

# WORCESTER medicine

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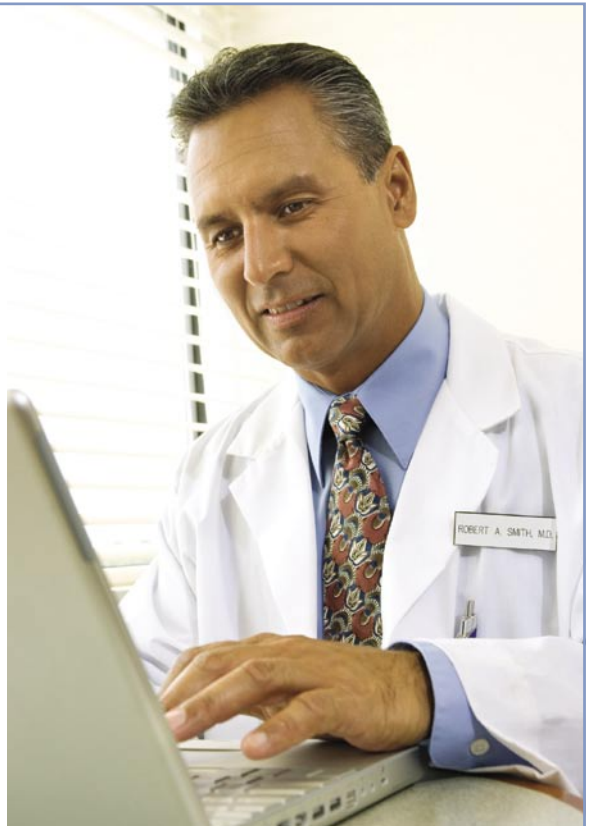
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**Jane Lochrie, MD**

This is my first editorial as Editor of *Worcester Medicine*. It is an honor to edit one of the oldest District Medical Society's publications. The first publication of Worcester Medicine (formerly Worcester Medical News) was in 1937 and it has been continuously published since that time. I welcome your suggestions and would like to see some responses in the form of Letters to the Editor.

This issue of *Worcester Medicine* owes a lot to Massachusetts College of Pharmacy and Allied Health Science (MCPHS). The College opened its doors in downtown Worcester in 2000 and is now composed of five main buildings that consist of 19 Foster Street, MCPHS Online, the Maher Building, The Borysek Living and Learning Center and 10 Lincoln Square. The Worcester Campus of MCPHS houses several Schools and Programs which include accelerated programs in Nursing and Doctor of Pharmacy, the Masters of Physician Assistant Studies Program for post-baccalaureate students, the Doctor of Physical Therapy Program, and the Doctor of Optometry Program. Approximately 1000 students matriculate in all the programs that are currently offered on the Worcester campus.

Ryan Attwood PharmD, BCPS and Jordan Rush, a third year pharmacy student, focused their article on medications that were used in the past for therapeutic indications and are now being used for antidotes. The authors caution that these drugs are being used for non-FDA indications and the available data must be evaluated for the drugs' efficacy and safety.

The mysteries of the pharmaceutical companies and the FDA are unlocked in Dr. Esposito's article that features the withdrawal of Xigris from the market. His description of Eli Lilly's push to have the drug approved to the marketing strategy that stated "It is unethical not to use Xigris" is riveting. He reminds us that "...any new drug should be considered a black box."

The Point/Counterpoint feature on the legalization of medical marijuana is certainly timely as it will appear as a ballot question in November. As always, Dr. Morse wrote eloquently, passionately and from the heart. "The medical profession needs to be educated based on clinical studies, not just personal testimony." Evan Horton, PharmD, makes a powerful argument for the continued research in this area.

Finally, Dr. Birbara's Oration is a presentation of his scholarly research over the past twenty-two years that has resulted in over fifty publications. This has benefited many patients in the Worcester community.

Jane Lochrie, MD  
Editor

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321 Main Street, Worcester, MA 01608  
e-mail: [wdms@massmed.org](mailto:wdms@massmed.org)  
web: [www.wdms.org](http://www.wdms.org)  
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## Worcester Medicine Survey

The WDMS Publications Committee and the Editorial Board would like to thank our members for taking the time to respond to a survey regarding Worcester Medicine. Survey results were very positive. The respondents found the magazine topical and relevant. Over 80% of the respondents gave high marks to the articles for readability, content, and quality. The outcome of the survey was shared with the Editorial Board to help in their deliberations about the future content of the magazine.

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# “Medical Marijuana” The Cart Before the Horse

Leonard J. Morse, MD

In November 2012, Massachusetts voters will be asked to check yes or no on the legalization of marijuana for medical use. Appreciating that most physicians are uninformed about the pharmacology of marijuana, I submitted a Resolution (206) for discussion and action by the Massachusetts Medical Society asking that: “medical marijuana be restricted to medical use only and prescribed by a Drug Enforcement Agency-registered physician,” and that the MMS conduct educational programs “on the pharmacology of marijuana and its many forms as a priority public health effort for all physicians in 2011.”(1) Now, the physicians of Massachusetts may become responsible for prescribing a “legalized,” gateway, addictive drug that is, perhaps, more popular than tobacco among adolescent youth and young adults.

Almost every day, three people (average age of 40) die in Massachusetts from drug overdose. In my opinion, unbridled drug use is the preventable plague of the 21st century. While the population of the United States represents less than five percent of the world’s population, we consume over 60% of its illicit drugs!

Marijuana (cannabis) is a Schedule I Controlled Substance along with heroin, lysergic acid diethylamide (LSD), peyote, methaqualone and methylenedioxymethamphetamine (“ecstasy”). “The drugs in this Schedule are those that have no accepted medical use in the United States and have high abuse potential” and therefore, may not be prescribed. (2) Hence, there is a serious disconnect between Federal law and the accepted mandate of legalizing “medical” marijuana.

