

Drug Information Letter

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The Millcreek Community Hospital, LECOM School of Pharmacy Drug Information Letter

The publication of this first issue of *The Drug Information Letter* marks the beginning of a cooperative effort between Millcreek Community Hospital and the LECOM School of Pharmacy. The goals are to provide experiential opportunities for School of Pharmacy students and residents and a service, at least initially, to health professionals at Millcreek Community Hospital.

The Drug Information Letter will be published monthly. Articles will be contributed by LECOM pharmacy students, residents, and faculty. Our editorial focus will be primarily on new drugs, safety issues concerning both old and new drugs, and emerging drug policy issues.

The Drug Information Letter joins a small but hopefully growing list of publications that regularly

include publically available Food and Drug Administration (FDA) reviews and advisory committee briefing documents as part of their editorial process. These documents contain analyses of data and trials submitted to the FDA by manufacturers which may or may not be published.

As a general rule *The Drug Information Letter* will not comment on a new drug until after the FDA posts its reviews. This is now necessary as over the last 15 years it has become increasingly more difficult to differentiate promotion from science in the peer-reviewed medical literature. In other words, it is no longer possible to conduct an independent review of the therapeutic value of a new drug by relying solely on the published medical literature. Study of the FDA reviews, before forming an opinion, in our view, is mandatory.

Readers interested in exploring the issue of medical journals as a means of scientific communication or as a platform for promotion are referred to a recent essay by Richard Smith, former editor of the *British Medical Journal*, with the provocative title "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies."¹

Other publications that regularly use FDA reviews and documents are the *Therapeutics Initiative Letter* from the University of British Columbia; *Prescribe International*, the English language version of a respected French drug newsletter; Washington DC based Public Citizen's *Worst Pills, Best Pills News* written for patients, and the Canadian Coordinating Office for Health Technology Assessment.

These are very interesting times in the drug policy arena. Not since the Kefauver Hearings held in the late 50s and early 60s, eventually resulting in the efficacy standard in U.S. drug law, has there been as much public scrutiny of the pharmaceutical industry. Suicidality in children and adolescents prescribed antidepressants, the Senate Finance Committee's rofecoxib (Vioxx) hearings, the revelations of FDA medical epidemiologist David Graham, lack of transparency in reporting the results of clinical research and in the FDA, and conflicts of interests are a few of the issues now swirling on Capital Hill. Legislation has, or will be proposed in the near future, addressing all of these issues and will have an effect, not only on the public, but also on health professionals.

Suggestions for articles are always welcome and may be sent to lsasich@lecom.edu.

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ARE THE ZZZZ DRUGS, ESZOPICLONE (LUNESTA), ZALEPLON (SONATA), ZOPICLONE, AND ZOLPIDEM (AMBIEN) BETTER SLEEPERS THAN THE BENZODIAZEPINES?

Outside of the U.S., the hypnotics zaleplon (Sonata), zolpidem (Ambien), and zopiclone are referred to euphemistically as the "Z- drugs." Zopiclone has never been marketed in this country, in fact, approval was denied because of pre-clinical animal testing that showed an excess of cancers in laboratory animals. However, zopiclone has been available in 85 countries since 1987.

The newest Z-drug on the market is eszopiclone (Lunesta), the s-enantiomer of zopiclone, approved by the Food and Drug Administration (FDA) on December 15, 2005. The butterfly used in the eszopiclone TV promotion has been effective. *The Wall Street Journal* reported that "Lunesta is backed by a \$60 million advertising campaign" and it "is off to one of the fastest prescription starts on record. In the seven days through May 9, it had 42,508 new prescriptions, giving it a 9.8% share of new insomnia-drug prescriptions."¹

Eszopiclone, zaleplon, and zolpidem could be called non-benzodiazepine-benzodiazepines as they share their mechanism with the benzodiazepines but have different chemical structures. All three are

controlled substances with a risk for dependence.

The FDA posted its eszopiclone reviews on the Internet in early May 2005. These documents can be found at www.fda.gov/cder/foi/nda/2004/021476_Lunesta.htm.

Six clinical trials were included in the submission to the FDA in support of the eszopiclone's approval. In four of these, the primary endpoint was Objective Latency to Persistent Sleep, or the time it takes to fall to sleep. The FDA medical officer described one of these four studies as having "serious problems" and that it "cannot provide clinically meaningful results."²

In the remaining three trials, the average time to fall asleep in patients taking 3 milligrams of eszopiclone ranged for 18.0 to 19.3 minutes. In patients given placebo the range was from 33.0 to 40.8 minutes. The difference in these three trials between eszopiclone and placebo ranged from 15.0 to 21.5 minutes. One of these three trials also compared eszopiclone 3 milligrams to placebo and also to 10 milligrams of zolpidem. On average, patients taking eszopiclone fell asleep in 18.3 minutes and patients on zolpidem 16.6 minutes. This is an average difference of 1.7 minutes favoring zolpidem.³

The FDA medical officer responsible for a major part of the eszopiclone review recommended that the drug not be approved. The major issues for her were tumors in

laboratory animals, and the drug's apparent genotoxicity.⁴

The Team Leader and the Division Director, the medical officer's two immediate supervisors, concurred with her recommendation not to approve eszopiclone.^{5,6} In addition, one of the reviewing pharmacologists also recommended against approving the drug.

