APPENDIX 2

MANUFACTURING CONSENSUS

David Healy MD FRCPsych. In Press in Greenslit, N (Ed). Pharmaceutical Cultures: Marketing Drugs and Changing Lives in the US Rutgers University Press.

BACKGROUND

27. Consider this excerpt from the 1993 FDA medical review of Janssen Pharmaceutical's application to market the antipsychotic drug, risperidone (Risperdal): "We would consider any advertisement, promotion or labeling for Risperdal false, misleading or lacking fair balance under Section 502 of the Act if there is a presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness" (Mosholder 1993).

28. The clinical trials undertaken by Janssen with Risperdal prior to marketing had compared it to an older antipsychotic, another Janssen drug, haloperidol. In a similar way, all recently released antipsychotics, including olanzapine (Zyprexa), quetiapine (Seroquel) and ziprasidone (Geodon), were compared to haloperidol in key pre-marketing trials. All companies used much the same dose of haloperidol—a dose that was no more efficacious than lower doses of haloperidol but which did cause more side effects. The company rationale for using haloperidol was that haloperidol was supposedly the market leading antipsychotic agent. Whatever the real rationale, it was generally accepted at the time these trials were conducted that newer agents stood their best possible chance of looking better in terms of key side effects—or at least no worse (if compared to the doses of haloperidol used in these trials).

29. The role of a drug regulator in addition to gate-keeping the entry of a new drug to the marketplace is to regulate any claims a manufacturer might make as regards a new product in its advertising or in any statements its personnel might make to doctors afterwards. This assessment by the FDA would appear to produce problems for any company that might wish to market Risperdal.

30. But regulators have no control over what academics say in lectures, report in medical journals or elsewhere. FDA in addition have no control over what assessments these academics might make in their roles as experts called on to contribute to an expert consensus on new versus older drugs. Shortly after Risperdal was launched, it was being widely touted by academics as superior to older antipsychotics on the market.

31. Aside from the perennial need to market the product, the 1990s brought a new hurdle for drug companies to vault. It was increasingly necessary to persuade clinicians and pharmacists that a new drug should be listed on hospital formularies. These formularies were created to ensure new agents would not be used without good evidence of cost-benefit returns. The formularies are notionally meant to be evidence based and cost-sensitive. A certain amount of trade-off was likely—if a new drug cost more but could show a real benefit over older agents it would be included.

32. No convincing evidence has ever been forthcoming that any of the new "atypical" antipsychotics are superior to the older "typicals" in either safety or efficacy. A study completed in 2003 by the VA hospitals compared olanzapine (Zyprexa) and haloperidol both in terms of efficacy and tolerability and found no difference between them; olanzapine in this study, however, cost approximately 80 times as much as haloperidol (Rosenheck, Perlick, Bingham et al 2003). Despite this lack of greater efficacy, olanzapine has won a place on formularies since its launch in 1996 to the extent that it has become the most profitable antipsychotic in the world.

33. In the absence of clear evidence from clinical trials sufficient to warrant claiming a new drug was superior to an older drug, it would appear difficult to make the extra step to advocating that the newer agent is more effective to the point of warranting a potential 80-fold increase in expenditure. Nevertheless, shortly after their launch, Risperdal and other recently released antipsychotics were available on most hospital formularies in both the United States and Europe.

34. Pharmaceutical companies have clearly found methods of circumventing these difficult areas of marketing terrain. Circumvention is achieved by recruiting senior academics and institutions to their cause, by means of three stratagems: consensus conferences, pharmaco-economic modeling, and ghostwriting.

CONSENSUS CONFERENCES

35. Consensus conferences aimed at producing guidelines for clinical practice came into existence in the late 1980s (Sheldon and Smith 1993). A range of bodies took up this apparently academic development. Within psychiatry, groups such as the British Association of Psychopharmacology and the European College of Neuropsychopharmacology, for example, produced guidelines on the treatment of a range of conditions from depression through to schizophrenia. This may have happened in part in an effort to establish a political profile. In a number of the organizations that produced guidelines, the influence of key individuals with links to pharmaceutical companies is apparent.

36. At the same time pharmaceutical companies began to sponsor meetings aimed at producing expert consensus on issues such as the appropriate use of medication in schizophrenia. These company sponsored meetings have often resulted in products that may appear almost indistinguishable from non-company sponsored guidelines or algorithms. While this might be thought as an exercise designed to confound the recommendations of independent committees, in fact committees that should be independent have come up with recommendations that barely differ from explicitly company-sponsored exercises.

37. Given the lack of evidence-base for the superiority of the new antipsychotics, just how have all these guidelines ended up endorsing newer, more costly agents over older, less expensive, but equally effective ones? One such guideline system, the Texas Medication Algorithm Project (TMAP), offers one set of answers (Petersen 2004)[1].