I attended a Legislative Hearing on House Bill 625 to legalize

marijuana for medical purposes on June 28, 2011 and listened to three hours of personal testimony in support of the legislation. The passion was overwhelming. Marijuana warrants medical study to verify its claims.

The medical profession and pharmaceutical industry must align to study various preparations of medical cannabis for administration so that an effective product line can be developed similar to other controlled, yet most effective, addictive drugs. Licensed physicians receive a “Controlled Substance Registration Certificate” from the United States Department of Justice, Drug Enforcement Administration permitting them to prescribe controlled drugs.

Marijuana should become a Schedule II substance, joining the ranks of other narcotic, stimulant and depressant drugs. Like marijuana, “The drugs in this schedule have a high abuse potential with severe psychic or physical dependence liability and include opium, morphine, codeine Dilaudid, methadone, pantapone, Demerol, cocaine, oxycodone, as well as, non-narcotic drugs such as amphetamine, metamphetamine, Preludin, Ritalin, amobarbital, secobarbital and Doriden.”(2)

The medical profession needs to be educated based on clinical studies, not just personal testimony, and to learn the routes of responsible prescribing. It is inappropriate to prescribe a plant product with varying concentrations of active pharmaceutical compounds so casually dosed as by smoking (3). This is long overdue. In California, certain counties claim over 60% of their income is from growing pristine marijuana. Such widespread use of an addictive drug is irresponsible and leads to predict-

able yet preventable tragedy. If it is predictable, it is indeed preventable! The United Nations estimates that 190 million people consumed cannabis in 2007, and a new industry has arisen around the cultivating and dispensing of “medical marijuana.”(4)

Since 1970, 16 states and the District of Columbia have legalized the “medical use” of botanical cannabis. Based on public claims attesting to the wonder of marijuana, the divide between the Federal and state governments continues to broaden. The pharmaceutical industry and the medical profession should become involved in product development, clinical testing, and physician education before medical marijuana becomes legalized. And physician prescribing should be only by Drug Enforcement Administration licensed professionals as it is for all other controlled substances.

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Dr. Morse is past president of the Worcester District Medical Society and the Massachusetts Medical Society and the former Commissioner of the Worcester Division of Public Health



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# Medical Marijuana: Evidence of Efficacy

Evan R. Horton, Pharm.D.

Marijuana has been a controversial topic, both medically and politically, for decades. The history of cannabis dates back to nearly 3000 B.C., where archeological findings in Asia suggest it was used for medicinal purposes.<sup>1</sup> Although federal law identifies the cannabis plant as a Schedule I narcotic, 16 states and the District of Columbia have passed legislation making it legal for patients with legitimate prescriptions from a physician to possess small amounts of marijuana (purchased from dispensaries) or cultivate a certain number of plants.<sup>2</sup> An additional 17 states are considering similar bills or ballot initiatives for the upcoming Fall 2012 elections. Based on individual state laws, medical marijuana can be legally prescribed for a number of afflictions including, but limited to: anxiety, spasticity, symptoms of multiple sclerosis (MS), glaucoma, nausea associated with chemotherapy, and anorexia from human immunodeficiency virus (HIV).

The criminalization of marijuana during the 1920s eliminated the potential for medical research in the United States; however, trials conducted in Canada and Western Europe, where government have taken a softer stance on cannabis, have been able to provide some evidence supporting its use.<sup>3</sup> In addition to cannabis, d9-tetrahydrocannabinol (9-THC) extract and Sativex® (extract of 9-THC and cannabidiol approved in Canada and Europe), as well as synthetics nabilone and dronabinol, have been studied.

Dronabinol (Marinol®), a Schedule III, and nabilone (Cesamet®), a Schedule II, are FDA-approved for use in nausea and vomiting associated with cancer chemotherapy.<sup>4,5</sup> Dronabinol is also indicated for anorexia associated with weight loss in patients with HIV. Due to the controversy surrounding un-

approved pure cannabis and cannabis extract, this review will only focus on studies involving those compounds.

## Tourette Syndrome

In response to published case reports on 4 patients with positive self-reported scores following smoking cannabis and a retrospective review of 17 patients, Muller-Vahl and colleagues conducted a randomized (R), double-blind (DB), placebo-controlled (PC), single-dose, cross-over study of 7.5 to 10 mg 9-THC followed by a 6-week R, DB, PC trial using 10 mg following dose titration.<sup>6</sup> The single-dose trial (n=12) showed improvements in self-reported tics (p=0.015) and obsessive compulsive behaviors (p=0.041), while the 6-week study (n=24) showed significant improvement based on examiner rating scales at weeks 2, 3, and 4 (p<0.05), as well as on self-reported symptoms (p=0.037). Neither study reported serious adverse drug reactions.

## Chronic Non-Cancer Pain

Four studies, randomizing a total of 156 patients, examined smoked cannabis for treating neuropathic pain, including two in patients with HIV. All four trials were PC, with three employing a cross-over design and one parallel-group. All showed significant reductions in pain as reported via visual analog scales (VAS) when compared to placebo. In both HIV populations, the approximate NNT for a greater than 30% reduction in pain was 3.5.<sup>7</sup> It should be noted that the potency of marijuana varied greatly among each study (range: 2.5 - 9.4% 9-THC).

Sativex® has been studied in several chronic pain syndromes.



One hundred twenty-five patients with neuropathic pain and allodynia took part in a cross-over trial with self-escalating doses of the oromucosal spray. VAS were significantly decreased with a NNT of 8.5. Eighteen percent of patients in the Sativex® group, compared to two percent of placebo, withdrew due to side effects.<sup>7</sup> A similar study of 48 patients showed similar reductions in pain scores and fewer side effects. Sativex® has also been shown to be effective in the treatment of central pain due to multiple sclerosis and rheumatoid arthritis.

