Legislative Lacunae: Executive Summary. March 5th 2025

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Increasing antidepressant use poses a growing public health problem. This use is linked to increasing rates of suicide, especially among young people, reduced reproductive rates and enduring sexual dysfunction, increased rates of alcohol consumption and other illicit drug use, dependence on antidepressant and antipsychotic drugs and increasing rates of treatment induced disability leading to unemployment and benefit claims.

New antidepressant usage among younger people is growing rapidly. There are still many more older folk taking antidepressants continuously, which has led to deprescribing efforts that have had a modest impact. In terms of years of life lost, however, which are linked to starting a drug rather than continuous usage, the years of life lost when a young person commits suicide are greater than when the same problem happens later in life.

The increase in antidepressant intake among the young is surprising in that it is not linked to pharmaceutical company marketing, nor driven by evidence these drugs work in this age group and is happening despite prominent warnings of a suicide hazard. There are however failures to warn about other significant hazards like permanent sexual dysfunction, infertility and dependence, and the role of antidepressants as a gateway to other drug use.

For three decades a failure to warn about the hazards of antidepressants has been linked to a stated regulatory desire not to deter people from getting the benefits treatments can offer. This position evolved at a time when virtually no younger person was being given these drugs – but it has persisted to this day when we face an epidemic of use among younger people. The 'ban' on warnings extends to threats that inhibit leading medical journals from publishing articles about hazards, inhibits Cochrane and NICE from downgrading the quality of evidence that company studies provide, and inhibits the BBC and mainstream media from asking questions.

These points are relatively well known but avoided. This paper deals with an almost unknown problem. Warnings need company participation. Company lawyers have had a head start of decades on regulators and medicine in anticipating the scenarios we have now which evolved from a situation no-one expected when SSRI antidepressants launched – namely that significant hazards of these drugs might remain contested after the patent on the branded product expired.

A decade ago, FDA outlined the need to address this problem but backed off. It is not clear that any government or its medicines' regulator is aware of or has addressed the problem.

This document outlines the evolution of our problem and possible solutions some of which might require a restructuring of the medicines' marketplace.

Unforeseen Consequences

In 1984, a Hatch-Waxman Drug Prices and Patent Restoration Act was passed in the United States. This opened an avenue for generic medicines to come on the market. The hope was this would lower drug costs. A medicine is comprised of a chemical and information designed to make unavoidably hazardous chemicals passably safe. The new Act required generic drugs to adopt the information in the branded label[1].

In August 2001, Prozac. Eli–Lilly's selective serotonin reuptake inhibiting (SSRI) antidepressant, went off patent, allowing generic fluoxetines to come on the market. Lilly devised a number of strategies to maintain their financial interests, including launching Sarafem, a new brand of fluoxetine, indicated for Pre-Menstrual Dysphoric Disorder (PMDD), once a week branded Prozac, and a Prozac-Zyprexa, fluoxetine-olanzapine, combination branded as Symbyax.

A more successful industry strategy, later adopted by most companies, was a turn to branded generics. Lilly, for instance, produced a generic fluoxetine branded as Prozac, which cost more than other generics but less than the prior branded product. Generic companies could not copy this named element. The original companies sponsoring a brand, meanwhile retained the option to have both generic Prozac and generic fluoxetine, which several companies have exploited.

Patents and Hazards

When the Hatch-Waxman Act was passed in 1984, no-one envisaged that after a decade or more on the market, some of the most significant hazards of a branded medicine might remain contested. In the 1980s, doctors established the hazards of prescription medicines emerging after their launch by publishing articles about these hazards in medical journals. In addition, doctors working for companies did clinical interviews with those doctors or patients reporting hazards, with the company doctor often concluding there was no explanation for the hazard other than the company drug had caused it.

The suicide inducing effects of SSRIs were established in this way. During 1990-1991, two years after Prozac's launch, a large number of clinical groups, many from prestigious institutions published articles outlining suicidality developing on Prozac, that cleared on stopping and reappeared on restarting[2]. By conventional canons of medical and scientific causality, Prozac had the capacity to cause suicide. These articles led to a regulatory crisis about Prozac, suicide and warnings.