38. Risperdal was launched in 1994. TMAP was instituted in 1995, initially funded by Janssen Pharmaceuticals (Johnson & Johnson), the makers of Risperdal. Soon afterwards it had attracted funding from all major pharmaceutical companies. TMAP drew up a panel of consultants to produce an expert consensus on the use of antipsychotics, and later on the use of antidepressants and mood-stabilizers (Gilbert, Altshuler, Rego et al 1998). Most had prior links to Janssen and the other major pharmaceutical companies operating in the mental health field.

39. The first set of TMAP guidelines concluded that the atypical antipsychotic medications Risperdal, Zyprexa and Seroquel were the drugs of choice for the management of schizophrenia (Chiles, Miller, Crismon et al 1999). A second set concluded that newer patented antidepressants, such as the SSRIs, Prozac, Paxil and Zoloft, were the drugs of choice for the treatment of depression rather than older agents such as the tricyclic antidepressants. Subsequently mood-stabilizers such as Depakote and Lamictal have been endorsed over other treatments for bipolar disorder. In all these instances, the claims have been that the new drugs were safer, more effective and better tolerated than the older agents. The expert panels then formulated a set of algorithms or care pathways for the treatment of schizophrenia, depression and bipolar disorder based on these guidelines.

40. In a number of US states, legislators have the powers to rule that algorithms and guidelines such as these must be applied in the care of any patients receiving treatment in public facilities. The logic here is that evidence based guidelines and algorithms, if they really do reflect reality, can be expected to be cost-effective over time. The legislators faced with the question of adopting the algorithm and guideline proposals in Texas meet infrequently, are poorly paid and are intensively lobbied. Not surprisingly perhaps, TMAP was administratively endorsed in Texas, and as a result state hospital doctors were required to follow its algorithms and use these newer drugs first.

41. Researchers linked to TMAP were also able to access the records of patients in state facilities, including prison hospitals and mental hospitals, and report on the cases that appeared to do favorably. These surveys produced data supporting the selection of Risperdal and Zyprexa, for instance, as first line treatments for schizophrenia, and later the selection of SSRIs or other newer antidepressants over older treatments for depression. On this basis, the TMAP guidelines and algorithms began to be referred to as evidence-based guidelines and evidence-based best practices.

42. A related panel formulated a set of medication algorithms for children, which recommended new antipsychotics and antidepressants, such as Paxil (paroxetine), for the management of children's problems (Hughes 1999). In this case, not only was there a lack of evidence for the superiority of the newer over the older agents; there was essentially no evidence base for the recommendations other than a set of then unpublished clinical trials.

43. The TMAP algorithm and guidelines were subsequently marketed to other states on the basis of the Texas precedent and instituted by administrative decision in a number of these other states also.[2] In this way a very few people had effectively paved the way for the acceptance of these guidelines and algorithms in many states, and produced a situation in which a growing cohort of patients treated in the public sector end up being put on and maintained on these drugs. It will probably come as no surprise that within Janssen there was a special unit aimed at maximizing the effectiveness of the companies marketing in the public sector.

FROM TMAP TO NICE

44. While the TMAP process appears close to egregious, something very similar happened within the socialized system of medicine in Britain. In the first place, opinion leaders in Britain were recruited to panels to produce evidence-based guidelines for antipsychotics. The experts invited to such meetings will have had no pressure put on them to come to a particular point of view. All of the publications of clinical trial data for antipsychotic drugs will have been made available to them on request, and they will have been encouraged to be evidence based.

45. Again as with TMAP, the results, despite the assessment of the FDA, which will have been unknown to any of the participating experts, must have been gratifying to the sponsoring company (Mortimer, Healy, Gray et al 1998).[3] The process involved no overt selling of named medications, but rather a set of positions endorsing the use of antipsychotics in monotherapy regimens, and in doses consistent with British National Formulary recommendations, and in a manner that would avoid precipitating acute treatment related side effects. These positions along with exhortations to adhere to an evidence based approach were considered by the company as an effective marketing tool.

46. Subsequently, a National Institute of Clinical Excellence (NICE) was set up in Britain with a brief to make recommendations as to the most clinically effective and cost-effective treatments for both physical and mental illnesses. The NICE guidelines for psychiatric treatment are an essentially similar creation to TMAP, and earlier UK based industry sponsored guidelines: a consensus of expert views rather than evidence based views. The process involves a small number of psychiatrists, psychologists and other stakeholders in mental health such as psychiatric pharmacists collating evidence, preparing draft reports and then sending these to selected experts for comments. Decisions are reached not by experiment or evidence but by agreement. The process will also have to take into account prior algorithms, guidelines and Delphi panel recommendations (see below). And finally, as has been pointed out publicly by the World Health Organisation, the process operates within the constraints of the unwillingness of pharmaceutical companies to share the raw data arising from clinical trials (WHO 2003).

