HEALTH AND STRESS

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WHY ARE DRUGS INCREASINGLY MORE EXPENSIVE AND DEADLY?

KEYWORDS: Prilosec/Nexium & Claritin/Clarinex scams, Neurontin, drugs from Canada, Medicare drug discount cards, ADHD, SSRI's, Paxil litigation, Serzone

Everyone knows that prices for prescription drugs have been going through the roof but few are aware of the reasons for this. Pharmaceutical manufacturers claim that it costs close to $900 million and takes an average of 12 years to gain FDA approval for a new product but this seems doubtful. The fact is that **over 75% of newly approved drugs are not new at all and offer little advantage over those being replaced, usually because of patent expiration**. From1990 to 2002 the FDA approved 1,035 drugs but only 23% were deemed to be a "significant improvement" over existing medication.

Often a minute chemical modification of a popular drug is patented as a new pharmaceutical and is then widely hyped as a major medical breakthrough. Almost all of these will be extremely profitable because there are few research costs and the market niche is guaranteed. FDA approval is also certain since it is only necessary to demonstrate superiority over a placebo rather than a similar product.

A good example is Prilosec, Astra Zeneca's "purple pill" for indigestion and ulcer pain, which raked in over $4 billion in 2000. Because its patent was expiring, the company replaced it with Nexium, which received FDA approval as a new drug in February 2001 even though it was essentially the same chemical. Due to aggressive marketing, more than 4 million prescriptions for this "new purple pill" were filled by the end of the year. The company subsequently received permission to market an over the counter salmon colored Prilosec pill to compete with Tagamet, Zantac and Pepcid.

Schering-Plough used the same deception to replace Claritin, its top selling antihistamine. While originally heralded as a "breakthrough" over existing and much less expensive drugs because it didn't cause drowsiness, the usual 10 mg. dose was barely better than a placebo. In higher doses that were effective it had very similar sedative side effects. Sales of over $3.1billion in 2001 accounted for almost half the company's net profits but Claritin's

ALSO INCLUDED IN THIS ISSUE

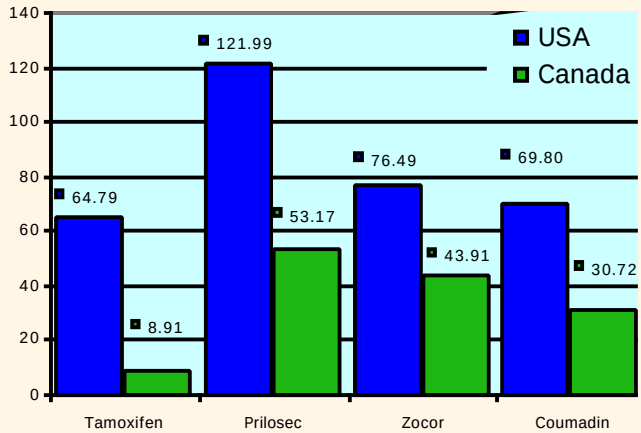
patent was expiring. It was crucial for the company to convince physicians to switch patients to Clarinex, a copy-cat version that offered no advantages and to then get Claritin approved for non prescription use. Both of these goals were achieved through aggressive advertising and lobbying that gave the company leadership in both markets but provided no savings or other benefits for patients.

Drug Prices And The Public Be Damned

The reason U.S. prescription drugs are so expensive is not due to the high cost of developing new products; it is because of the astronomical sums manufacturers spend on marketing and lobbying activities. One industry sponsored group alone will spend over $150 million this year to lobby Congress, the FDA and others to promote pharmaceutical interests such as fighting any attempts to impose price controls. Some companies will also shell out additional millions in campaign contributions or to lobbyists to protect or increase sales of specific products. There are over 600 registered drug company lobbyists, more than two for every member of Congress as well as others that are not registered.

All of the above is a drop in the bucket compared to the over $3 billion spent annually just on direct to consumer TV and print advertising. Pharmaceutical manufacturers also spend $11 billion annually to promote their products to physicians through conferences, direct mail and medical journal advertising and for an army of around 90,000 drug reps who make personal calls at a cost of $10,000 to $13,000/doctor/year. However, these are all excellent investments since they bring in an average 200% to 300% return.

