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CAN ANYTHING BE DONE TO STOP DECEPTIVE DRUG PROMOTIONS?

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Previous Newsletters have provided numerous examples of the adverse health consequences of misleading drug advertisements, particularly with respect to statins and more recently antidepressants. This has become a particular problem with respect to TV and print promotions directed to the public. Common side effects and contraindications may be listed as required by regulations but these are usually in fine print or quickly glossed over.

As illustrated in the last issue, many of the ads for antidepressants make claims for efficacy and safety that are not only unsupported but are actually contradicted by studies that the manufacturer and in many instances the FDA are well aware of. These include little evidence of significant superiority compared to placebos and claims of the absence of serious side effects as well as lack of dependency. The FDA, FTC and FCC are responsible for protecting the public from such deceptive and false advertising but have failed to do so for several reasons.

A major problem is the tremendous influence pharmaceutical companies have over these regulatory agencies as well as Congress because of their tremendous financial clout. In many instances, FDA Advisory Panels responsible for approving drugs as well as what claims can be made are composed largely of employees, consultants and others with hidden financial ties to the company whose product they are reviewing. Even when dangerous errors are subsequently demonstrated and strongly protested, attempts to correct them have been thwarted by the FDA.

In 2002, the last year for which records are available, the pharmaceutical industry spent $91.4 million on federal lobbying activities that are required to be disclosed. Drug companies had 675 registered lobbyists (more than seven for each senator) and 26 of these were former members of Congress. At least another $50 million was spent to influence Congress and others through advertising, direct mail, telemarketing and grants to supportive advocacy groups and academics. It is likely that millions more that were not revealed were spent in other covert promotional activities.

ALSO INCLUDED IN THIS ISSUE

As will be seen, these investments have paid for themselves several times over. In addition, they are just a drop in the bucket compared to the $36 billion in profits taken in last year by just the 10 top drug companies. That's five-and-a-half times more than the median profits for all the Fortune 500 companies.

Whom Does The FDA Really Protect?

The expert panel that was responsible for the British ban on the use of antidepressants for children produced documents showing that manufacturers were well aware that they increased risk for suicide **and were barely more effective than placebos in some studies and actually less effective in others**. While several drug companies sent letters to all U.K. physicians with appropriate warnings, none were sent to doctors in the U.S. although the FDA also had this information. This resulted in a demand for a hearing to determine whether similar sanctions should be imposed here.

A public hearing on SSRI safety and efficacy was held last February, which the FDA also tried to manipulate. The agency refused to allow three experts with damaging testimony to appear before its advisory panel. It explained that in order to avoid bias, it would have one of its senior scientists review 20 clinical trials on eight antidepressants involving over 4,000 children and present his findings at the hearing. When this individual reported that, like the expert British panel, he also found a definite link between antidepressants and suicidal behavior in kids, he was told that his report was not needed and was being replaced by a review that failed to find these dangers.

One of the most powerful FDA policy makers is Daniel Troy, who became its chief counsel in August 2001 and essentially ran the agency until Mark McClellan was appointed FDA commissioner in November, 2002. During that period, internal documents show that he held at least 50 private meetings with representatives from drug companies and industries the FDA regulates. According to his office, he kept no minutes, memos or written notes but it is quite evident that after some of these meetings, Troy took industry's side.

In the 2001 California Paxil suit banning misleading advertising, Glaxo SmithKline met with Troy, who promptly filed a brief stating that the FDA agreed with Glaxo that Paxil is not habit-forming. He argued that the drug did not cause physical dependence, which would make it habit-forming and that the various complaints described were not withdrawal symptoms, but due to a "discontinuation syndrome" seen with other drugs. In addition, the FDA had the ultimate authority to decide the issue. The judge was forced to lift the ban.

Pfizer was sued in 2002 by the family of a patient who committed suicide after taking six tablets of Zoloft, its top-selling antidepressant. Troy was very familiar with Pfizer since he had served as their attorney until a few months before joining the FDA. Shortly after the one-year federal restriction on action involving his former clients expired, Troy filed a brief stating that the FDA had dismissed the notion that antidepressants increased risk of suicide. If Pfizer were to include such a label warning, they would have violated the law.