47. The upshot of this in the case of the antipsychotics has been a set of guidelines indistinguishable from the ones drawn up by TMAP, or by other guideline groups linked closely to pharmaceutical companies (NICE 2003). NICE recommends the use of the new antipsychotics over old, even though it acknowledges it does so without having any evidence base for this. In fact, the NICE guidelines fly in the face of evidence that new antipsychotics compared in clinical trials with the older antipsychotics and placebo produce significantly higher death rates from a variety of causes and significantly higher suicide rates, as well as a range of physical problems, from cardiovascular to endocrine disorders, that were not linked as frequently to the older antipsychotics.

48. In a public health system such as the NHS, NICE guidelines are implemented in a very similar way to the TMAP guidelines. The medical directors of hospitals will ordinarily seek to ensure that their clinical staff adhere to NICE guidelines. As a direct result of NICE then a much larger number of patients will end up being given new rather than old antipsychotics than would otherwise have been the case, with a probable resulting detriment in the collective patient health, brought about at vast cost. It is all but impossible for individual clinicians to opt out of the system as the public health system endorses adherence to these guidelines and practicing outside the guidelines may not be regarded as evidence based.

49. The critical influence here lies with the clinical trials that supposedly form the basis for the guideline process. Newer agents almost invariably have more and larger trials than older agents, especially if this is for indications that have been "created" since the older drugs went off patent. A great number of older agents may in fact have minimal trial data. Those constructing the guidelines rarely appear to take into consideration the fact that the larger the trials needed, the weaker the drug must be, and that in general trials are only needed when there are some doubts as to whether the drug actually works or not. But, even more critically, the underlying data that might reveal increased deaths from suicide and other causes that might occasion a different set of conclusions are never available to those constructing the guidelines.

50. While the data that might have led NICE to a different conclusion were not available in the reports of randomized trials of these agents, a good deal of relevant data was in fact publicly available in reviews published by the Food & Drugs Administration (FDA) for each of the new antipsychotics at the time of licensing. In the case of suicides, a great deal of the data was available in a paper on rates of suicides and suicidal acts in clinical trials with novel antipsychotics.

51. These published data show high rates of suicide on Risperdal and perhaps the highest rates of suicide in clinical trial history on Zyprexa (see table 1). But the most surprising thing is that the paper offers no figures for suicidal acts on Zyprexa, while it does offer figures for

suicidal acts in the clinical trials programs for the other new antipsychotics. Against a background of possibly the highest suicide rates in clinical trial history, this absence of data on suicidal acts for Zyprexa is striking. Eli-Lilly, the makers of Zyprexa, have since refused to answer questions as to what the rate of suicidal acts on their drug might be. Despite this, this drug has become the best selling antipsychotic on the marketplace.

52. NICE guidelines however as mentioned endorse the use of both Risperdal and Zyprexa over older agents, although given the absence of these key data and public knowledge about this key absence, it is difficult to see how any patient taking Zyprexa can be taking it on the basis of informed consent. While NICE guidelines do not have the force of law, it would be difficult for clinicians in the UK to flout this guidance. Thus, there are good grounds to think that the availability of NICE, TMAP and other guidelines has resulted in a vast increase in the expenditure of drugs in the mental health domain at a presumptive cost to the development of other services, and this increase has also taken place without any reasonable expectation of health gains at either the individual or systems level.

PHARMACO-ECONOMICS

53. In the case of these newer agents, another method resorted to by companies has been a set of pharmaco-economic procedures. Pharmaco-economics as a discipline began in the 1970s, heavily subsided by the pharmaceutical industry (Healy 1998). It basically involves estimating and comparing the costs of leaving a condition untreated against the costs of treatment. The original view of the first pharmaco-economists was that the complications of establishing treatment effects and outcomes for psychotropic drugs across a range of domains of value in mental health meant it would be impossible to apply the procedures of pharmaco-economics to psychiatric conditions and treatments.

54. Nonetheless the emergence of a set of SSRI antidepressants and atypical antipsychotics that could not be distinguished from older agents in terms of efficacy or tolerability, but which were associated with greatly increased costs, led to a flurry of pharmaco-economic exercises. This is exemplified nicely by the emergence of supplements to major journals detailing a range of pharmacoeconomic approaches that probably did a good deal to smooth the marketing path of the SSRI antidepressants (Eccleston 1993).

55. One of these methods involved the establishment of Delphi panels of experts. Delphi panels invite experts to consider clinical trial data and estimate the likely translation from the actually published randomized trial evidence to possible outcomes in clinical practice if the drugs are adopted widely. These outcomes are then costed by economists working to the manufacturing company.