Pharmaceutical manufacturing is far and away the most lucrative U.S. industry. Net profits are more than triple the average for all other businesses and drug companies also pay about 41% less in taxes. However, none of this benefits American patients who pay far more for prescription drugs than others anywhere else on earth. We are the only country without price controls on patented drugs. As a result, many on fixed incomes who require several costly medications are increasingly getting them from Canada or Mexico. Vermont seniors pay an average of 81% more than Canadians a few miles across the border for the 10 most commonly prescribed drugs and some 7,000 are hospitalized each year because they can't afford the daily medicines they require. Synthroid and Premarin cost three times as much, Zyrtec and Allegra are double and some other comparison prices are illustrated below.



Average U.S. & Canadian Costs for Common Prescriptions

Drug companies are trying to prevent Canadian drug sales to the U.S. and some have threatened to boycott participating wholesalers. The FDA has also tried to halt the practice since it is technically illegal but these attempts have failed due to public outrage. Several states and cities have saved millions by buying drugs from Canada but repeated legislative attempts that would authorize this with safeguards has been stonewalled. As Congressman Dan Burton noted in a recent *60 Minutes* interview, "*This is a perfect example, in my opinion, of where a special interest, **the pharmaceutical industry, has been able to manipulate the Congress and the government of the United States to their benefit, and to the detriment of the American taxpayer and the American people***."

The Perils Of Being A Patient

Senior citizens who are likely to require multiple medications are really getting shafted since pharmaceutical companies can charge whatever they choose for patent protected products. Since 2000, these drug prices have risen 28%. The

average price increase for the top 30 used by Medicare recipients last year was 6.5% compared to a 1.9% rise in overall inflation. Wisconsin and at least 13 other states have sued some 20 drug companies for posting inflated wholesale prices that are used as a basis for drug reimbursements. The Wisconsin suit claims manufacturers "embarked on an unlawful scheme" as early as 1992 to distort the drug pricing system. It seeks to force them to stop the practice and set up a restitution program with forfeitures of up to $10,000 per violation if they were against senior citizens.

The recent Medicare Art with its drug discount cards are not likely to provide any significant relief and illustrates the tremendous political clout of drug companies. Under these new regulations, Medicare is specifically prohibited from negotiating drug prices with manufacturers. As Congressman Burton also commented, "*That is unconscionable. The government of the United States negotiates prices in the Defense Department, in every area of government. And here we are, going to spend billions and billions and billions and probably trillions of dollars on pharmaceutical products. And we cannot negotiate the prices with the pharmaceutical industry. That s just not right.*" It also means Medicare will pay more for the same drugs than the VA, HMO's and insurers that can bargain.

The Medicare drug cards hardly guarantee any price savings since their "discounts" can be changed at any time to maximize profits and drugs can be dropped. Of the 73 companies approved to participate in the program, 20 have been convicted of fraud for drug charge abuses. One paid the government an $87.3 million fine for overcharging federal employees. These 20 are less than a third of the total number but they represent over 60% ($3.1 million) of the contributions made to Bush and his cohorts by drug card companies since he took office. Draw your own conclusions.

In addition to being increasingly more expensive, drugs have become deadlier. Well over 100,000 deaths in U.S. hospitals/year are due to pharmaceuticals prescribed by physicians according to the manufacturer's directions. Many more result from unapproved uses. Put into perspective, total fatalities from prescription drugs would exceed those from a 9/11 disaster every week for over a year and a half. But that's just the tip of the iceberg.

No information is available on the number of non hospital deaths due to the same and other drugs prescribed by doctors. Even the FDA acknowledges that adverse drug reports they receive probably represent only 5% of the total number. **However, the hospital figures alone make prescription drug deaths the third leading cause of death and some place them at the top of the list.** In addition, adverse drug reactions occur in 18% of outpatients and account for 17% of all hospital admissions.

More than half of all drugs have serious side effects that are not detected before approval. Since the FDA speeded up its approval process due to pressure from drug companies, at least 16 new drugs had to be banned, with almost half in less than two years. This is often because they have not been tested long enough or in the populations most likely to use them. In other instances, trials showing that they are unsafe or ineffective are not published. Recent surveys showed that only one of 37 clinical trials of nonsteroidal anti-inflammatory drugs reported to the FDA had been published and a mere 23 of some 200 studies of the cardiovascular risks of hormone-replacement therapy.