In defense of Prozac, Eli Lilly published an article purporting to meta-analyze the clinical studies they had done seeking a license to claim Prozac was an antidepressant[3]. Lilly claimed their

[1] Healy D. Shipwreck of the Singular. Healthcare's Castaways. Samizdat Toronto 2021.
[2] Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990, 147, 207–210.
[3] Beasley CM, Dornseif BE, Bosomworth JC et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991, 303: 685–92.

analysis did not show Prozac caused suicide and pitched their approach to the problem as the science of cause and effect, compared to which the reports of 30, 40 or more cases of suicidality on Prozac were anecdotes. They invited doctors, the public, the media and scientists to choose between the science and the anecdotes.

Lilly's article had been rejected before the company approached BMJ. A BMJ reviewer pointed out that the study data did not support claims Prozac did not cause people to commit suicide. There were more suicidal events on Prozac than on placebo. Lilly argued that the difference was not statistically significant and therefore in effect there was no excess of events on Prozac. Had the reviewer and editor read the small print, they would have seen the data showed a statistically significant excess of suicidal events on Prozac. BMJ published the paper with wording that suggested there was no evidence Prozac made people suicidal[4].

In 1991, there was little recognition that companies do randomized controlled assays (RCAs) designed to get licenses rather than randomized controlled trials (RCTs) designed to inform clinical practice[5]. That the patients in company assays may not exist. That companies can use a range of coding tricks - words like emotional lability, and other maneuvers as Lilly demonstrated in this 1991 article by adding a suicidal event to the placebo arm that didn't happen on placebo.

Lilly's article was published on the day FDA held a hearing on whether Prozac should carry suicide warnings. It was likely influential in an FDA decision not to issue warnings despite presentations of a series of Prozac induced suicides at the hearing. FDA did not contest that an SSRI could cause suicide, but opted not to warn on the basis that warnings might deter people from seeking the benefit of treatment.

In opting not to warn FDA took the position that the studies done by Lilly to obtain a license to market Prozac as an antidepressant showed a greater benefit than hazard. There was in fact, clear evidence of a significant excess of suicidal acts on Prozac compared to placebo and an excess of suicidal acts on other SSRIs compared to placebo in the marketing applications from GlaxoSmithKline (GSK) for Paxil (paroxetine) and Pfizer for Zoloft (sertraline), along with breaches of FDA regulations by Lilly, GSK and Pfizer in their submissions to the agency in respect of this hazard[6]. These data were not in the public domain or in published articles in medical journals.

Lilly's article created Evidence Based Medicine (EBM). It demonstrated to industry how EBM could facilitate rather than constrain company marketing. Many doctors have since in practice come to view evidence based medicine as a matter of prescribing according to company labels

[4] Healy D. Let Them Eat Prozac. New York University Press, New York 2004.
[5] Healy D. Randomized Controlled Assays and Randomized Controlled Trials. A Category Error with Consequences. Ethical Human Psychology and Psychiatry 2023, 25, 119-134, http://dx.doi.org/10.1891/EHPP-2023-0006.
[6] Healy D (2006). Did regulators fail over selective serotonin reuptake inhibitors. BMJ 333, 92-95.

– with off-label prescribing increasingly frowned upon. Few doctors understand that labels are intended to constrain company claims rather than medical practice.

Journals like NEJM and BMJ stopped taking reports on the hazards of prescription medicines written by doctors for fear of being sued for libel.

Other regulators, Britain's MHRA, European, Canadian and Australian regulators followed FDA's lead in not adding explicit warnings of a suicide risk to the labels of Prozac or other SSRIs.

Warnings After Patent Expiration

The 1990-1991 antidepressant and suicide crisis demonstrated growing company abilities to defend their product against warnings. The question about what to do if a need arose to institute significant warnings after the expiration of a patent on a drug moved from being a notional to an actual regulatory issue in 2004, with a second suicide crisis that resulted in class-wide Black Box Warnings on antidepressants, an option that Lilly had rejected in 1991.

The second crisis stemmed from legislation that offered branded companies facing patent expirations the possibility of patent extensions if they ran studies to demonstrate the safety of their products in minors. This resulted in trials of SSRIs in minors, in which there was an excess of suicidal events on active treatment compared to placebo – similar to the data for adults. The trials in minors, however, showed no apparent benefit making it impossible to argue that benefits outweighed the hazards[7].