### Spasticity from Multiple Sclerosis

Zajic et al. performed both a 15-week multicenter (33 sites), DB, PC, R trial utilizing both natural and synthetic cannabis extract, followed by a 12-month follow up.<sup>8</sup> Six hundred and sixty-seven patients were evaluated and, although objective measures in neither trial showed statistical significance, patient reported ratings of pain and MS symptoms did show improvement. Zajic conducted a similar 12-week follow-up involving 22 centers and 279 patients. Patients in the cannabis extract group showed significant decreases in spasticity rating scales compared to placebo counterparts ( $p=0.004$ ). Additional trials of cannabis extract have not showed significant decreases in pain or spasticity versus placebo.

Trials of Sativex in the treatment of MS spasticity and pain have shown similar results to cannabis extract alone. Although patients often self-report symptom improvement, objective measures of spasticity do not significantly improve.<sup>8</sup>

### Glaucoma

One DB, PC, single-dose, cross-over study evaluated the use of inhaled marijuana on intraocular pressure (IOP) in 18 patients with glaucoma.<sup>7</sup> Within 60 to 90 minutes, a majority of patients experienced both hypotension followed by a decrease in IOP. The frequency of tachycardia, palpitations, and other adverse effects were a concern to the authors regarding the use of cannabis in this population of patients.

### Challenges

Several challenges exist in how to accurately interpret available data surrounding inhaled cannabis trials. There are over 70 psychoactive compounds found in any given strain of cannabis.<sup>9</sup> Two strains of medical marijuana, Sativa and Indica, have been primarily used and the differences in their potency may result in variable positive and negative effects. Medical marijuana laws allow for either the purchase of cannabis from dispensaries or the legal cultivation within the home. Both of these options allow for the possibility of genetic alterations through

advances in botany, which further complicate the potency of available medical marijuana. Second, the actual amount of cannabinoids that reach the blood stream via alveoli varies based on the individual user's inhalation/exhalation technique.<sup>7</sup> These differences blur the lines of what constitutes an effective dose and may contribute the third challenge, risk of addiction. Finally, physicians must assess the risk of exposure to contaminants such as *Aspergillus* and heavy metals due to how and where medical marijuana is cultivated.

Oral formulations utilizing 9-THC and cannabidiol extracts may decrease some of these challenges, but proponents of inhaled medical marijuana claim that the high number of psychoactive compounds and the reaction caused by burning the dried leaves may add to the efficacy. The argument is that extracts only contain one piece of the cannabis puzzle and may limit the effect that some patients receive from the treatment. Regardless of the political implications, the fact remains that as long as marijuana is classified as a Schedule I narcotic, the scientific information we receive will continue to come from other countries and our knowledge of the true risks and benefits of cannabis will not be fully realized.

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*Evan R. Horton, Pharm.D., is Assistant Professor of Pharmacy Practice, Massachusetts College of Pharmacy & Health Sciences – Worcester/Manchester.*

# 216<sup>th</sup> Annual Oration of the Worcester District Medical Society

## 50 Years of Medicine: Less Art, More Science

Charles Birbara, MD

This year, 2012, marks my 50th year as a physician. During this time, changes in the delivery of medical care have been monumental; take, for instance, the introduction of Medicare, managed care, and the electronic medical record. Equally impressive have been advances in the treatment of many chronic diseases which all too often resulted in significant long term morbidity and even increased mortality. Over the past 35 years, I have been fortunate to be involved in many clinical trials of novel agents to treat chronic systemic inflammatory diseases and will recount some of them here.

The destructive processes of all systemic inflammatory disease states are regulated by cytokines, which are small glycoproteins whose primary function is to allow communication between cells of the immune system. These are the extracellular communicators which allow macrophages, lymphocytes and dendritic cells to relate to each other. Cytokines function by binding to specific receptors of the membranes of target cells which then initiate events within these cells, ultimately leading to the production of new messenger RNA and protein.



Charles Birbara, MD

Tumor necrosis factor- $\alpha$  (TNF) has for years been recognized as a key cytokine in the initiation and progression of the inflammatory process in diseases such as rheumatoid arthritis (RA), psoriasis and Crohn's disease. Inhibiting its function by binding monoclonal antibodies to its molecular structure stops or curtails the inflammatory process at a very basic level, allowing for symptom resolution and even, in some cases, complete remission.

In the case of RA, the propagating pathology can be very heterogeneous, so that the role of TNF in its pathogenesis may be variable. In such patients, inhibiting the contribution of cellular elements may be more efficacious than down regulating TNF. There are two available FDA approved medications which target lymphocytes and which are capable of inducing clinical improvement and even remission in RA. These are Orencia (abatacept) and Rituxan (rituximab), neither of which has yet demonstrated sufficient efficacy in diseases other than RA to gain FDA approval.

Currently, considerable research dollars are being invested to develop small molecules which, unlike monoclonal antibodies,

can be taken orally. These drugs block intracellular signaling molecules called “kinases” so that the ability of these immune cells to secrete pro-inflammatory cytokines is blunted. Unlike monoclonal antibodies which are molecule specific, inhibiting these kinases results in the measured diminution of multiple mediators which contribute to the inflammatory response. The most advanced of these drugs is” tofacitinib” (Pfizer) which is likely to garner FDA approval for RA later in 2012.

Over the past 10-15 years, considerable progress has been made in the treatment of the osteoporosis that is so prevalent in our aging population. While bisphosphonates such as alendronate, risidronate and ibandronate have had a major impact on reducing the incidence of fractures in people with increased bone fragility, there are well-recognized limitations to the use of bisphosphonates over extended time periods. For this reason, alternatives to currently available medications could have broad clinical appeal. More recently, denosumab (Prolia), which is given subcutaneously every 6 months and which inhibits the formation and function of osteoclasts, has become available. Because this molecule does not embed itself in bone, it may well have some advantages with respect to resulting in fewer instances of osteonecrosis of the jaw and atypical femoral fractures which are being increasingly noted with prolonged bisphosphonate use. On the horizon and well into Phase 3 clinical trials is a Merck compound which inhibits cathepsin K, an enzyme primarily found in osteoclasts and which functions to break down bone matrix. Multiple studies have demonstrated that inhibition of cathepsin K results in preventing loss of bone strength and decreasing fracture incidence in post menopausal women. This medication appears to have an acceptable safety profile, making it likely that it will be commercially available within the next 2 years.