56. The participants in these exercises will again be unaware of assessments such as those made by the FDA, or the data on suicide or death rates from trial programs. The invariable outcome of these proceedings has been sets of models indicating that treatment with newer agents costing ten to eighty times more than older agents would in fact lead to savings in either for profit healthcare systems such as that of the United States, or socialized medical systems such as the UK mental health system (Guest et al 1996).[4]

57. No one seems prepared to say what the original exponents of pharmaco-economics realized, namely that short-term trials cannot be used for this purpose. This issue is now further complicated by something that would once have been all but inconceivable, which has been hinted at above and is developed below, namely, the fact that in a growing number of cases critical aspects of the raw data are substantially at odds with the published data.

GHOST-WRITING

58. In the 1980s, pharmaceutical companies began to outsource a range of functions, such as the running of clinical trials and medical writing, to other companies. Medical writing was outsourced to medical communication agencies. With this development, the practice of ghost-writing academic articles picked up pace. Ghost-writing involves medical writers writing articles, which subsequently appear under the apparent authorship of academics who might or might not have reviewed the piece before publication; the ghost traditionally is the medical writer who receives no credit for her input. For some time it was believed that this form of medical communication was largely confined to journal supplements or peripheral journals (Healy 2003, & 2004). The first hints that the picture might be somewhat different came in the mid-1990s. Flanagin and colleagues for example reported in 1998 that up to 11% of articles published in six mainstream peer reviewed journals involved the use of ghostwriters (Flanagin, Carey, Fontanarosa et al 1998).

59. Recently a document became publicly available covering the co-ordination during the course of 1998 of medical articles on Pfizer's antidepressant Zoloft (sertraline) by a medical communications agency, Current Medical Directions (CMD). This has permitted the comparison of published articles written for Pfizer with other articles on Zoloft in terms of the impact factor of the journals in which they appeared, prior publication history of the respective authors and subsequent citation rates of the respective series of articles.

60. The analysis showed the journals in which Pfizer's articles were published had an impact factor three times greater than the journals in which other articles on Zoloft were published. The authors on Pfizer's articles had nearly three times more previously published articles, as cited in Medline and Embase, than the authors of articles not linked to Pfizer. Of greatest importance was the subsequent citation rate. It might be thought that, despite publication in the most prestigious journals and under the apparent authorship of the most distinguished academics, clinicians and researchers would find this literature too obviously industry linked and would not be influenced by it. However, the subsequent citation rates for the Pfizer-linked articles were three times greater than that of the non-Pfizer articles (Healy and Cattell 2003).

61. The profile of this so-called scientific activity suggests that Pfizer ended up with a set of authors whose background increased the possibility of the company's publications appearing in the most prestigious journals. The combination of distinguished journal, distinguished author, an efficient distribution system and sponsored platforms appears to have led to an impact on the therapeutics domain greatly in excess of 50% of the impact of the rest of the literature on Zoloft. At present roughly three-quarters of all randomized trials appearing in JAMA, NEJM or the Lancet are industry funded.

62. The impact of this literature on third party payers is at present unquantifiable, but authorship by perceived opinion leaders with minimal company representation and non-declaration of other authorship inputs increase the likelihood that these articles will be influential with purchasers as well as prescribers.

63. Academics become opinion leaders in a therapeutic field because they have their names on a larger proportion of the literature appearing in the most prestigious journals than their colleagues, and because they get asked to international meetings to present this data (with which they may not, in fact, have first hand acquaintance. This, allied to the volume of industry-linked authorship, is arguably leading to a situation in which the dominant figures in therapeutics actually have little first hand research experience and may have no raw data that they can share with others and probably have simply never seen the raw data. This is a situation in which, in contrast to the traditional perception of who the ghost authors are in the medical literature, our leading academics have become ghosts or ciphers.

64. It is in fact a situation in which ghost-writers increasingly have to take on ghost-acting as part of their repertoire. This happens because the apparent authors of a study will often now have so little familiarity or association with the basic data, that they either cannot present it at major meetings or are not inclined to do so in for instance poster form. As a result it is becoming increasingly common to find medical writers presenting posters at academic meetings, where they will in all probability often be assumed to be doctoral students linked to the research being presented.[5]

65. The situation that has developed underlines the significance of the proprietary control of raw data. The raw data from one trial of Zoloft compared to mianserin or placebo in the CMD series, for instance, shows that one patient on Zoloft committed suicide and three others had

their treatment discontinued because of increasing suicidal ideation. In contrast there was just one case of emergent suicidality on the comparator drug mianserin and no problems on placebo. But the final published article makes no reference to any patient becoming suicidal in any way (Malt, Robak, Madsbu *et al* 1999).

66. Second, within the CMD series of articles on Zoloft, there were six that dealt with the use of Zoloft for children. Of these six articles, only one mentions suicidality—one single suicidal act. There were in fact six suicidal acts on sertraline in the trials that these articles report: a rate approximately six times higher than the published rate in adults.[6] The rate of suicidality in depressed children taking sertraline was in fact nine per cent. However the article dealing with the hazards of treatment in children who are depressed only reported on the side effects that occurred at a ten per cent rate or more (Alderman, Wolkow, Chung *et al* 1998).

