and the variables that may affect these outcomes (43).

Return of investment is based on allowing a relatively long period of patent protection rights. The effective patent life of a drug is reduced from the statutory 20 years duration of the standard patent to an average of 12–13 years, resulting from an inherent lag between the filing of patent application on a new chemical compound (usually delayed until shortly before clinical trials begin), and FDA approval. To compensate, U.S. Congress has added an extended exclusivity before competition by a generic alternative is permitted (44). Notably, the high pricing of new drug products during the patent protection period allows recovery of development costs at the price of a prolonged period of reduced access, limiting both lower income patients and developing countries from receiving up to date treatments, and creating a heavy burden on health care providers (45). This partly inherent cost of progress, places regulatory agencies in a constant need to reprioritize limited health coverage funds in order to allow the inclusion of redefined clinical indications and new technologies into binding health policy programs. It is imperative that this investment is indeed channeled to provide innovative technologies that offer fundamental improvements in efficacy or tolerability based on unbiased long-term evidence. Understandably, once the original patent indication runs out, drug companies attempt to further extend their revenue, by reintroducing the same agent with a slightly modified profile (e.g., extended release, active isomer preparations, etc.) or by introducing a new clinical indication (e.g., smoking cessation). Concerns have been raised that direct to consumer marketing strategies aimed to reshape consumer attitudes for commercial incentives may result in large scale unnecessary drug exposure (e.g., "disease mongering") (46). A serious concern is that such practices generate in turn mistrust regarding clinically important indications such as affective disorders, not only among lay media and public, but also among authoritative leaders in academia (47) and policy makers (48). This unfortunately is likely to contribute to the current grim situation where a majority of depressed patients do not receive adequate needed life-saving treatment (49).

The relationship between physicians and the pharmaceutical industry has been a focus for recent concern. There has been criticism of direct and indirect funding by pharmaceutical companies of medical education (50), prescription preferences (51), and research (52, 53). The prevailing standards assuming that small gifts do not influence physician behavior and that disclosure of financial conflicts is sufficient to protect patients' interests have recently been challenged, with suggested guidelines for much stricter physician-industry boundaries (54, 55). It is

of vital importance for medical practice to remain credible and free of commercial bias. However, physicians are not the primary cause of the current situation, and any call for erecting a wall between the pharmaceutical enterprise and the medical profession must provide realistic guidelines for the inherent role that medicine has to maintain in directing both the research and development and the translation of drugs to clinical practice.

The current situation is not likely to change without a fundamental modification in the rules of play. Some of the recent countermeasures already under way include Federal financing of phase IV studies designed to establish efficiency and safety and guide clinical decisions in real life (3, 4, 8), requirements to register drug trials and disclose all available data (56), open access to published biomedical research results (57), insistence on independent statistical analyses in studies published by the industry (58) and stricter guidelines for reporting conflicting interests (55).

Getting to the heart of the problem requires more fundamental changes, although it is unclear whether such a revolution is achievable, as such transformation may only occur through enforcement of public health interest considerations into the free market dynamics of drug development and marketing. Both the current patent and regulatory approval mechanisms would have to be modified to create a more effective incentive to develop innovative drugs and to ensure their long-term added efficiency and safety. Major items for change should include reprioritizing of drug research and development based on public health needs, putting stricter criteria for efficacy and safety assessment of patent drugs, allocating public funding for drug trials based on clinical need for evidence-based data, and enhancing the provision of drugs to cure disease, based on health care needs, by securing their affordability and accessibility.

Implementing real change is likely to require proactive health policy regulatory interventions balancing the basic respect for a free market economy profit-driven corporate culture that remains the cultivating soil motivating high cost entrepreneur investment, with enforcement of strategic long-term public health needs. Are these realistic objectives? Can public health needs be enforced upon financial opportunity considerations to guide new drug development? Can regulatory authorities find ways to increase the share of investment going to novel mechanism drugs by for-profit companies? Can international health policies derived from WHO surveys of health research priorities based on global burden of disease unmet needs be implemented in some way to increase the share of investment in drugs much needed for diseases endemic in developing countries or orphan drugs or pediatric indications where return of financial investment is appreciably lower?

Estimates of net income from leading drug products show a considerable margin of profit (45), suggesting a margin for intervention in free economy dynamics does exist. As succinctly noted by Wood (59), the current uniform application of patent protection to high risk "first in line" and low risk "me too" drugs perversely motivates redundancy in place of innovation, and drugs are currently developed to reduce symptoms of Alzheimer's disease or osteoarthritis rather than to prevent them because the presently applied standard patent protection period is likely to expire before long-term preventive efficacy could even be demonstrated (59). Current investment in research and development is too low in proportion to investment in marketing (44). Wood (59) proposed including "economic Darwinism" principles in the drug approval process by creating variable incentives for enforcement of public health interest either through granting an additional extension of exclusivity rewarding high commercial risk "first in class" innovations that address indications for which current alternatives lack efficacy or pose toxicity, especially when carrying a large potential impact on disease burden, or through granting provisional approval for marketing that will be withdrawn if stringent clinical data cannot be provided to establish unique advantages in terms of clinically important benefits, or long-term safety data, or phase IV commitments, along a prescheduled timeline. Along similar lines, Barton and Emanuel (44) proposed including complementary reforms requiring comparative post approval testing against existing alternatives (rather than placebo) rewarding evidence-based performance (e.g., demonstrated reductions in the number of patients or improving quality of life), implementing international tiered pricing

(lower in developing countries), and increasing government-funded research that creates incentives based on disease burden rather than market appeal through selective funding of research and development or reimbursement on sales of products based on health care desirability considerations.