FDA had already licensed Prozac for depression in minors at this point even though in the trials Lilly submitted for licensing Prozac did not meet the effectiveness criteria. FDA subsequently issued an approvable letter for Paxil for adolescent depression on the back of three negative trials[8]. This approval did not go ahead because of the crisis that blew up but the approval for Prozac, which was no more solid than the case for Paxil, was not retracted.

The 2004 crisis had one further consequence. The National Guideline Apparatus in Britain (NICE) was in the midst of writing guidelines for treating depression in adolescents and minors when the crisis broke. It became clear that all of the published literature was ghost/company written and that the published results were at odds with what the data showed when accessed. The authors of the proposed guideline pulled out of the exercise, leading to an editorial in the Lancet 'Depressing Research' intimating that it would not be possible to write any guidelines for any treatments involving on-patent drugs[9].

[7] Healy D, Le Noury J, Wood J. Children of the Cure. Samizdat Press, Toronto 2020.
[8] Healy D, Le Noury J, Wood J. Children of the Cure. Samizdat Press, Toronto 2020
[9] Editorial, Depressing Research, *Lancet* 363, (2004), 1335.

A similar situation faced groups who do Systematic Reviews, like the Cochrane Collaboration, who had been including company studies in their reviews. But Cochrane, NICE and major journals like The Lancet continued as before – treating company assays as equivalent to medical trials – stating on the British Parliamentary record that the only problems were with small fly-by-night companies and peripheral medical journals with little influence[10]. The inside word was that Cochrane and the NICE Guidance apparatus were scared of libel actions if they did anything that indicated company studies were anything less than stellar research.

Mensing to Dolin

These growing concerns and debate about how best to alert the public to significant risks now interface with the question of who will be legally liable for any warnings and how to ensure that warnings are effective, given increasing evidence that neither doctors nor patients pay as much heed to warnings as they once did.

In a series of cases taken by Gladys Mensing in 2010-2011 through a District Court, Appeals Court to the U.S. Supreme Court, it was decided that even in the event of a hazard like tardive dyskinesia that was unquestionably caused by the generic drug, the generic manufacturer was not liable for the injury if the branded label contained no mention of the problem.

In 2017, in Dolin v GlaxoSmithKline (GSK), the plaintiff's legal team successfully argued that GSK, the branded company, should be the defendant although the plaintiff's suicide had been induced by generic paroxetine. The jury found against GSK, accepting paroxetine had caused the suicide. GSK's element of responsibility was discharged by an Appeals Court, who argued that in 2006 FDA had blocked GSK's effort to warn more clearly[11].

While the Dolin case was happening FDA were engaged in reviewing possible reforms, requiring generic companies to update their labels. They abandoned these efforts in 2018, claiming that it would increase the cost of generic drugs by too much and might create significant differences between labels[12].

Following Dolin, companies sought to divest themselves of off-patent branded products. Merck transferred its Singulair brand to Organon, Pfizer transferred the Zoloft brand to Mylan/Viatris. Other companies have made similar arrangements. In some respects Viatris offers clearer warnings for Zoloft than Pfizer had done.

[10] Horton R, Chalmers I. House of Commons. Health Committee. The Influence of the Pharmaceutical Industry London: The Stationery Office Limited (2005).
[11] Healy D. Shipwreck of the Singular. Healthcare's Castaways. Samizdat Toronto 2021.
[12] Withdrawal of Proposed Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products. Federal Register 12/14/18.

It is not clear the market authorization holder is the same in all countries raising harmonization issues. Nor is it clear that regulators recognize the key features of a new situation.

Recent moves by Lilly in respect of Prozac may bring these issues to a head. In contrast to other companies, Lilly initially held on to generic Prozac and generic Cymbalta, Prozac's successor. At the end of 2024, however, Lilly discontinued production of both of these drugs and divested themselves of the brands without passing them on to another company. There appears to be no market authorization holder for either of these drugs. Cymbalta has recently been linked to cancer.

Labels without Brands

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As with Prozac and suicide, the potential for significant problems linked to sexual function and dependence were clearly apparent before the launch of the SSRI group of drugs. There has been a case for significant warnings for close on four decades with this case growing during the two decades these drugs have been off-patent[13].