THE CONSENSUS ON TREATING CHILDREN WITH PSYCHOTROPIC DRUGS

67. The consequences of these developments came to a focus in 2003 on the issue of treating children with psychotropic drugs. The TMAP children's algorithm project outlined above endorsed the use of SSRI antidepressants for treating childhood nervous disorders, largely on the basis of a series of unpublished trials. Although unpublished, the experts formulating algorithms for TMAP and the experts running these trials and appearing as authors on the few published trials were in many instances the same people. These experts therefore had a better opportunity to know what the raw data looked like than anyone else. As a result, the issue of treating children with psychotropic drugs offers a good case example to bring out a number of features of the new world of manufactured consensus.

68. There has been a long-standing awareness that it is difficult to show in clinical trials that antidepressant drugs offer benefits for children. Despite this there were grounds for using psychotropic drugs for children, and guidelines on the treatment of children who were depressed endorsed such usage (Healy and Nutt, 1998). The advent of the SSRI antidepressants offered some hope that these agents might be shown to be effective for children where efforts with older agents had failed.

69. In the early 1990s, regulatory authorities approved the use of the SSRIs Paxil and Zoloft for the treatment of depression for adults. They had previously approved Prozac and subsequently approved Celexa and Efexor. From the 1990s, standard letters of approval to companies noted that as these drugs were likely to be used to treat children studies to establish the safety of the drugs in these populations would be helpful. This encouragement led to a series of studies of SSRIs in children during the early to mid 1990s. A further incentive was put in place in 1998 with an FDA Modernization Act (FDAMA) (Sharav 2003), which offered patent extension on the basis of testing for rather than proving safety; if the drugs showed hazards, the company still got patent extension but had to incorporate this information in the label.

PROZAC

70. In the case of fluoxetine an early series of clinical trials failed to establish efficacy for this drug in treating childhood nervous problems. This work led to a study that started in 1990, which involved extensive pre-screening of patients so that less than one-fifth of those screened entered the study, and those who did were put through a placebo washout phase in an effort to reduce the high rate of placebo responsiveness found in SSRI trials in children. Using these procedures, an article that appeared in 1997 claimed that Prozac could produce beneficial effects for children and adolescents (Emslie, Rush, Weinberg et al 1997). However, in fact on the primary end-point measure, Prozac was no better than placebo and on secondary measures benefits were apparent on physician-based ratings but not on patient or carer ratings. In addition, there was a 29% drop-out rate on Prozac and the rate of behavioral side effects was greater on Prozac than on placebo.[7]

71. This Prozac study had been run under the auspices of the NIMH. Subsequently another study funded by the makers of Prozac, Eli Lilly, led to a comparable result (Emslie, Heiligenstein, Wagner et al 2002). The second study, in contrast to both the previous Prozac study and studies of other SSRIs and in contrast to clinical practice, showed no greater rate of adverse events on Prozac than on placebo. This combination of studies led to a license for Prozac for the treatment of depression in children and adolescents in 2003.

72. A further study had been undertaken on Prozac for obsessive-compulsive disorder (OCD). This showed somewhat more clearly positive results for Prozac over placebo, but equally an excess of suicidality over placebo.

PAXIL

73. The first study undertaken with Paxil, protocol 329, was conducted in the early to mid-1990s. The published report from 2001 pointed to mixed benefits of Paxil on the primary endpoints of the trial, with apparent responsiveness on some measures accompanied by non-responsiveness on others, concluded that Paxil is effective, safe and generally well-tolerated (Keller, Ryan, Strober *et al* 2001). But in this study there was an increased rate of suicidal acts on Paxil (5/93, a 5.4% rate) compared with either imipramine (1/95) or placebo (0/89). The difference between Paxil and placebo was close to significance at the 95% level ($p = 0.06$), and the difference between Paxil and comparators (1/183) was significant.

74. These figures were not apparent from the published the paper, where suicidal children were coded as having had emotional lability. Hostility was also a reported side effect in 6.5% of Paxil patients in this study versus 1.1% on placebo. While the published paper does outline that emotional lability might include suicidal acts, this is not a common meaning of the term for most clinicians, who will be unaware that dictionaries for coding side-effects, such as the ADECs system, offer the possibility to code suicide, suicidal acts and suicidal ideation under the heading of emotional lability. The same dictionary codes homicidal acts, homicidal ideation and other aggressive acts under the heading of hostility.

75. A second, protocol 377, and a third protocol 701, and a fourth trial protocol 716 failed to demonstrate efficacy for Paxil for depression, and also seem to have returned an increased frequency of suicidality on Paxil. The first two of these studies, which appear to have been completed by 2000, were presented in part in abstracts in 2001 and 2002 that concluded that Paxil was effective, safe, and generally well-tolerated (Wagner, Wetherhold, Carpenter *et al* 2002). The fourth apparently remained unscrutinized by FDA, when FDA undertook a review of SSRI agents in children in 2003.