Prior to 2002, the FDA's Division of Drug Marketing issued over 90 warning letters a year to drug companies for questionable advertising claims. During Troy's tenure, this dropped to less than 30/ year because of his new policy that all enforcement letters had to be approved by his office. According to one FDA veteran "The underlying message is to be less regulatory." Before coming to the FDA, Troy successfully sued the agency to let drug makers promote doctors on "off label" (unapproved) uses of their drugs. He still supports this, which includes antidepressants for kids.

"All The News That's Fit To Print"?

The pharmaceutical industry also has a powerful influence on the media because of the $3.2 billion it spent on direct consumer advertising last year. The testimony from families at the 10-hour February hearing was compelling, and in an unprecedented action, the advisory panel urged the FDA to immediately warn physicians and the public that SSRI's "might be linked to suicidal thinking and behavior, hostility or other forms of violent behavior." The FDA said it would take everything under consideration,

was still investigating the matter and planned to hold still another meeting sometime this summer to determine what, if any changes should be made.

So what happened since then? The FDA could not afford to dismiss the recommendations of its own advisory panel. On March 22, it "requested" that warnings be placed on the labels of ten antidepressants about "the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening." It did not indicate that most clinical trials and its own records suggested that this was most likely due to these drugs.

The *New York Times* first page coverage of this and a follow-up article the next day quoted several psychiatrists, all of whom opposed the warning, but in violation of its own standards, did not reveal their ties to drug companies. Dr. Harold Koplewicz, director of the NYU Child Study Center stated "The fear I have about this warning is that many teenagers will not get the medicine because it will build resistance among their parents, and that is really a tragic outcome." No mention was made of the very substantial funding to Dr. Koplewicz or his Child Study Center from the drug industry.

Dr. Koplewicz co-authored a report on a major study that claimed Paxil was "well tolerated and effective" for adolescents. The FDA has now discredited this study because of an internal company memo stating that only the positive data from the study would be published, but none of the negative findings. This memo was obtained through litigation, not the FDA, although they had long been aware of it.

Dr. Jeffrey Lieberman, professor of psychiatry at the University of North Carolina, received grants and research support from Upjohn, Bristol Myers Squibb, Novartis, Eli Lilly, Janssen, Pfizer, Hoechst and Astra Zeneca and is a consultant and speaker for many of them. Dr. Regina Casper, a Stanford professor of psychiatry, received compensation for collaboration with Eli Lilly researchers. Dr. Madhukar Trivedi, director of the mood disorders program at University of Texas Southwestern Medical School, feared that "patients may become afraid of their pills and the consequences for not treating depression are very high." He was largely responsible for developing a Texas program that promoted anti-depressants as the treatment of choice for kids. It was sponsored by every major antidepressant drug manufacturer and he received research grants and speaker's fees from at least 16 of these! The *New York Times* concealed all of the above serious conflicts of interest.

Both *Times* reports ignored the disparity between published reports about antidepressant trials and drug company data that had been kept secret for over a decade showing a two-to-three fold increased risk of suicidal behavior in children taking antidepressants compared to placebos. Yet, on March 28, in *The Week In Review*, Gina Kolata wrote, "After all, suicides are rare enough that there are no firm human data on whether the drugs can cause them." The vast majority of people supported the labeling change and many felt it did not go far enough since no deadline was listed and manufacturers could ignore it. However, the only four letters the *Times* printed were from doctors and others who opposed it. On March 30, Tanya. Lurman wrote in the *Times Science Section*, "Antidepressants, whatever their side effects, work for many people and have undoubtedly prevented countless suicides." There is no evidence to support this statement.

On April 2, the *Times* reported a survey showing that from 1998-2002, antidepressant use in those under 18 increased 50 per cent. The largest rise was in kids under five, doubling in girls and up 64% in boys. The potential dangers of this were not mentioned.