The most common and immediate effect of an SSRI drug is a degree of genital dysesthesia, primarily genital numbing. This was apparent in healthy volunteer trials in the 1980s prior to launch, with suggestions of persistent sexual dysfunction in some of these phase 1 studies along with clinical reports of persistence of sexual dysfunction in people after stopping clomipramine, a potent pre-SSRI serotonin reuptake inhibitor.

To this day, there have been no clear warnings about sexual dysfunction, commensurate with the hazard. There have been no indications that companies or regulators have considered the possibility that many of the partners of individuals prescribed an SSRI might believe they too should know about a hazard like sexual dysfunction before their partner starts treatment.

There have been no warnings stemming from animal studies reported two decades ago pointing to plummeting sperm counts in males and implantation problems and birth defects in females likely leading to fertility problems, again with no apparent consideration as to whether partners,

[13] Healy D. Sexual and Fertility Effects of Selective Serotonin Reuptake Inhibitors. What role for informed consent? Ethical Human Psychology and Psychiatry https://connect.springerpub.com/content/sgrehpp/early/2024/11/26/ehpp-2023-0024.

in addition to the person starting treatment, should be informed about these hazards. There is no national conversation about these fertility and sexual effects at a time when many governments are concerned about reproductive rates that have fallen well below replacement rates, threatening social structures.

The SSRI group of drugs became antidepressants, in part because of concerns about dependence on benzodiazepine anxiolytics. At that point, antidepressants were not linked to dependence and marketing the SSRIs as antidepressants looked an easier option[14]. The phase 1 trials of these drugs, however, produced rates of dependence in up to 80% of volunteers after two week exposures. Within 3 years of paroxetine's launch in Britain, there were more reports to regulators of dependence on it than there had been during the previous 20 years for all benzodiazepines combined.

We now have 15% of the populations of most developed countries taking SSRIs and related medicines. Until very recently, this figure was growing year on year, not because more people were being put on these drugs but because a large proportion of those put on one of these drugs in any one year were unable to stop it. This is a public health crisis.

May Contain Nuts

For a period of time, the Black Box warnings allied to a message that these drugs did not appear to work particularly well for minors meant antidepressant prescribing remained relatively restrained in younger populations. However, a constant stream of articles arguing against the warnings, linked to a growing use of these medicines despite warnings, and apparently growing mental health problems among adolescents, has led to a rapidly escalating use of these drugs since 2015, particularly among young women.

In Australia between 2015 and 2019 there was a 50% increase in young people taking these medicines for the first time, while there has been a 10% fall in new use among older people (>65) there[15]. Both the rise in new use by the young and fall among older people are replicated in other countries. The fall among the elderly appears likely linked to concerns about a growing rate of polypharmacy among the elderly, which has been linked to shortened life expectancy, increased rates of hospitalization and a poorer quality of life. This awareness has prompted efforts to deprescribe, which may have had some success, but a reduced rate of starting is at present doing little to reverse the steadily increasing rate of continuing intake.

[14] Healy D (1991). The marketing of 5HT: anxiety or depression. British J of Psychiatry, 158, 737-742.
[15] Costa J, Gillies M, Schaffer A, Peiris D, Zoega H, Pearson S-A. Changes in antidepressant use in Australia: A nationwide analysis (2015–2021). Aus & New Zeal J Psychiatry 2023, 57 49–57. DOI: 10.1177/0004867422107974

A polypharmacy pandemic affecting the elderly came into view around 2000. The problems affecting adolescents and minors emerged a decade ago. Many more years of life are lost when young people die prematurely than when older people do and there are greater implications for disability payments and reproductive rates, if young folk exist in a medicated but disabled state. These elements make the young the group that is now should perhaps be of greatest concern.

Politicians have two problems. It is not clear that regulators know how to manage the current situation. In addition there is a how to make warnings effective problem. Black Box Warnings in general across many medicines have become May Contain Nuts labels – they do not deter doctors from prescribing or us from taking these medicines any more than the equivalent labels deter people with a peanut allergy. The labels are seen as regulators and companies covering their backs rather than evidence of a concern for us

Effective Warnings

Between 1990 and 2000 the system that guaranteed effective warnings was dismantled. Up till then physicians paid heed to reports of hazards by other physicians in medical journals. After 1990, these slowly dried up as journals got more money from publishing company studies than from medical reports. There was a growing concern among journal lawyers that articles claiming there was a hazard on treatment might result in a libel action from the company making the drug. The absence of articles by doctors in medical journals has had a chilling effect.