76. At much the same time studies of Paxil in obsessive-compulsive disorder (OCD) were instituted, protocols 453 and 704. Reports of these studies in abstract form also claimed that Paxil was effective safe and generally well tolerated (Geller, Wagner, Emslie *et al* 2002). However, company data on file point to an increased rate of side-effects on Paxil compared to placebo, in the domains of hostility, agitation and hyperkinesis. In 453, 6.3% of children taking Paxil (n = 97) became hostile compared with 0% on placebo (n=100). In 704, 9.2% of children became hostile on Paxil (n = 98) with 1% becoming hostile on placebo (n = 105). There was also an increased frequency of suicidal acts on Paxil (1/195) compared to placebo (0/205).[8]

77. Finally, a study of Paxil was conducted in social phobia, protocol 658. The unpublished results indicate that Paxil might in some cases produce a beneficial effect in children, but as with depression and OCD there was a higher rate of adverse events in the behavioral domain on Paxil compared to placebo. In this case there appear to have been three suicidal acts in 165 children on Paxil compared to 0 in 157 on placebo.[9]

ZOLOFT

78. In the case of Zoloft, in the mid-1990s, a double blind placebo controlled study was undertaken in OCD, which reported that Zoloft can have a greater beneficial effect on core features of OCD than placebo (March, Biederman, Wolkow et al 1998). This paper, which was one of the CMD series, noted one suicidal act on Zoloft. A background expert report on the study, however, points to two suicidal acts on Zoloft compared with one that might have been on placebo.[10] In the absence of the raw data, it is not clear whether this suicidal act on placebo actually occurred during the randomized phase of the trial, as in the case of Pfizer's clinical trial program in adults suicidal acts that occurred during the washout phase of trials were coded under the heading of placebo (Healy 2003).

79. At the same time, Pfizer initiated open trials of Zoloft in children who were depressed. In the first of these, also reported in the CMD series of papers, 44 children were given Zoloft of whom four became suicidal, a 9% suicidality rate. The article reporting these results portrayed Zoloft as likely to be effective, and generally well-tolerated; this article also restricted itself to reporting on the side-effects that occurred at a 10% rate or more (Alderman, Wolkow, Chung *et al* 1998). A further open study of Zoloft in depression, also in the CMD series, reported that there were three suicidal acts among 53 children who were depressed, a 5.6% rate (Ambrosini, Wagner, Biederman *et al* 1999).

80. The expert report on these early OCD and depression studies undertaken for Pfizer commented, "Clinical studies in pediatric patients with OCD (aged 6-17 years) have shown that sertraline is well tolerated. The adverse events which led to discontinuation were generally psychiatric in nature, and there were no discontinuations due to laboratory safety data following administration of sertraline"[11]

81. Subsequently, Pfizer conducted two randomized controlled trials on Zoloft in depression. These were both negative; combined, however, they were reported as showing Zoloft was effective and well-tolerated (Wagner, Ambrosini, Rynn *et al* 2003). In fact, 59% of children on Zoloft showed a change of 5 points on a Clinical Global Impression scale against 49% of children on placebo showing comparable changes, a finding that only reached statistical significance when both studies are combined. In the case of the side-effect profile, there was a doubling of the rate of behavioral problems, including suicidal acts, suicidal ideation and aggression in children on Zoloft (6/189) compared to children taking placebo (2/187), and a 9% drop-out rate on Zoloft versus 3% on placebo for adverse events, but in fact 46 of 189 children on Zoloft, 24%, dropped out for one reason or another (Garland 2004).

82. The actual drop-out rates on Zoloft contrast with a lower rate of reported behavioral problems in this study compared to earlier studies on both Zoloft and Paxil. In addition it can be noted that the design in this study did not encourage detection of adverse events. In SSRI studies where side effects are more actively sought, the rates are higher. For example, in a study of fluvoxamine in anxiety, increased motor activity was found in 27% of children compared to 12% of placebo patients (p=0.06) (Walkup, Labellarte, Riddle et al 2001). This study in contrast to the Zoloft studies above used side effect checklists.

EFEXOR

83. In the case of Efexor, two studies have been undertaken in depression and two in generalized anxiety disorder. One study published in 1997 suggests venlafaxine was safe, and well-tolerated, but that efficacy had not been established (Mandoki, Tapla, Tapla *et al* 1997). However it now seems that in the combined depression studies there was an increased rate of children becoming hostile (2% v < 1% on placebo) and suicidal on venlafaxine compared to placebo (2% v 0%) (Kuslak 2003). There seems no prospect that the full findings from these studies will be published.