Psoriasis is a systemic inflammatory disease with an incidence of about 2% of the population. Though striking treatment advances have been made in the past 10 years with the use of TNF inhibitors and monoclonal antibodies directed to IL-12/23 (ustekinumab, Stelara), there is still a significant unmet need in that many patients either fail to respond or lose efficacy to these currently available medications. In a recent issue of the New England Journal of Medicine (March 29, 2012), clinical trials with monoclonal antibodies inhibiting the function of IL-17 have shown remark-

able efficacy in resolution of psoriatic plaque lesions. Because very few adverse effects were noted in these short Phase 2 trials, further clinical trials are being initiated at this time. If the currently perceived efficacy and safety profile is maintained in these longer trials, I would expect that these agents will be another significant treatment option for patients who fail to respond to currently available agents. Clinical Pharmacology Study Group, my clinical trial group, is delighted to have been chosen to participate in the development program of both of these inhibitors of IL-17.

Considerable advances have also been made in the management of tophaceous gout with the recent FDA approval of Krystexxa, a recombinant uricase, which has demonstrated a dramatic ability to rapidly decrease serum uric acid and debulk tophi in a matter of weeks.

*Charles Birbara, MD, has practiced rheumatology in Worcester since 1970. He is associate professor of medicine at the University of Massachusetts Medical School and medical director of the Clinical Pharmacology Study Group.*





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# Why FDA Approved Drugs Are Withdrawn from the Market ~ The Cautionary Story of Xigris

Anthony L. Esposito, MD



**Anthony L. Esposito, MD**

Physicians practicing at the turn of the 20th century would be dazzled by the variety of therapeutic agents currently available, and they would be awed by the range of human maladies now prevented, controlled or cured by contemporary pharmacologics. And if they were to seek the source of this river of medicinal marvels, their journeys would certainly take them to the gateways of the nation's pharmaceutical industry.

Drug development is a complex, tedious, and expensive process, and pharmaceutical companies must expend an enormous effort to bring a new agent (or new chemical entity) to market. Years may lapse between the time a compound is created and the time it enters clinical trials; indeed, many drugs fail prior to being tested in humans. New chemical entities are also abandoned after early clinical trials. The most common reasons for terminating drug development in Phase I trials are toxicity (43%), lack of efficacy (36%), and pharmacokinetic problems (14%); in Phase III studies, the most common are lack of efficacy (53%) and toxicity (35%), the most frequent of which is hepatotoxicity. Not surprisingly, the preapproval costs for developing a new chemical entity have been estimated to exceed \$500 million dollars.

In spite of efforts by pharmaceutical companies and the Food and Drug Administration (FDA) to confirm efficacy and to identify toxicities in novel chemical entities, approximately 8% of newly approved drugs acquire a black box warning indicating the potential for a serious adverse drug reaction (ADR) and

about 3% are withdrawn from the market, usually within a few years of introduction. The primary reason for removing an agent from the market is toxicity (94%); the more common ADRs leading to drug withdrawal are hepatic, hematological, and cardiovascular toxicities.

Some of the drugs withdrawn from the market since 2000 and their toxicities are included in Table 1. Notable are the spectrum of chemical compounds in Table 1 and the variety of diseases or conditions for which the drugs were initially approved. Also remarkable is the number of deaths associated with some of these agents; for example, drug-associated deaths from rofecoxib (Vioxx), troglitazone (Rezulin), cisapride (Propulsid) and trovafloxacin (Trovan) are reported to have been 27,000, 400, 80, and 6, respectively.

The primary reason why serious ADRs are identified only after novel compounds are introduced into general clinical use is that serious ADRs are often uncommon and thus unobserved until thousands of patients have been exposed; in short, the preapproval studies are underpowered to detect ADRs. Other factors include the highly selected patients recruited into clinical trials and the finite time study subjects are given the investigational drugs. By extension, once an agent is available, practitioners may elect to use the drug in patient populations never studied and for conditions beyond those approved. On occasion, a drug with unique properties will be approved in spite of a serious ADR observed during trials and subsequently withdrawn. Finally, post-marketing surveillance via the FDA's Adverse Event Reporting System is largely a voluntary activity, and, as a result, inadequate clinician, industry and patient reporting can lead to delays in identifying ADRs.

### Selected Medications Withdrawn from Clinical Use in United States Since 2000

Medication	Class / Indication	Introduced / Withdrawn		Reason for Withdrawal
<u>Troglitazone</u> (Rezulin)	oral hypoglycemic / diabetes mellitus	1997	2000	hepatotoxicity, deaths from liver failure
<u>Cisapride</u> (Propulsid)	gastroprokinetic / gastroparesis, gastric reflux	1993	2000	cardiac arrhythmias with deaths
<u>Trovafloxacin</u> (Trovan)	fluoroquinolone antibiotic / pneumonia, other infections	1998	2001	hepatotoxicity with deaths
<u>Cerivastatin</u> (Baycol)	HMG-CoA reductase inhibitor / hypercholesterolemia	1998	2001	rhabdomyolysis, renal failure and deaths
<u>Rofecoxib</u> (Vioxx)	anti-inflammatory analgesic / osteoarthritis, acute pain	1999	2004	myocardial infarctions and deaths
<u>Pemoline</u> (Cylert)	CNS stimulant / attention deficit disorder, narcolepsy	1975	2005	hepatotoxicity with deaths
<u>Aprotinin</u> (Trasylol)	antifibrinolytic / to reduce bleeding in cardiac surgery	1998	2008	renal failure, myocardial infarction, stroke and death
<u>Efalizumab</u> (Raptiva)	immunosuppressant* / psoriasis	2004	2009	progressive multifocal leukoencephalopathy (PML)
<u>Sibutramine</u> (Meridia)	anorexiant / obesity	1997	2010	myocardial infarction, stroke and deaths
<u>Drotrecogin alfa</u> (Xigris)	anti-inflammatory, anti-thrombotic** / severe sepsis	2001	2011	lack of efficacy