The huge economic toll estimates associated with the under-diagnosis and under-treatment of prevalent disorders, indicates how much is to be gained from such interventions even when considering a narrow economical perspective. Unipolar depression provides an illustrative case in point. The multiple new generation antidepressant drugs introduced from the late 1980s, largely represent parallel attempts to mimic precursor traditional drug action. While not offering enhanced efficacy, they do offer an improved adverse profile over tricyclics and monoamine oxidase inhibitors. For the highly prevalent depressive and anxiety disorders this should have translated into increased access to treatment in the community setting. Worldwide population data consistently document association of increased second-generation antidepressant prescription with reduced suicide rates (29–32). However, large-scale translational research has been retarded, with meager increments in adequate psychiatric treatment rates noted in the last two decades. A sad reminder from the recently published data of the National Comorbidity Survey Replication (NCS-R) shows that 60% of subjects with an axis I psychiatric disorder in the U.S. have not received any treatment in the preceding year, and of those who did seek help, only a third received treatment qualifying as minimally adequate (60). Despite the slight increase seen in rates of treatment between 1990 and 2003, the majority of patients with an axis I mental disorder still do not receive treatment in the U.S. today (61). Similar data were reported by the WHO world mental health survey consortium for 14 countries surveyed (62). The 12-month rate of reported mental health care use by NCS-R respondents between 2001–3 (17.9%) shows a small increase to that found in the Epidemiologic Catchment Area Study (12.3%) conducted in the 1980s before the introduction of second-generation drugs (60). While the key for this increase results from increased awareness, with consequent treatment initiation and referral by primary care physicians, the rate of minimally adequate treatment remains poor and the large majority of patients with a mental disorder in the U.S. today remain untreated or poorly treated (60). Personal suffering aside, this carries an enormous annual financial loss to individuals and society at large (63). Depression alone carries an estimated annual cost of 83.1 billion dollars in the U.S., related to increased suicide rate, added health care costs, and loss of productivity (64). This suggests that much is to be gained by economies implementing proactive strategies to address unmet public health needs. Cost-benefit calculations of enhanced depression care indeed suggest a large saving in dollars to patients, employers, and society (65). Such calculations may be used as a way to finance guided interventions, if long-term reduction in economic health burden is responsibly taken into account. The problem however, is more complex in that it requires redefining the roles of some of the major players as well as the politics of their interplay. The drive for change will depend on responsible action by legislative authorities for implementation of multifaceted regulatory interventions, guided by long-term public health interest, as well as increased availability of integrated proactive mental health services within general health settings. In what relates to mental health care, psychiatrists are likely the key informed agents situated to initiate a change in views of public, consumers, general health care providers, media, policy makers, and industry.

The issue contains a discussion about the relationship between the pharmaceutical industry and the medical profession. In the following articles, Prof. Brezis, an authority on clinical quality of health care, presents some of the major obstacles and stumbling blocks, as well as health care implications of pharmaceutical industry conduct. The discussant is Professor Belmaker, the current President of the CINP and a leading psychiatrist in Israel.

References

1. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Economics 2003;22:2:151–185.
2. Insel TR. Beyond efficacy: The STAR*D trial. Am J Psychiatry 2006;163:5–7.

3. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223.
4. Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. Arch Gen Psychiatry 2006;63:1079–1087.
5. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med 2005;143:415–426.
6. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252–260.
7. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 2008;5:e45.
8. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163: 28–40.
9. Rosenheck RA, Leslie DL, Doshi JA. Second-generation antipsychotics: Cost-effectiveness, policy options, and political decision making. Psychiatr Serv 2008;59: 515–520.
10. Charatan F. Merck to pay $5bn in rofecoxib claims. BMJ 2007;335:1011.
11. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: A case study of industry documents from rofecoxib litigation. JAMA 2008;299:1800–1812.
12. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: A case study based on documents from rofecoxib litigation. JAMA 2008;16;299:1813–1817.
13. Lenzer J. Drug company seeks to suppress internal memos. BMJ 2007;13;334:59.
14. Hammad TA. Review and evaluation of clinical data. Washington, DC, Food and Drug Administration, Aug. 16, 2004 (http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf)
15. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164:1035–1043.
16. Laughren T. Briefing document for December 13 meeting of Psychopharmacologic Drugs Advisory Committee. Available at www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-index.htm (accessed April 3, 2007).
17. Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. N Engl J Med 2007;356:2343–2346.
18. Licinio J, Wong ML. Depression, antidepressants and suicidality: A critical appraisal. Nat Rev Drug Discov 2005;4:165–171.
19. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Mann JJ. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007;164:1356–1363.
20. Katz LY, Kozyrskyj AL, Prior HJ, Enns MW, Cox BJ, Sareen J. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ 2008;178:1005–1011.
21. Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ 2008;336:542–545.
22. Biddle L, Brock A, Brookes ST, Gunnell D. Suicide rates in young men in England and Wales in the 21st century: Time trend study. BMJ 2008;336:539–542.
23. Simon G. Antidepressants and suicide. BMJ 2008;336: 515–516.
24. Hazell P. Depression in children and adolescents. Clin Evid 2006;15: 398–414.
25. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. Lancet 2004;363: 1341–1345.
26. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297:1683–1696.
27. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Psychiatry 2007;164:1029–1034.

28. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry 2007;164: 1044–1049.
29. Isacsson G, Rich C L. Antidepressant drug use and suicide prevention. Intl Rev Psychiatry 2005;17, 153–162.
30. Ludwig J, Marcotte D E. Anti-depressants, suicide, and drug regulation. J Policy Anal Manage 2005;24, 249–272.
31. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry 2006; 163:1898–1904.
32. Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. Br J Psychiatry 2006;188:354–358.
33. Leckman JF, King RA. A developmental perspective on the controversy surrounding the use of SSRIs to treat pediatric depression. Am J Psychiatry 2007;164:1304–1306.
34. Dubicka B Wilkinson P. Evidence-based treatment of adolescent major depression Evid Based Ment Health 2007;10:100–102.
35. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538.
36. Jeste DV, Blazer D, Casey D, Meeks T, Salzman C, Schneider L, Tariot P, Yaffe K. ACNP white paper: Update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacol 2008;33:957–970.
37. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943.
38. Food and Drug Administration. FDA public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. (Accessed November 3, 2005, at http://www.fda.gov/cder/drug/advisory/antipsychotics.htm).
39. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart MA. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341.
40. Presne C, Fakhouri F, Noël LH, Stengel B, Even C, Kreis H, Mignon F, Grünfeld JP. Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int 2003;64:585–592.
41. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S. International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003;60:82–91.
42. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003; 290:1467–1473.
43. Barbui C, Cipriani A. Evidence-based psychopharmacology: An agenda for the future. Evid Based Ment Health 2007;10:4–6.
44. Barton JH, Emanuel EJ. The patents-based pharmaceutical development process: rationale, problems, and potential reforms. JAMA 2005 ;294:2075–2082.
45. Scherer FM. The pharmaceutical industry — prices and progress. N Engl J Med 2004;351:927–932.
46. Healy D. The latest mania: Selling bipolar disorder. PLoS Med 2006;3:e185.
47. Atkinson T. Lifestyle drug market booming. Nature Med 2002;8: 909.
48. United Kingdom Parliament. (2005) House of Commons health report. London: United Kingdom House of Commons. Available: http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/4202.htm. Accessed 14 October 2005.
49. Licinio J, Wong ML. Depression and obesity treatments are life saving. Nat Med 2002;8:1336.
50. Steinbrook R. Financial support of continuing medical education. JAMA 2008;299(9):1060–1062.
51. Lenzer J, Brownlee S. Doctor takes "march of shame" to atone for drug company payments. BMJ 2008;336:20–21.
52. Schulman KA, Seils DM, Timbie JW, Sugarman J, Dame LA, Weinfurt KP, Mark DB, Califf RM. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. N Engl J Med 2002;347:1335–1341.
53. Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Ghost authorship in industry-initiated randomised trials. PLoS Med 2007;4:e19
54. Brennan TA, Rothman DJ, Blank L, Blumenthal D, Chimonas SC, Cohen JJ, Goldman J, Kassirer JP, Kimball H, Naughton J, Smelser N. Health industry practices that create conflicts of interest: a policy proposal for academic medical centers. JAMA 2006;295: 429–433
55. DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science: The adverse effects of industry influence. JAMA 2008;299:1833–1835.

56. Hirsch L. Trial registration and results disclosure: Impact of US legislation on sponsors, investigators, and medical journal editors. Curr Med Res Opin 2008;24: 1683–1689.
57. Lenzer J. US Congress and European Research Council insist on open access to research results. BMJ 2008;336: 176–177.
58. DeAngelis CD. The influence of money on medical science. JAMA 2006;296:996–998.
59. Wood AJ. A proposal for radical changes in the drug-approval process. N Engl J Med 2006;355:618–623.
60. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:629–640.
61. Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med 2005;352:2515–2523.
62. The WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004;291:2581–2590.
63. Kessler RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, Wang PS, Zaslavsky AM. Individual and societal effects of mental disorders on earnings in the United States: Results from the National Comorbidity Survey Replication. Am J Psychiatry 2008;165:703–711.
64. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the United states: How did it change between 1990 and 2000? J Clin Psychiatry 2003; 64:1465–1475.
65. Wang PS, Patrick A, Avorn J, Azocar F, Ludman E, McCulloch J, Simon G, Kessler R. The costs and benefits of enhanced depression care to employers. Arch Gen Psychiatry 2006;63:1345–1353.

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