New York State is suing Glaxo for not revealing four studies showing that Paxil was not effective for treating depression in kids and teens and also increased risk for suicide. Glaxo conducted five Paxil studies in this age group but published only one that had mixed results. Income from Paxil sales to children was over $55 million in 2002. New York City is also suing for the millions of dollars its Medicaid program spent because Glaxo unfairly kept generic versions of the drug off the market by obtaining more than a dozen "frivolous" patents on Paxil over the past decade.

Pfizer Agrees To Pay $430 Million In Fines

As noted in a prior Newsletter, one of the most flagrant examples of drug company abuse was the marketing of Neurontin by Warner-Lambert. Neurontin had been

approved only as a supplemental drug for epileptics who continued to experience frequent seizures on their regular medications. It obviously had very limited indications so what accounted for its blockbuster status of over $2.7 billion in revenue last year? The explanation is that once the FDA approves a drug, physicians are free to prescribe it for any complaint or condition they choose. However, it is illegal for the manufacturer to advertise or promote it for any unapproved use.

Warner-Lambert got around this by paying physicians huge sums to recommend it for the treatment of pain due to everything from migraine and ulcers to backache as well as bipolar disorder, restless leg syndrome and other disorders. Physicians were paid to write reports on how it had benefited a few of their patients and to speak about their results to others at company sponsored meetings. In many instances, much larger than approved doses were advised. The company also monitored doctors' prescriptions to see if the numbers increased after they had attended such meetings. One Connecticut physician wrote 58 prescriptions for unapproved uses of the drug after he attended a meeting where other doctors spoke about Neurontin's numerous benefits. He had never written a Neurontin prescription prior to the meeting and was later paid over $1000 for speaking to other doctors about the drug's alleged ability to relieve pain

These and other illegal actions came to light in a 1996 lawsuit filed by whistle-blower David Franklin, who worked for Warner-Lambert before it was acquired by Pfizer in 2000. Franklin accused Warner-Lambert of hiring an outside firm to write at least 20 articles for medical journals that extolled unauthorized uses of Neurontin and then paid doctors for use of their names as authors of the reports. Company sales and medical personnel also presented a distorted picture of the drug's effectiveness when talking to doctors.

A senior company official told sales reps, "We need to be holding their hand and whispering in their ear, Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything!" Franklin claimed that the company's sponsored clinical trials had shown no benefit for Neurontin over placebo for treating migraine and bipolar disorder, but this information was concealed. Various inducements were used to get doctors to prescribe Neurontin off-label, including tickets to the Olympics, trips to Disney World and retreats to golf resorts with their families. Court papers revealed that Medicare and Medicaid paid hundreds of millions of dollars for unapproved uses of Neurontin that accounted for over 90 percent of its sales.

Pfizer recently agreed to plead guilty to criminal wrongdoing and will pay about $430 million in fines in a settlement that includes a $240 million criminal fine, $152 million in civil fines to be divided between state and federal Medicaid agencies, and $38 million to state consumer-protection divisions that investigate wrongdoing by drug companies. David Franklin, the whistleblower who made the first allegations of illegal marketing, will receive about $24.6 million. Pfizer also agreed to sign a "corporate integrity" covenant that permits monitoring of its marketing practices.

However, this settlement only applies to Neurontin sales from 1994 through mid-2000 when it was acquired by Pfizer to cover the estimated $421.6 million that Medicaid spent on unapproved use during this period. Medicare and other fiscal intermediaries could file similar suits to recover for payments they made. Franklin's bonanza could also encourage other whistleblowers to come forth.

Not surprisingly, the settlement will have very little significant financial impact on Pfizer. The world's largest drugmaker with over $45 billion in sales last year had already set aside funds needed for the settlement. In addition, Pfizer has applied for FDA approval of a successor to Neurontin called Lyrica (pregabalin). Lyrica is expected to be approved in Europe this year for the treatment of epilepsy, neuropathic pain and general anxiety disorder.