\*recombinant monoclonal antibody

\*\*recombinant form of activated protein C

Since the costs of bringing a new compound to market are enormous, the pressures on pharmaceutical companies to generate sales are extraordinary. As a result, companies aggressively promote the introduction of novel agents by intensively marketing to physicians and consumers, a practice that can yield an explosion in prescription writing and the first-time use of a compound by hundreds of thousands of patients. Other factors that fuel a marketing surge include a desire to foster favorable prescribing patterns and to blunt the impact of yet-to-be-approved competing agents. A need to demonstrate robust sales increases to stimulate a rise in stock values has also been cited as playing a role. Regardless, the rapid exposure of a vast and heterogeneous population to a novel agent may reveal a serious drug problem and, unfortunately, injure large numbers of people. For example, 19.8 million Americans were exposed to five drugs (terfenadine, bromfenac, fenfluramine, dexfenfluramine and mibefradil) that were all withdrawn in a 12 month period in 1997-1998; in contrast, a total of 12,340 subjects were exposed to these agents during preapproval trials.

The stories behind the withdrawal of approved medications sometimes read like fiction, and occasionally pharmaceutical industry protagonists appear to play conspiratorial roles. A brief Google or FDA website search of any of the drugs in Table 1 will provide facts regarding the events leading to a drug's withdrawal; you as the reader can infer the protagonist's intent.

One agent in Table 1, Xigris (drotrecogin alpha or activated protein C), merits special comment, as it is one of the few FDA-approved agents ever withdrawn from the market because of a lack of efficacy. In brief, severe sepsis results from a cascade of coagulation and immune mediators usually unleashed by a bacterial pathogen and resulting in unfettered and injurious inflammation. In spite of supportive care and appropriate antimicrobials, severe sepsis is associated with case fatality rates of 30 to 50%. Since prior studies designed to arrest or temper the dysregulated

systems had failed to reduce case fatality rates, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study published in 2001 was hailed by some as a landmark advance. In that report, the overall 28 day survival rate for patients with severe sepsis treated with Xigris was 24.7% versus 30.8% for those given placebo ( $p=0.005$ ); among patients with severe sepsis and a high risk of death, the respective survival rates were 44% and 31%. The primary ADR was serious bleeding, including intracranial hemorrhage, which occurred more commonly among Xigris treated patients (3.5% versus 2.0%;  $p=0.06$ ).

Based on data from the PROWESS trial alone, the FDA approved the use of Xigris for patients with severe sepsis and a high risk of death in 2001. However, the decision to approve was supported by only half of the members of the Anti-Infective Drugs Advisory Committee; the other half had concerns about protocol changes during the trial and bleeding risks. As a result, the review panel requested further research to address methodological and other concerns with the PROWESS study, and the FDA asked the company developing the drug, Eli Lilly, to perform additional studies in specific patient subgroups, including that for which Xigris had been approved.

Questions about the validity of the PROWESS data combined with a \$6,800 to \$8,000 cost per course spawned ambivalence



in the medical community, restrictive guidelines in many intensive care units, and lower than expected sales. In particular, in contrast to Lilly's predicted annual sales of \$300-500 million, actual sales in the first year were about \$100 million.

To promote the use of Xigris, Lilly hired a new public relations firm that developed a marketing strategy anchored on the premise "that it was unethical not to use the drug." The marketing campaign was designed to "raise awareness" that life-saving drugs were being "rationed" in intensive care units and to foster and support the creation of sepsis treatment guidelines, which of course would include the use of Xigris. Lilly gave a \$1.8 million dollar grant to establish a Values, Ethics and Rationing Task Force of physicians and ethicists to address the concocted issue of rationing, and the company generously funded the Surviving Sepsis Campaign, which convened experts in infectious diseases and critical care medicine and which led to sepsis management guidelines published in Critical Care Medicine in 2004. Of note, many professional societies were listed as sponsors of the Surviving Sepsis Campaign Guidelines; reassuringly, the Infectious Diseases Society of America declined to endorse the guidelines, citing among other factors pharmaceutical company sponsorship. In short, the marketing campaign was designed to drive demand for Xigris. However, the impact was modest, as annual sales rose to about \$200 million.

The fate of Xigris was ultimately determined by the outcome of clinical trials completed after the drug was approved in 2001. Initially, a survival benefit of activated protein C without an increased risk of serious bleeding appeared to be confirmed in one single-arm, phase-3B, mortality and safety study (ENHANCE US published in 2004). However, in septic adults with a low risk of death, Xigris failed to show a mortality advantage and was associated with a statistically higher risk of serious hemorrhage (ADDRESS, 2005). Activated protein C also failed to show a benefit in children with severe sepsis (RESOLVE, 2007) and in adults with septic shock (PROWESS-SHOCK, results released in late 2011). Of note, the PROWESS-SHOCK study was undertaken at the request of the European Medicines Agency, which is the equivalent of the US FDA and which in 2007 asked Eli Lilly to confirm the findings of the 2001 PROWESS study and to substantiate the claim that the benefits of Xigris outweighed its risks. When the results of PROWESS-SHOCK failed to demonstrate a survival advantage, Eli Lilly withdrew Xigris from the worldwide market in October 2011, and the company discontinued all ongoing clinical trials.

Drugs acquiring new black box warnings or drugs withdrawn from the market are a reminder that although pharmaceutical companies, clinical investigators, and the FDA are committed to providing safe and effective therapies, limitations exist in the

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design of clinical trials and in the review and approval process. And because post-marketing drug safety surveillance remains a voluntary activity, serious adverse events may not come to light unless practitioners, industry, and consumers report untoward events. On a broader note, clinicians should perhaps avoid using new drugs when older and equally effective agents are available, and they should inform patients of the limited experience with recently introduced medicines. In addition, practitioners should be aware of the limitations in the preapproval processes and the post-marketing systems for detecting potential harm, and they should willingly report possible ADRs via the FDA's MedWatch program. As the agents in Table 1 illustrate and as Lasser and colleagues conclude, "Any new drug should be considered a black box."