This change in journals tied in with another development. Unlike Europe, where doctors report hazards to regulators, in America, it was traditional for doctors to report hazards to the company making the product as one might with any other consumer product. Pharmaceutical companies employed doctors who would contact the reporting physician or the patient, seek access to the medical record and taking the same approach to establishing causality as physicians reporting suicidality on Prozac in 1990 had taken, would not infrequently conclude that the company drug had caused the problem.

This led to a label change and Dear Doctor letters from the company spelling out its belief that their drug could cause problem X. Doctors paid heed to company letters like this.

In 2005, FDA Guidance on Good Pharmacovigilance practice assumed this system was still in place[16]. Around 2000, however, lawyers advised companies that legal defenses against claims that SSRIs cause suicide, hinged on persuading courts that company studies offer a science of cause and effect and individual physicians' views are anecdotal. Company doctors making

[16] Food and Drug Administration. Guidance for industry. Good pharmacovigilance practices. US Dept of Health and Human Services, FDA-2004-D-0041 March 2005 A. Food and Drug Administration. Conducting a clinical safety review of a New Product Application. US Dept of Health and Human Services, February 2005 B.

causal determinations would undermine this defense. Company employees switched from investigating reports into doing little more than passing these reports on to regulators.

As of 2008, adopting the European model, American companies openly advocated reporting directly to FDA rather than to them. They knew FDA do not have doctors to establish whether a case reported as linking a drug to a hazard is causally linked or not. This has a knock-on effect for European as well as American safety, as Europe had essentially been getting a free ride on American safety structures that are no longer in operation.

This was illustrated vividly in 2024, when Sanofi lost a European court case centred on birth defects caused by sodium valproate. The company then conducted research on what doctors and patients understood about the warnings issued by European regulators over the prior decade and decided these were not sufficient to keep the company safe and needed strengthening[17].

Similarly in 2020, FDA placed an ineffective Black Box Warning on Singulair (montelukast) for neuropsychiatric adverse events[18]. In early 2024, New York's Attorney General's Office wrote to FDA indicating that this warning has had no effect and asking what the agency now proposed to do about a continuing deterioration in the health of minors linked to this drug.

Not only are companies now able to block warnings for decades when their income from an on-patent product is maximal, we also now have a situation where our abilities to disseminate effective safety information appears to be compromised, with apparently little understanding as why this might be.

Finally I am currently involved in a legal action linking acetaminophen (Tylenol) to autistic spectrum disorder. Here companies are arguing since the CARES Act finalized the monographs for OTC products like Tylenol – the monographs had been temporary for the previous 55 years - companies have lost the ability to update the label with new hazards like neurodevelopmental delay.

They now argue that essentially FDA are the Market Authorization Holders for OTC products – the owners of the brand.

This suggests that following Dolin, the only recourse for anyone injured by these drugs is to sue FDA/US Government – as Sanofi have done in the case of valproate and autistic spectrum disorders and the French government.

Unforeseen elements of the arrangements we put in place in 1962 in the wake of the thalidomide crisis have made the current regulatory system incoherent

[17] **Follow Guidelines to avoid valproate complaints and claims**

[18] Clarridge K, Chin S Eworuke E, Seymour S. A Boxed Warning for Montelukast: The FDA Perspective J Allergy Clin Immunol Pract 2021, 9, 2638 – 2641

Remedies

In 2018 FDA abandoned moves to require companies to update generic labels. We need clarity on the legal liability issues that led to this retreat.

Given a medicine is a chemical plus information, this regulatory retreat removes an incentive to make a better medicine by improving the information component of the product.

Making some drugs available OTC might help but would need a major change to OTC labelling. Companies would have to provide more effective information than is currently supplied in patient information leaflets for prescription medicines. Aside from that, we might be safer if able to bring our natural caution into play rather than have it inhibited by doctors reluctant to believe us when we report events not currently found in drug labels. We have less problems with OTC serotonin reuptake inhibiting antihistamines than prescription only SSRIs.

Allied to the above, if physicians were incentivized to get us to consult them, they might re-embrace medical professionalism rather than simply parrot views designed to ensure the health of company products.