THE UNRAVELING OF THE CONSENSUS

84. In addition to a small number of publications (six full articles with three abstracts) from approximately 15 randomized trials in children, there were approximately 70 publications of open studies or case reports with Celexa, Prozac, Paxil, Zoloft, Luvox and Efexor. The open studies and published double blind trials universally portrayed these drugs as safe, well-tolerated and effective when given to children.

85. In 2002, the issue of *Newsweek* coinciding with World Mental Health Day carried a cover feature of a depressed teenage girl (*Newsweek* 2002). The inside story outlined that there were three million depressed teenagers in the United States, and that if left untreated this would lead to high toll in substance abuse, failed marriages and careers and deaths from suicide. The article noted that there were a number of new antidepressants, such as Paxil, Zoloft and Prozac, which could help. Such articles commonly have input from PR companies working to pharmaceutical companies. The expectation in this case would appear to have been that a number of SSRIs would shortly have a license to treat teenage depression.

86. It is important to understand what licensing means in this context. It does not mean that physicians would thereafter be enabled to treat children who were depressed in a way that they had been unable to do before. It means rather that Pfizer, Lilly and Glaxo SmithKline would be enabled to convert the vicissitudes of teenage angst into an illness, one supposedly stemming from a chemical imbalance, and one that it was appropriate, indeed almost morally necessary to detect and treat.

87. There are no grounds to believe that NICE would have come to any different conclusions to TMAP on the issue of how to treat depressed children, when they in due course had gotten round to considering this issue, as they would have been called on to do had the drugs been licensed in the United Kingdom. Fate and the media intervened to ensure this never happened.

88. As a result of a Glaxo SmithKline application to the regulators for a license for Paxil to treat childhood nervous disorders, the raw data from clinical trials were lodged with a number of national regulators. Within a fortnight of seeing the raw data in response to queries as to the events behind the term emotional lability, in May 2003 the regulators in the United Kingdom issued a warning against the use of Paxil (Seroxat) for minors. A few weeks later, Glaxo SmithKline wrote to all doctors noting that Paxil use was linked to suicidality and that withdrawal from Paxil was also linked to an apparent doubling of the rate of suicidality. Three months later, Wyeth recommended against the use of Efexor in children, in similar terms. Later that year in December, the British regulators issued a position statement in which they stated that none of these drugs, bar Prozac, had demonstrated efficacy in depression.

89. These developments led to a projected FDA hearing for 2 February 2004. Ten days before this hearing, a working group for the American College of Neuropsychopharmacology reported that after reviewing the evidence it was the task force's view that SSRI drugs were safe and effective and well-tolerated by children (Emslie, Mann, Beardslee et al 2004).[12] The authors of this report included Emslie, Wagner and Ryan who had all been authors on study 329, and between had been authors on most of the randomized trial literature on SSRIs given to children. These three authors and their co-authors however noted that they might not be correct in their conclusions that there were no problems with SSRIs in that they had not seen the raw data.

90. Despite this move which was widely seen as a pre-emptive strike, in February 2004, an FDA hearing on the use of psychotropic drugs for children recommended strengthening the warnings on these drugs, against a background of regulatory assessments that at least 13 of the 15 studies undertaken of antidepressants in children failed to show efficacy for the drug,[13] and panel views that there appeared to be an activation syndrome on these drugs.

91. It transpired that in 1998, a SmithKline Beecham assessment of the Paxil studies, which had been completed at that time, 329 and 377, indicated that the drug did not work for depressed children, but that the data would not be submitted to the regulators, as a statement to the effect that the drug had not been shown to work for children would have a negative commercial impact.[14] Selected positive data, however, would be progressed to publication.

92. What lessons can be drawn from this situation which probably offers the greatest divide in all of medicine between the raw data on an issue on the one side and the published medical accounts purporting to represent those data on the other?

93. First, this divide gives the lie to a body of close to 100 papers and abstracts universally reporting the benefits of these drugs. These open and randomized trials it would seem have the appearances but not the substance of science. The discrepancy between the papers and the underlying data may stem from the possibility that many if not close to all of the key studies have been ghost-written. It is difficult to avoid such a conclusion when even the notional authors of the key papers claim not to have seen the raw data.

94. It follows from this that it is almost impossible to accept that these are scientific papers. What the field would appear to need is a new term with which to designate such infomercials, and a set of criteria that might reliably identify this new genre of marketing product that aims at manufacturing a clinical consensus. This it should be noted is the aim of all good marketing—to own the market, not just to sell the product (Applbaum 2004).

95. A second point is that while pharmaceutical companies know exactly how many prescriptions have been issued and just what each physician writes, almost no-one knows how many children or adults are on any psychotropic drugs. When this fact is allied to the fact that serious adverse events are reported by physicians to regulators in no more than one in one hundred cases, a picture emerges in which Americans and others track the fate of parcels put in the post 100 times more accurately than they track the occurrence of adverse events on these drugs. The quality of the information reported by patients on adverse events indeed would appear to be much better than that reported by physicians (Herxheimer and Mintzes 2004). This is a situation that could not have been tailored better to maximize the consensus building capacities of pharmaceutical companies.