The FDA, Ephedra & "The Dirty Dozen"

The most dangerous and deceptive ads are for nutritional supplements, over which the FDA has no control. The Dietary Supplement Health & Education Act of 1994 allows supplement makers to make any claims they wish without showing evidence of efficacy or safety. There is also nothing to guarantee that the contents of the container bear any relationship to what is listed on the label. In addition, deaths and adverse reactions to supplements are not required to be reported. The only way the FDA can ban a

supplement is by proving that it puts the public at unreasonable risk.

The FDA first tried to restrict ephedra sales in 1997 but backed off after pressure from the $18 billion/year supplement industry and powerful individuals like Orrin Hatch, Utah's Republican senator and co-author of the 1994 law. Dietary supplements that bring in $3 billion a year are Utah's third-largest industry. Supplement companies have reported contributing $157,000 to Hatch's campaigns and $2 million to his lobbyist son. There may well be other donations that have been made in ways not required to be reported. Since 1993 the Food and Drug Administration has received 16,961 reports of adverse events, including heart attacks, strokes, seizures, and 155 deaths associated with ephedra supplements. More than 14,500 of these adverse events were among young consumers using Metabolife supplements, records of which the manufacturer withheld from the government for five years. A March 2003 report showed that ephedra products accounted for 64 percent of all adverse reactions to supplements reported to the American Association of Poison Control Centers.

The FDA had a golden opportunity in 2002 to obtain detailed consumer complaints about Metabolife that had been introduced in a private lawsuit. These could have provided the proof needed to show that it "put the public at unreasonable risk." Not surprisingly, our old friend Daniel Troy took no action. When Dennis Baker, then the FDA's associate commissioner for regulatory affairs objected to Troy's decision to do nothing, he was transferred to an FDA office in Dallas.

Baker knew all about Metabolife and ephedra. He worked for the Texas Department of Health in the late 1990s, when that agency tried to ban ephedra. Metabolife spent more than $4 million in Texas between 1998 and 2000 to hire powerful lobbyists with close ties to then Gov. George W. Bush to kill the effort. Between 1999 and 2002, it also spent $1.2 million lobbying Congress and the FDA. Texas did order warning labels for all ephedra products. The FDA first proposed this in 1997 but did nothing.

Ephedra was banned by the International Olympic Committee in 2000 and the National Collegiate Athletic Association and National Football League in 2001, and since then has been banned in several states, Canada and some European countries. Following the death of a baseball player due to ephedra last year, the FDA again "proposed" warning labels. On the last day of 2003, commissioner McLellan announced that the FDA was now "planning to ban" ephedra products". Nothing happened until February 6, when the agency set April 11 as the date for the ban to actually become effective. This gave consumers plenty of time to stockpile ephedra and for 62 ephedra manufacturers to attempt to find replacement products and reverse the ruling by lobbying and litigation. Two such lawsuits have already been filed in Alabama and New Jersey and others are likely to follow.

In the interim, a host of products just as dangerous have been introduced or continue to be sold despite bans elsewhere. *Consumer Reports* magazine's May cover story referred to their **"dirty dozen"**: **snakeroot**, banned in Europe, Egypt, Japan and Venezuela; **kava**, banned in Germany, Canada, Singapore, South Africa and Switzerland; **comfrey**, which the FDA advised industry to remove from the market in 2001 and is banned in other countries, as are **androstene, chaparral, germander, bitter orange, lobelia, pennyroyal, skull cap and yohimbe**. **Organ/glandular extracts**, banned in France and Switzerland because of risk of mad cow disease, were also included. In January 2004, the FDA did ban high-risk materials from older cows but high-risk parts from cows under 30 months are still permitted.

Supplements To Reduce Stress &Weight?