Whistleblowers And Suppression Of Data

In July 2002 Allen Jones was appointed lead investigator at the Pennsylvania Office of the Inspector General (OIG) after uncovering evidence of funding

by Pfizer and Janssen Pharmaceuticals into an off-the-books account earmarked for "educational grants." He found that payments from the account had actually been made to state officials responsible for developing formulary guidelines for state mental facilities recommending expensive new drugs over cheaper and safer ones proven to be effective. After he began to discover additional abuses, Jones was suddenly dropped from the case. He was told by a superior that "drug companies write checks to politicians on both sides". Some of Jones' findings were reported in the media, including the *New York Times* and *British Medical Journal*.

One highly recommended and costly drug was Janssen's Risperdal, a medication used for schizophrenia that hag potentially lethal side effects. On April 27, 2003, the FDA sent a warning letter to Janssen stating that information about the drug was "false, or misleading" because it failed to disclose or minimized risks relating to "serious adverse events including ketoacidosis, hyperosmolar coma, and death." The next day, Allen Jones was physically escorted out of his office and warned "not to appear on OIG property" because he had talked to the press. On May 8, Jones sued, accusing his employer of tying to bury important evidence of wrongdoing and his findings. His attorney called the case a critical test of the right to a free press, noting, "If they shut the employee up and they have all the documents locked up in a drawer there is no free press."

The OIG refused to comment on the corruption allegations or why Jones had been dismissed. When asked whether the state could withhold information of public interest, a spokesperson said, "The OIG is specifically exempt from right-to-know laws." Jones' allegations of improper influence are now before Pennsylvania's Ethics Commission. Federal authorities are also investigating and have ordered Janssen to submit all Risperdal related documents and correspondence.

Dr. Nancy Olivieri, Professor of Pediatrics and Medicine at the University of Toronto, was hired by Canada's largest drug company Apotex to test a new drug to treat Mediterranean anemia at the university's Hospital for Sick Children. She found that not only did it not work as well as the company expected but also had very serious side effects that warranted prompt publication. Apotex halted the trial and threatened to sue her in 1996 for violating her confidentiality agreement she attempted to report her results or discuss them with anyone. The hospital also fired her. It turned out that Apotex was going to donate $12.7 million to the University and its president had been lobbying the Canadian government on the firm's behalf. It took five years for Olivieri to be exonerated and reinstated.

Dr. Betty Dong, a pharmacologist at University of California San Francisco, was hired in 1987 to conduct a clinical trial comparing Synthroid, Flint's synthetic thyroid, to that of three competing formulations. At the time, Synthroid was the top seller and the most expensive drug in this $600 million/year market. Everyone expected the results would show that Synthroid was superior but by 1990 it was clear that all four drugs showed essentially the same results. Dong submitted a paper with her findings to JAMA in 1993 but withdrew it three months later because Flint threatened to sue her for breach of contract.

A recent Yale report found that 80% of drug company sponsored clinical trials reported positive findings, compared to 50% for those conducted by independent academics. Oxford University researchers, who reviewed the original paperwork from over 100 studies, reported that almost two-thirds of the published results omitted concerns over significant adverse effects. In some cases, the stated purpose of the trial was changed so that favorable findings could be published. In another survey, 20% of 2200 researchers said they had delayed publication for more than six months to allow for patent application or conceal results that might slow sales of their sponsor's product. Over two thirds admitted having significant financial ties to drug companies.

Medicine Is Now All About $$ And Profits

The Betty Dong fiasco is a good example of the power of drug companies to

control and manipulate the media, including respected medical journals and academic institutions. As Dr. Drummond Rennie, deputy editor of *The Journal of the American Medical Association* put it: "*This is all about bypassing science. Medicine is becoming a sort of Cloud Cuckoo Land, where doctors don't know what papers they can trust in the journals, and the public doesn't know what to believe.....**The drug companies are run by hard-nosed marketers, not by the physicians and the scientists. These are not benign people who are interested in helping people with their new wonder drugs. They use what works, and money works***."

Dong's paper had received favorable reviews from five outside consultants, was scheduled for publication, and the page proofs were already at the printer. The company, however, had hired their own consultants, many of whom had previously been paid for giving lectures or serving on their Thyroid Research Advisory Council. The only information these consultants received was supplied by the company and Dong had no input. The consultants' conclusion that her study was seriously flawed was forwarded to editors of *JAMA* and other journals warning that it not be published, especially since Dong's contract forbade this without obtaining written company consent.