96. There would appear to be reasonable grounds to state that there must be some fundamental opposition between marketing and science in that the former explicitly operates to build consensus, while the latter supposedly moves forward by fracturing consensus. When we have arrive at a situation in which the mental sets of clinicians have been captured so that it is difficult for them to conceive of alternatives to those being sold to them, there are reasonable grounds to state that such a field is no longer scientific. When there is almost no possibility of discrepant data emerging to trigger a thought that might be unwelcome to the marketing department of a pharmaceutical company, these marketing capabilities would seem appropriately described as totalitarian.

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154. Table 1:

INCIDENCE OF SUICIDES AND SUICIDE ATTEMPTS IN ANTIPSYCHOTIC CLINICAL TRIALS DRAWN FROM REGULATORY LICENSE APPLICATIONS

	Number of Patients	*Number of Suicides*	*Number of Suicide Attempts*	*All Suicidal Acts as %*
Risperidone	2,607	9	43	2.00%
Comparator	621	1	5	1.00%
Placebo	195	0	1	0.50%
Olanzapine	2,500	12	?	?
Comparator	810	1	?	?
Placebo	236	0	?	?
Quetiapine	2,523	1	4	0.20%
Comparator	420	0	2	0.48%
Placebo	206	0	0	0.00%

Sertindole	2,194	5	20	1.14%
Comparator	632	0	2	0.32%
Placebo	290	0	1	0.34%
Ziprasidone	2,993	6	?	
Comparator	951	1	?	
Placebo	424	0	?	
Total				
New Antipsychotic	12,817	33	(72	1.0%)
Comparator	3,434	3	(10	0.6%)
Placebo	1,351	0	(2	0.3%)

The data here comes from FDA medical and statistical reviews of risperidone, olanzapine, quetiapine and ziprasidone and from Lundbeck pharmaceuticals in the case of sertindole. Analyzing the data on suicides using an exact version Mantel Haenszel procedure and a one-sided test for significance yields an odds ratio with a Confidence Interval of (1.0825, Infinity), p = 0.03955, for new antipsychotics compared to placebo.

1 Note: In connection with TMAP, this article has benefited hugely by work undertaken by Allen Jones, Special Investigator in the United States OIG Office of Special Investigations, detailed in Dwight McKee and Allen Jones v Henry Hart, Sydni Guido, Wesley Rish, Albert Masland, James Sheehan and Daniel P Sattele, CIVIL ACTION No: 4:CV-02-1910, in the United States District Court for the Middle District of Pennsylvania. Back

2 As of 2004, these guidelines had been adopted at some point by Pennsylvania, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, South Carolina, Maryland, Missouri, and Washington DC, or by jurisdictions within those states. Back

3 It is important to note that the author participated as a guideline panel member in this Risperdal exercise. Back

4 It is important to note that the author also participated as a Delphi panel member in this Risperdal exercise. Back

5 This claim is based on the personal experience and discussions with ghost-writers/actors. Back

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9 Data on File. Important Safety Information regarding Paxil in Pediatric Patients, Glaxo SmithKline, Therapeutic Products Directorate: TDP-Web, 18 July 2003. Health Canada, www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/paxil-pa-e.html Back

10 Pfixer Expert Report 1997. Sertraline hydrochloride for obsessive compulsive disorder in paediatric patients. Approved 20 October 1997. Back

11 Pfixer Expert Report 1997. Sertraline hydrochloride for obsessive compulsive disorder in paediatric patients. Approved 20 October 1997. Back

12 This was initially only available through GYMR, a Washington based public relations company, who specialise in translating the language of science and medicine into the more understandable language of health. From GYMR.com, GYMR was "founded in 1998 by a team of experts in healthcare and social change . . . [it] offers clients marketing and communications expertise that strategically support public policy goals . . . [clients] include many of the nation's most respected associations, government agencies, pharmaceutical companies, philanthropic organizations and health initiatives." "Whether it's provoking action on a national health issue or crafting an organizational image that appeals to internal and external audiences, GYMR excels at designing and implementing issue and image campaigns." "Our media events are successful because we have a nose for news. We know how to take the language of science and medicine and transform it into the more understandable language of health. We advise clients of the best dissemination strategy for their news and make sure that the message they

deliver is compelling, documented and contributes to other national dialogues in a real and meaningful way." Back

13 www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.htm Back

14 Central Medical Affairs Team. Seroxat/Paxil. Adolescent Depression. Position Piece on the Phase 111 studies. October 1998. SmithKline Beecham Confidential Document, available from the author. This is also available on the Canadian Medical Association Journal Website. Back

Previous Contents Next

Commons Parliament Lords Search Enquiries Index

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