It is likely that the ephedra ban will be delayed by court challenges but all the publicity has led to a host of ephedra free supplements, some of which may also be dangerous. Many contain bitter orange, whose active ingredient, synephrine, a close chemical cousin of ephedra, has many of the same side effects. Often included is green tea extract, which contains catechins that exaggerate the ephedra effects of bitter

orange. These are further augmented by caffeine found in guarana and other supplements that are frequently added. None of the above are effective in promoting weight loss. Supplement manufacturers who have jumped on the stress ➜ obesity bandwagon offer less harmful products with preposterous promises of dramatic weight loss because of their ability to reduce stress. **After all, what could possibly be more appealing than a pill that would reduce stress, make you lose weight, was safe, had scientific backing and did not need a prescription.**

One of the top sellers is **Cortislim**, which has been heavily promoted as a "fat burner to lose weight by negating the effects of cortisol, the body's main stress hormone". The composition of this powerful potion is confusing and deceptive since its main components are Cortiplex™, Leptiplex™ and Insutrol™. These names have been carefully chosen to support claims that are made about important effects on cortisol, leptin and insulin activities. There is no proof and little scientific support for these wild assertions. The only difference from other weight loss supplements is Cortiplex™'s magnolia bark extract, which contains a magical chemical called honiokol.

Honiokol "controls cortisol levels within a healthy range to help reduce fat storage and promote fat mobilization — especially fat stored around the midsection in the tough-to-lose abdominal area. ... It can help to 'de-stress' you without making you sleepy. When compared to pharmaceutical agents such as Valium (diazepam), honokiol appears to be as effective in its anti-anxiety activity, yet not nearly as powerful in its sedative ability."

Similar claims are trumpeted by other supplements containing magnolia, like **Relora**. Its "patented blend of plant extracts is the result of screening more than fifty plant fractions from traditional medicines used around the world. Relora exhibits excellent stress management abilities without sedation". It allegedly lowers cortisol while boosting DHEA.

Do not confuse this with **Relacore**, whose manufacturer wants to know "Is Stress Making You Fat? Excess tummy flab is not your fault! Relacore is the solution to excess abdominal fat and stress reduction!" So is **Cortitrol Stress Control Formula**, "a unique dietary supplement that helps you cope with stress by modulating healthy levels of cortisol." Or you could consider **CortiDrene**. This "Breakthrough Product Solves Stubborn Stress Fat as well as delivering Dual Action Anti-Aging Antioxidants." Its proprietary formula is simply a combination of green tea extract, St. John's wort and other readily available supplements that "absorb fat, control the effects of cortisol overproduction, provide energy, relieve stress, control cravings, and promote weight loss."

CortaLean similarly "suppresses appetite, boosts metabolism, melts abdominal fat away and blocks cortisol levels induced by stress. The only thing you have to lose is Stress Related Fat." It is described as the "Most Advanced Stress Reducing — Weight Loss Formula Ever Created." CortaLean contains magnolia bark but its alleged superiority is attributed to its content of high amounts of B complex vitamins. This "could save 300,000 lives a year from heart attacks" according to a *JAMA* article that was not pertinent. Citing irrelevant articles from respected journals to provide a patina of authenticity that would otherwise not exist is a common deceptive practice.

There is also **TheraStress**, "the most scientifically advanced stress reducing, fatigue fighting, fat reducing, health enhancing natural product available." It contains "adaptogens", exotic oriental herbs that "stimulate the body's own regenerative process" and "balance the secretions of the adrenal cortex." All this from just 20-40 drops in a glass of liquid once a day.

Anti-aging And Other Supplement Scams

Some of the most outrageous claims are found in the promotional advertising for HGH (Human Growth Hormone) supplements to prevent aging. These are based on evidence that injections of approved human growth hormone can improve energy, sexual, and exercise performance, kidney and immune function, hypertension, cholesterol, sleep, memory, mood, vision, and wound healing. In addition, muscle mass increases significantly without exercise and causes weight loss without the need to diet.

Other bonuses include younger, tighter skin, wrinkle removal, elimination of cellulite and hair regrowth.

The reference cited to support all of these claims is a 1990 article published in the prestigious *New England Journal of Medicine*. This was a small study that simply showed that human growth hormone injections three times a week could increase lean body mass in 21 men aged 61-81 who had low growth hormone levels. Human growth hormone is a substance secreted by the pituitary gland that promotes growth during childhood and adolescence. It stimulates production of IGF-1 (insulin-like growth factor-1) from the liver and other tissues, which is responsible for its growth promoting effects and also reflects the amount produced. Blood levels of circulating IGF-I tend to decrease as people age or become obese.