Her university also withdrew all support for similar reasons. They had earlier planned to back her but as the threat of an expensive lawsuit loomed, the dean of the Pharmacy School explained that while the university did consider academic freedom to be a critical value, "the difficulty here is weighing the right to publish against a likely claim against the university for breach of contract and the possibility of significant damages." A university attorney warned Dr. Dong and her co-authors that they would have to defend themselves in court without any support from the university. The legal costs would have been prohibitive, and after consulting with her co-authors, Dr. Dong telephoned the editors of JAMA and instructed them to pull the article.

In March 1995, Flint was taken over by BASF a German chemical and pharmaceutical company that started marketing Synthroid through its subsidiary Knoll Pharmaceutical. Dr. Gilbert Mayor and some other Knoll associates then wrote a sixteen-page critique in which they appropriated Dr. Dong's data and reanalyzed it to argue that the other synthetic thyroid drugs were not equivalent to Synthroid, exactly the opposite of what she and her colleagues had concluded. This was published in the *American Journal of Therapeutics*, where Mayor was an associate editor.

Prominent researchers disagreed with this and following a carefully researched April 1996 article in *The Wall Street Journal*, Knoll began receiving mounting criticism and the FDA decided to investigate. Knoll's president and some board members met with University of California officials a few months later and (while Knoll continued to insist that Dong's study was flawed) it agreed that it would no longer attempt to stop its publication. In April 1997, after *JAMA* finally published the study, a class action lawsuit was filed against BASF and Knoll Pharmaceutical accusing them of suppressing a medical study in an effort to control the American market for thyroid drugs. It is estimated that **if less expensive thyroid drugs were used instead of Synthroid, had Dong published her results in 1990, patients could have saved $356 million/year**.

Knoll settled the suit in just four months by agreeing to set aside $98-$135 million to reimburse each patient a little less than $19.00. This, despite evidence of overpayment of $264 to $408 for each patient on Synthroid the full 6.5 years that Dong's results were suppressed. For the estimated 8 million patients, this overpayment totals $2.1 to $3.2 billion and Knoll's maximum $135 million represents less than a year of overpayment to patients on Synthroid. However, law firms involved in this class action ripoff will earn their typical millions of dollars in fees before any patients are paid, which may explain the unusually rapid settlement. **It would seem that nobody is really concerned about protecting the public's interests. It's all about money and greed.**

Are Kids Becoming More Demented?

It would certainly seem that way from the apparent surge in attention deficit, hyperactivity disorders, autism, depression, and a host of other emotional and behavioral disturbances in children. This disturbing trend was confirmed by a recent report showing an almost **50% rise over the past three years in the use of attention deficit/hyperactivity disorder drugs in kids under five years of age**. Spending on behavioral disorder drugs for children and teens for the first time is greater than for antibiotics and asthma medications. Sales of antidepressants increased 21% and drugs for autism and other conduct disorders jumped 71% compared to only a 4.3% rise in antibiotics.

This is probably due to the popularity of newer longer acting drugs over Ritalin and others that are usually administered two or three times daily. Taking a single morning dose avoids the embarrassment of having to line up in the afternoon for a pill from busy school nurses or day-care officials. Some authorities are concerned that parents and school officials have been too eager to medicate disruptive children because of pervasive direct to consumer advertising of these drugs. Others point to the powerful influence pharmaceutical companies have over the FDA, National Institutes of Mental Health and other regulatory bodies as well as industry-funded "advocacy" groups such as the National Alliance for the Mentally Ill. The failure of these advisory groups to discourage inappropriate prescribing of psychoactive drugs (especially to preschool children) has provided a tacit seal of approval. Critics claim this has put many healthy toddlers at increased risk for growth retardation, mania, aggressiveness, explosive violence, as well as drug dependency.

The director of the American Academy of Pediatrics' drugs committee admitted that there may be "initial overprescribing" for attention deficit disorders but the children are usually taken off the drugs if they don't work. There is much more concern about the meteoric rise in prescriptions for antidepressants in kids because of recent allegations about their safety.