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Dr. Anthony Esposito is Chair, Department of Medicine, St. Vincent Hospital and an WDMS Editorial Board Member.

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# Old Drugs with New Uses: Focus on Antidotes

Ryan Attwood, Pharm D, BCPS and Jordan Rush, BS



**Jordan Rush, BS**

Medications are often used for off label uses, and it is not uncommon to see older medications being used for new indications. This is especially true in the field of toxicology, where many unlikely agents are used to reverse or mitigate the adverse effects of overdosage or drug toxicity. This article will review some old medications that have recently found a new use as antidotes.

## Intravenous lipid emulsion (IVLE) for lipophilic drug toxicity

The administration of IVLE emulsion has long been used to supplement patients receiving intravenous total parental nutrition. The use of IVLE has also recently gained attention as an antidote for several severe lipophilic drug toxicities. Approximately 42 cases of IVLE use for drug toxicity have been reported since June, 2010, with several cases of beta blocker, calcium channel blocker, and antidepressant toxicities reported.<sup>1</sup>

There are several proposed mechanisms of actions for IVLE therapy. The most widely accepted is the “lipid sink” phenomenon suggested by Weinberg.<sup>2,3</sup> This theory suggests that the infusion of the lipid emulsion increases the lipid compartment in the body. The lipophilic drug will then redistribute from the cardiac and brain tissues, through the plasma, and into the circulating lipid droplets. Other proposed mechanisms include an increase in ATP synthesis through fatty acid oxidation and an increase in intracellular calcium levels, leading to increased heart contractility.<sup>2,4</sup>

Although there is no definitive dosing protocol established, one source recommends a 1.5 mL/kg 20% lipid emulsion bolus, which can be repeated two additional times in 5 minute intervals if cardiovascular circulation is not restored.<sup>2,5</sup> This is then followed by a 0.25 mL/kg/min infusion, with an upper limit of 10 mL/kg for 30 minutes.

There have been few adverse events reported for this use of IVLE therapy. Case reports include an increase in amylase levels and the development of acute lung injury.<sup>6,7</sup> Overall, this therapy can be considered safe and is a viable option for patients who have failed traditional overdose protocols.

## Octreotide for sulfonylurea induced hypoglycemia

Octreotide is a long-acting somatostatin analog, a natural hormone found in the body that suppresses the release of various endogenous chemicals and hormones and has long been used in the treatment of acromegaly and the management of some cancer-related side effects. Octreotide’s effect on insulin and glucagon secretion makes it a suitable treatment option for sulfonylurea-induced hypoglycemia.

The traditional approach to sulfonylurea-induced hypoglycemia utilizes dextrose infusions to increase serum glucose levels.<sup>8,9</sup> The infusion of glucose causes the body to secrete insulin; however, this results in rebound hypoglycemia. To break this cycle, octreotide has been introduced as a new therapeutic option.

The recommended adult dosing regimen is 50 µg of octreotide subcutaneously every 8-12 hours.<sup>9</sup> Octreotide has been effective in cases of pediatric sulfonylurea toxicity as well, with one suggested dosing of 1-1.25 µg/kg.<sup>9</sup> Currently no adverse reports have been reported.<sup>8,9</sup>



Glucagon, insulin and dextrose for beta blocker and calcium channel blocker overdose

Beta blocker and calcium channel blocker overdose is associated with cardiovascular toxicity including conduction disturbances, bradycardia, and cardiogenic shock.<sup>10</sup> Management involves agents including atropine, intravenous calcium, inotropes, vasopressors and cardiac pacing to ameliorate these effects.<sup>11</sup> Two additional therapies, glucagon and insulin / dextrose, are drugs that have long been used for other purposes and are now part of this treatment algorithm.

Glucagon is a 29 amino acid polypeptide which maintains plasma glucose levels during fasting / stress states and has an established use in the management of insulin induced hypoglycemia. It has also been used as an antidote to beta blocker / calcium channel overdose. The proposed mechanism of glucagon's activity is via activation of adenylate cyclase, resulting in an increase of cyclic AMP and leading to an increase in cardiac inotropy and chronotropy independent of beta receptor activation.<sup>12</sup>

Glucagon has been shown to be effective in animal models of beta blocker and calcium channel blocker toxicity, and volunteer studies have found that IV glucagon administration is associated with an increase in cardiac index.<sup>13,14</sup> Early reports suggest a dose of 50 ug/kg IV (3-5 mg intravenously); however, doses of up to 10 mg have been used.<sup>15,16</sup> Glucagon has a relatively short duration of action, and a continuous infusion is sometimes required.<sup>17</sup> Tachyphylaxis has been reported and repeat bolus dosing may be recommended over a continuous infusion.<sup>18</sup> Commonly reported adverse effects include gastrointestinal side effects, glucose and electrolyte abnormalities.

Another treatment for beta blocker / calcium channel overdose is the administration of high dose insulin with supplemental dextrose to prevent hypoglycemia. The administration of insulin is associated with increased inotropy and an increased glucose uptake and utilization.<sup>19</sup> Typical treatment protocols consist of an initial bolus of 1 unit / kg intravenous regular insulin followed by a maintenance infusion of 0.5-1 units / kg titrated to clinical response.<sup>19</sup> Doses up to 10 units / kg have been reported.<sup>20</sup> As expected, hypoglycemia may occur with this therapy and a dextrose bolus is generally recommended if a patient's serum glucose is less than 200 mg / dl, followed by a maintenance infusion as needed to prevent hypoglycemic events.<sup>11</sup> Hypokalemia may also occur and serum potassium should be actively monitored and replaced.