An accompanying editorial warned that some of the subjects had experienced side effects and that the study was too short to evaluate long-term complications that have been reported, including an increase in cancer. It also warned that the hormone shots were expensive (around $1000/ month) and that the men who received them had no evidence of any improvement in muscle strength, mobility, or quality of life.

The products being hawked are oral amino acids and other, cheap, widely available supplements called "secretagogues". These supposedly stimulate natural growth hormone production" but since nutritional supplements can make any claim they choose, they are not taken seriously unless scientific support in a respected peer reviewed publication can be cited.

Few people are able or bother to check on such references and it is difficult to stop these deceptive abuses. NEJM became concerned when it became dear that this article was being widely abused by anti-aging supplement makers since it implied their endorsement. The editor indicated it receives more "hits" on its web site and requests for this in a week than any other article published in 1990 has in a year. Due to numerous consumer complaints, he asked the attorneys general of two states to investigate ads citing the Journal for marketing purposes. Last year, he devoted an editorial to this problem along with an article by the author whose 1990 editorial accompanying the study had obviously been distorted. Both of these stressed that oral or inhaled versions of HGH and supplements touted as natural HGH releasers sold as anti-aging products have absolutely no evidence to back them up. Anyone who reads or downloads the article on NEJM's site will now also receive these two rebuttals along with a warning that the article has been used in "potentially misleading" ads without any additional charge.

Nevertheless, anti-aging clinics continue to proliferate because of false advertising that implies scientific support and lavish testimonials that are obviously fraudulent about reversing the aging process. Regulatory individuals apparently are powerless to do anything about it but a national TV program did try to discredit this. They followed a 57-year old woman who visited an anti-aging clinic in Las Vegas. After undergoing $1,500 worth of tests, she was offered a 40-pills-a-day and hormone supplement program that would cost her $1,500 a month. She was told that although she tested at age 54, her hormone levels were still deficient. However, taking the treatment program for a year would restore her to the optimal level of a 30-year-old.

Other hucksters offer worthless supplements for multiple sclerosis, Parkinson's, Alzheimer's and other neurodegenerative diseases that desperate patients are attracted to because "it can't hurt and might help." Some cite studies showing how stress can contribute to these disorders to imply scientific support.

Control Of Medical Press & Institutions?

In addition to Congress, regulatory agencies and the media, pharmaceutical companies have very powerful influences on medical journals and institutions. A leading kidney journal rejected a guest editorial questioning the efficacy of epoetin in end stage renal disease for fear of losing lucrative advertising. The editorial was requested because Medicare alone had spent over $7.6 billion on epoetin between 1991 and 2002 with no evidence of any benefits. It cited a 2002 review of all epoietin trials that found "any benefits of epoietin are

outweighed by the risk of increased hypertension and mortality." European guidelines had also reached the same conclusion.

In a letter to the author of the proposed editorial, the executive editor of the journal stated "I have now heard back from a third reviewer of your EPO editorial, who also recommended that it be published. **Unfortunately, I have been overruled by our marketing department with regard to publishing your editorial.** As you accurately surmised, the publication of your editorial would, in fact, not be accepted in some quarters. ... and apparently went beyond what our marketing department was willing to accommodate. Please know that I gave it my best shot, as I firmly believe that opposing points of view should be provided a forum, especially in a medical environment, and especially after those points of view survive the peer review process. I truly am sorry."

Last January 16, Juan Ramón Laporte, a respected Spanish pharmacologist was in court to defend himself in a lawsuit brought by MSD (Merck, Sharp, and Dohme) over an article published in the July-Sept 2002 issue of his drugs and therapeutics bulletin. In it, he had described "irregularities" surrounding clinical trials of Vioxx and Celebrex. He also criticized a study published in the *New England Journal of Medicine* two years previously that minimized the unexpectedly high incidence of heart attacks in patients receiving Vioxx compared to naproxen. Since a *Lancet* commentary showed that MSD already knew about this before the study began, selection bias may have actually minimized Vioxx's cardiovascular dangers.