One report on 300,000 patients under the age of 19 found that the use of antidepressants rose from 5,880 in 1998 to 9,013 in 2004. During this same period, it doubled in girls aged five and under and shot up an alarming 64% for preschool boys. Has depression really escalated this much in kids? A government survey showed that the diagnosis of depression in children and adolescents doubled from the early 1990s to 2001 but the number of prescriptions for SSRI antidepressants more than tripled. One explanation may be their increasing use for the treatment of "social anxiety", obsessive-compulsive disorder, dyslexia and other behavioral problems.

What is particularly disturbing are studies showing that SSRI's are no more effective than placebos for children and that they may be harmful. Prozac is the only SSRI approved in the U.S. for use in children, but doctors are allowed to prescribe others like Paxil, Zoloft, Effexor and Celexa despite evidence that the risks for these far outweigh any benefits. Last year, British regulators banned the use of SSRI's other than Prozac for anyone 18 years old or younger. The U.K. recommendations followed an expert panel's examination of information from internal drug company memos and clinical trial results that had been suppressed.

The first SSRI to be banned was Paxil and while Glaxo sent a letter to all British physicians warning that Paxil should not be given to children, this was never revealed to U.S. doctors. Two Congressional committees sent a strongly worded letter to the FDA in March asking why the agency did not take more stringent action and why they prevented its own expert, Dr. Andrew Mosholder, from presenting a review at a February public hearing that found SSRI's significantly increased suicidal risk in children. His report was replaced at the last minute by a more favorable conclusion by an FDA official who had approved many of these drugs. The FDA was ordered to release all records involving this change as well as all pediatric clinical trials, all analyses of side effect data and all correspondence with any antidepressant drug manufacturer.

Updating NIH & FDA Conflicts Of Interest And Actions Against Antidepressants

Last December, it was revealed that 94% of the more than 5,000 scientists at NIH were engaged in lucrative conflict of interest activities and not filing public income-disclosure reports and that top officials had received over $2.5 million in fees and stock options from drug companies over the past decade. Congress demanded a full investigation and Director Elias Zerhouni appointed a "blue ribbon" panel to recommend new conflict of interest policies that would mandate public disclosure of all outside compensation and ban all top officials from doing any outside work. But the panel's initial report in May would allow most scientists to continue current practices if they limited these to less than 500 hours a year and only suggested increased "internal disclosure" that would be exempt from the Freedom of Information Act and keep payments blocked from public view. At $500/hr. this could amount to roughly $250,000, not exactly pocket change, and more than double most salaries. Some Congressmen who feel this is a whitewash and that they are being stonewalled have demanded to see all documents that led to the panel's preliminary conclusions.

New York's June 2 lawsuit charged that Glaxo had "engaged in repeated and persistent fraud by misrepresenting, concealing and otherwise failing to disclose" important information about the safety and efficacy of Paxil. A few days later, British regulatory authorities (MHRA) announced they were conducting a criminal investigation "to make sure the company had complied with its legal obligations under UK and European law." The Times of London reported: "Depending on its findings, the MHRA could choose to prosecute either Glaxo as a company or go after named individuals. If found guilty, the penalties could include fines or imprisonment." Other SSRI manufacturers are also likely to come under scrutiny. One analysis of the statistics that was sent to Congress in April stated, "**Since 1988, 68 million Americans have used Paxil, Prozac and Zoloft. Using a most conservative excess suicide rate, at least 21 thousand avoidable suicides may have been induced**, without any warnings to the victims or their families." Many feel that antidepressants should also be banned for children in the U.S. but the FDA has only "urged" drugmakers to put new warning labels alerting doctors and consumers to watch for suicidal tendencies, hostility and agitation in patients taking SSRI antidepressants. This is not mandatory.

Over a year ago, the FDA was also petitioned to withdraw Serzone, another antidepressant, because of numerous cases of death and liver failure. Although the drug had already been banned in Europe, Canada and other countries, there was no response from the FDA. In March, the FDA was sued for its refusal to ban Serzone. In May, Bristol-Myers Squibb announced that it would stop sending Serzone to wholesalers after June 14 due to declining sales and continued to deny that it was dangerous. However, the drug will still be available in the U.S. as generic nefazodone despite several lawsuits that are now pending against manufacturers and the FDA. Stay tuned for more!

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Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief
www.stress.org
e-mail: stress124@optonline.net