## Conclusion

As many practitioners know, there are often situations where drugs are used for unapproved indications. Quite often the agent may be somewhat novel and work via mechanisms that may be surprising based on the original indication for use. Although the use of these agents may become widespread, it is important for clinicians to critically evaluate the available data for the drug's efficacy and safety.

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Ryan Attwood PharmD, BCPS is an Assistant Professor of Pharmacy, Department of Pharmacy Practice. Massachusetts College of Pharmacy and Allied Health Science. Worcester. Email: [Ryan.Attwood@mcphs.edu](mailto:Ryan.Attwood@mcphs.edu)

Jordan Rush BS is a third year pharmacy student at Massachusetts College of Pharmacy and Allied Health Science. Worcester. Email: [Jordan.Rush@my.mcphs.edu](mailto:Jordan.Rush@my.mcphs.edu)



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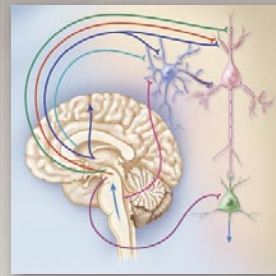
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THE OPENING WORDS FROM THE FIRST ISSUE. WARREN J. REMARKS ON ANGINA PECTORIS. N ENGL J MED SURG 1812;1:1-11.



1812

The first issue of the *New England Journal of Medicine and Surgery and the Collateral Branches of Medical Science* is published in Boston.



1872

The concept that **one cerebral hemisphere can influence both sides of the body** is introduced in a lecture on the symptoms of brain disease.

BROWN-SEQUARD CE, WEBBER SG. THE ORIGIN AND SIGNIFICATION OF THE SYMPTOMS OF BRAIN DISEASE. BOSTON MED SURG J 1872; 87:261-3.

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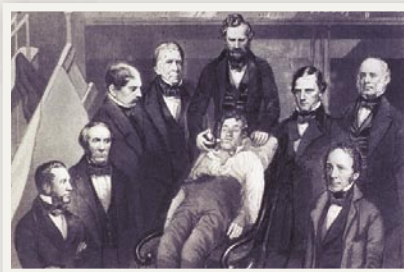
1880

1900

1846

A report on the first **public demonstration of ether anesthesia for surgery** is published.

BIGELOW HJ. INSENSIBILITY DURING SURGICAL OPERATIONS PRODUCED BY INHALATION. BOSTON MED SURG J 1846;35:309-17.



1906

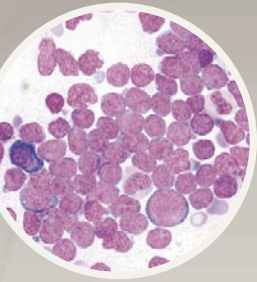
The first histologic proof that **blood platelets are made in bone marrow** is published.

WRIGHT JH. THE ORIGIN AND NATURE OF THE BLOOD PLATES. BOSTON MED SURG J 1906;154:643-5.

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Successful **treatment of early childhood leukemia** with folate antagonists is first reported.

**FARBER S, ET AL.** TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN). *N ENGL J MED* 1948;238:787-93.

1973

The first report of **polypectomy using a colonoscope** introduces a prophylactic procedure during screening to reduce subsequent cancer risk.

**WOLFF WI, SHINYA H.** POLYPECTOMY VIA THE FIBEROPTIC COLONOSCOPE — REMOVAL OF NEOPLASMS BEYOND REACH OF THE SIGMOIDOSCOPE. *N ENGL J MED* 1973;288:329-32.



2001

The beginning of personalized medicine. A **targeted therapy** for chronic myelogenous leukemia.

**DRUKER BJ, ET AL.** EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA. *N ENGL J MED* 2001;344:1031-7.



1920

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1960

1980

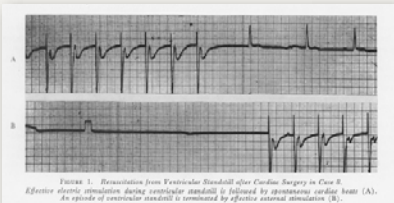
2000

2012

1952

The first **successful use of an external pacemaker** to resuscitate the heart is described.

**ZOLL PM.** RESUSCITATION OF THE HEART IN VENTRICULAR STANDSTILL BY EXTERNAL ELECTRIC STIMULATION. *N ENGL J MED* 1952;247:768-71.

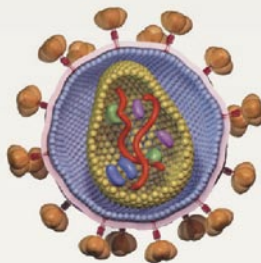


1981

Some of the earliest descriptions of **AIDS**, and then of its treatment, are reported.

**GOTTLIEB MS, ET AL.** *PNEUMOCYSTIS CARINII* PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN — EVIDENCE OF A NEW ACQUIRED CELLULAR IMMUNODEFICIENCY. *N ENGL J MED* 1981;305:1425-31.

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# Checkup System Passes Test

Lynda Young, MD

Massachusetts law establishes a physician profile system solely for those who are licensed to practice in the commonwealth.

In the Massachusetts Medical Society's 230-year history, we have a long list of firsts. But we can take special pride that we were the first in the nation to promote the public release of the disciplinary records of all actively practicing physicians in our state. Our approach became the model for states across the nation.

The profiles were developed principally to help patients choose their physician. In fact, during the state's own testing of the program in the 1990s, it was clear it would achieve its purpose. Patients said they were most pleased to see the information about physicians' practice locations, office hours, credentials, and the health plans they accepted. Disciplinary records were almost secondary.

A recent article in the *Telegram & Gazette* asked some pointed questions about the state board of registration in medicine, the system of physician profiles, and public reporting.

The article first questioned why the records do not cover care delivered outside of hospitals. The answer is clear: The program was written to report only on disciplinary actions in hospital settings, because in those venues, due-process protections are provided to both the physician and the person filing the complaint. There are no such due-process rights in other settings, such as nursing homes and clinics. Due process must be a basic building block of any public reporting system on standards of care provided by physicians.