The FDA had also warned MSD against promoting Vioxx using material in which adverse cardiovascular events were not clearly indicated. MSD sued Laporte and the publisher of his bulletin for "extremely serious false accusations" which damaged the company's name. They demanded a retraction be published both in the bulletin and on its web site stating that the increased heart attacks in patients on Vioxx compared to naproxen was due to the latter's cardioprotective effects. The judge ruled in favor of both defendants, noting that two prior editorials in the *Lancet* and *British Medical Journal* had also "commented on irregularities" in the same study of a similar nature that were never challenged.

There is strong pressure on Harvard Medical School to rescind its strict regulations designed to minimize conflict of interest problems between faculty members and pharmaceutical companies whose drugs they are evaluating. These specify that researchers cannot own more than $20,000 of stock in companies that finance studies in their laboratories. They also cannot receive more than $10,000 in consulting fees from those companies and cannot spend more than 20 percent of their time on such research. Harvard was on the brink of relaxing its policy four years ago until the sudden death of an 18-year-old subject in a University of Pennsylvania gene therapy experiment. Harvard's dean put things on hold after it was revealed that one of the researchers involved had financial ties to a company that would profit from the research.

Merck, Pfizer, and Novartis recently moved large portions of their research operations to a few miles from the medical school, hoping that this will lead to profitable new drugs. Harvard has been praised for its policies and although some think they should be tightened further, its president is known to favor relaxing them, as do many of the faculty. The dean finally appointed two committees; one to set policy for doctors conducting clinical drug trials and another for basic science research not involving humans. Their reports were due last June but the results have still not been announced.

A Few People Are Fighting Back. Is There Some Light At The End Of The Tunnel?

There is little doubt about the clout drug companies can exert on academic medicine that could influence Harvard policy makers to think twice about making changes. A good example is David Healy, a prominent British psychiatrist who filed a $9.4-million lawsuit in September 2001 against the University of Toronto and an affiliated teaching hospital alleging his employment contract was revoked one week after he delivered a lecture linking Prozac to suicide. It states that on November 30, 2000, Healy, who had

accepted an offer of $250,000 / year to serve as Professor of Psychiatry at the University and Clinical Director of its Centre for Addiction and Mental Health, told a conference there that he believed Prozac could cause some patients to commit suicide. One-third of all drug-related suicidal attempts in the entire FDA database since 1990 showed a possible association with Prozac alone. Although he had written a book about this and had abundant additional evidence, Healy received a letter on Dec. 7 from Dr. David Goldbloom, Professor of Psychiatry at the University, withdrawing the offer, stating that "Essentially, we believe that it is not a good fit between you and the role as leader of an academic program. This view was solidified by your recent appearance at the Centre in the context of an academic lecture." The suit alleged that Dr. Charles Nemeroff, a psychiatrist and major shareholder in Eli Lilly, who was at the conference, spoke to Dr. Goldbloom about Dr. Healy's comments. Goldbloom also met with personnel from Eli Lilly, who had contributed at least $1.5 million to the hospital, presumably to promote Prozac. The suit was settled in April 2002 and although the details were not made public, the university stated that Dr. Healy would be appointed as a Visiting Professor.

The FDA was recently sued by a consumer watchdog group claiming failure to respond to a request over a year ago that the antidepressant Serzone be banned because of deaths due to liver failure. It was already banned in seven countries. On March 24, a nine-page letter sent to the FDA by the House Energy and Commerce Committee, and Oversight and Investigations Subcommittee, (which has oversight authority over the FDA) requested information about the use of antidepressants by children and the possibility of increased suicidal behavior, and details on how the FDA handled information received about this. Among other questions, they want to know (1) What did the FDA know about issues of safety and efficacy of anti-depressants in children after companies submitted their data from clinical trials and (2) When was the FDA provided a complete set of pediatric clinical data from these respective companies? They requested all documents pertaining to the planning and agenda of the FDA Feb 2 Advisory committee meeting, their own senior scientist's negative report (which they refused to accept) and all documents pertaining to each of the antidepressant manufacturers' pediatric trials, including e-mail correspondence. The documents must be submitted by April 5. Will anything come of this? Stay tuned!

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