The article also highlighted the case of a physician who had a jury return a large verdict against her and in favor of a baby

born with cerebral palsy. The care took place in 1996, the physician was licensed in Wisconsin in 1999, and the jury verdict came in 2005. The article suggested that the Massachusetts profiling system somehow is deceiving the public by not now, in 2012, more than a decade after the care, having information about this case listed in perpetuity.

Massachusetts law establishes a physician profile system solely for those who are licensed to practice in the commonwealth. I would suggest that every state bears the responsibility of doing its own homework on every prospective licensee, particularly since any state licensing agency can retrieve any malpractice verdict or other disciplinary action from the National Practitioner Databank. It's not a difficult task, since every physician has a unique identifier that does not change, even if the physician changes his or her name.

The article further suggested that the medical profession is lax in holding its members accountable for not disciplining those who fail to meet standards of good medical care. However, the article uses entirely suspect information to reach that conclusion, by noting that physicians refer their colleagues to the medical board an average 41 times each year.

Leaving aside the wholly subjective judgment about whether 41 is a high number or low number, the report paints a substantially incomplete picture of what the profession does. The number does not count the physicians whose issues were addressed in peer review, rigorous highly structured peer counseling, or otherwise. I submit that one would be hard-pressed to find another profession that holds itself accountable to such a high degree.

Additionally, the article cites Public Citizen, a national non-

profit that describes itself as a government watchdog, whose reports equate the number of annual disciplinary actions by state medical boards with their competence. For many reasons, that methodology is even more suspect. To construct its rankings, Public Citizen takes the number of serious disciplinary actions and divides it by American Medical Association data on the number of doctors in a state.

But raw numbers don't and can't tell the whole story: Massachusetts has far fewer physicians engaged in actual patient care than the 35,000-plus cited by the Public Citizen's report and in the Telegram's report.

Physicians clearly support appropriate intervention for colleagues who engage in improper behavior, fail to meet clinical standards, or put patients at risk. Each case deserves its individual hearing, assessment and disposition. Discipline is only one tool in public protection. The oversight of the practice of medicine is a complex endeavor that cannot be adequately judged by raw numbers or one or two sensational cases.

Certainly, transparency can address much of what ails the health care delivery system — as long as the information is accurate and is fair to all stakeholders. The Massachusetts physician profile program currently passes both tests.

*Lynda Young, M.D., a Worcester pediatrician, is president of the Massachusetts Medical Society, the statewide association of physicians with more than 23,000 members.*

*Editor's Note: This commentary first appeared in the Worcester Telegram & Gazette on March 30, 2012.*

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# A Message from the Worcester Free Clinic Coalition

Dear Central MA Physicians,

We are writing to ask for your help in supporting the free medical programs in Worcester. These programs have been providing medical care to those without insurance or with inadequate insurance for over 17 years and we continue to see high patient numbers. In order to run, the clinics need a licensed physician present at all times. We are grateful for all of the help we have received from UMass Memorial Medical Group physicians and others who have volunteered their time; however, we still have slots to be filled in the coming months. In addition to physicians, the clinics are staffed by nurses, nursing students, medical students and others such as church volunteers.

There is a clinic each weeknight (Monday - Thursday) from 6:00 pm-8:30pm. You can volunteer as often or as infrequently as you would like – many of our current volunteers choose to volunteer monthly or quarterly. Before your first shift, we will give you a tour of the clinic and a brief orientation to the specific clinic with which you will be involved. Experienced students will be at each clinic during all shifts and they will guide you through the logistics and help to answer any questions you may have.



Harvey G. Clermont, MD, Founder, St. Anne's Free Medical Program (right)

One of the most common questions that arises from our physician volunteers involves malpractice and liability insurance. If you are currently practicing, your current insurance may extend to your work at the clinics. If you are a member of the UMass Memorial Medical Group, we have a process for this. If you are affiliated with another medical group or are an independent practitioner, please check with your administrator or insurance representative. If you are a retired physician and not actively doing paid work, Mass

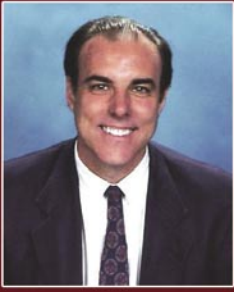
Medical Society generously provides coverage for volunteer work. We are happy to help with your individual situation.

If you are interested in becoming involved or if you have any questions or concerns, please email us at [worcesterfreeclinics@gmail.com](mailto:worcesterfreeclinics@gmail.com).

Best,

Melinda Palma & Karen Tenner  
Volunteer and Physician Coordinators  
Worcester Free Clinic Coalition





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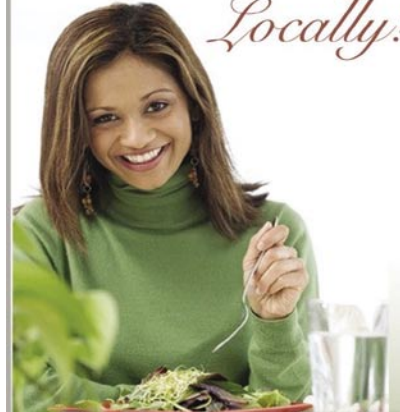
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## 2012

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- 2) A current curriculum vitae of the nominee
- 3) Letters of support are encouraged

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Phone: 508-753-1579

***DEADLINE: AUGUST 6, 2012***

***Please print all information***

Nominator \_\_\_\_\_ Phone \_\_\_\_\_

Email \_\_\_\_\_ Fax \_\_\_\_\_

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Name of Nominee \_\_\_\_\_

Email \_\_\_\_\_

Hospital Affiliation \_\_\_\_\_





Worcester District Medical Society congratulates Dr. Michael Hirsh and the Goods for Guns Program for receiving the Center for Nonviolent Solutions Award on March 24, 2012. Dr. Hirsh is pictured with Michael True, board member for the Center for Non-Violent Solutions.



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