The Division Director wrote in his February 20, 2004 memo:

I think that the mouse tumors (and, to a lesser degree) the rat pulmonary findings, are true findings, and pose a least a potential risk for humans, for the reasons given above. Given this conclusion, it is, of course, impossible to predict how significant a risk (if any) this poses for humans, but it would appear small. I would argue, however, that a risk of this sort (carcinoma), in the setting of recently approved drugs [zaleplon, and zolpidem] without such a potential risk, for the indication insomnia, for a treatment with no evidence of a benefit of any sort compared to other available treatments, is too great a risk to justify approval.⁷

The recommendations of four qualified FDA scientists were overridden in the upper administration of the Center for Drug Evaluation and Research (CDER). It was conceded that eszopiclone had

“no advantage over alternatives.” The rationale for approving the drug was stated in a memo:

My conclusion that the drug can be considered approvable is based on my view that 1) the carcinogenicity findings with the racemate are very weak in the first place and 2) are simply not present in the single enantiomer studies. I do not believe that an unreplicated weak finding should lead us to conclude that there is a human risk.⁸

This memo did not discuss that eszopiclone may be genotoxic, or that in single enantiomer studies of eszopiclone the dose was ½ that in the studies of the racemic mixture.

The British National Institute for Clinical Excellence (NICE), an organization created as a fourth hurdle to drug reimbursement in the United Kingdom, reviewed the Z-drugs in April 2004. Their conclusion:

It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.⁹

The editors of *The Medical Letter on Drugs and Therapeutics*

reviewed eszopiclone in their February 28, 2005 issue. Their less than enthusiastic conclusion was that:

The main difference between all of them [eszopiclone, zaleplon, zolpidem], except for half-life, may be that the manufacturer of Lunesta sponsored a 6-month trial and submitted the results to the FDA, while the other 2 manufacturers did not.¹⁰

There is, of course, another major difference between eszopiclone, zaleplon, and zolpidem and generic oxazepam (Serax), for example, a short acting benzodiazepine – the cost.

The table below lists the retail cost of a 30 day supply of generic oxazepam, eszopiclone, zolpidem, and zaleplon as posted on the Web site of a popular Internet pharmacy.

RETAIL COST OF A 30 DAY SUPPLY OF SLEEPING PILLS	
Oxazepam capsules 10 milligrams	\$12.99
Eszopiclone (LUNESTA) tablets 3 milligrams	\$98.99
Zolpidem (AMBIEN) tablets 10 milligrams	\$87.99
Zaleplon (SONATA) capsules 10 milligrams	\$85.27

The FDA should not have approved this drug. There is no clear evidence to differentiate the Z-drugs from one another or the short-acting benzodiazepines other than price. Even overlooking the potential safety concerns associated with

eszopiclone, this is a Do Not Need drug.

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COMMUNICATING OUTCOMES FIRST THE NNT (NUMBER NEEDED TO TREAT) AND NOW THE NTN AND ITI

The Number Needed to Treat (NNT) has become a staple practice of evidence-based medicine to aid clinicians in assessing the value of an intervention and to extrapolate the results of clinical trials to at-risk groups. The NNT is the number of patients who need to be treated to obtain one good outcome or one less bad outcome over the same duration of treatment as the patients in a clinical trial. The calculation is the reciprocal of the absolute risk difference between treatment and control groups.¹

Epidemiologists from the Quebec Heart Institute and McGill University Health Center writing in the April 9, 2005 issue of *The Lancet* expressed their dissatisfaction with the NNT as placing too much emphasis on the positive side of an intervention while obscuring the very large numbers of patients that may be treated without benefit.²

Their suggestion is a new metric that would complement the NNT and give clinicians a broader perspective of the therapeutic value of an intervention. They would call it the Numbers Treated Needlessly (NTN). For example, if the NNT is 100 over five years to prevent one negative outcome, then the NTN would be 99. The higher the NTN, the greater the treatment burden this is borne by patients. Said another way, the NTN quantifies the number

of patients who will not benefit but who will face the potential harm and cost associated with the intervention.

Carrying the NTN a step further, the Canadian epidemiologists propose that the NTN be expressed as the percentage of patients that would be treated without benefit. This they would call the Index of Therapeutic Impotence (ITI). The ITI for an NNT of 100 would be 99 percent.

Their reasons for proposing the new numbers are important, particularly to patients:

We believe its interest lies in its salutary reminder that we should not be complacent about our inability to better identify patients who will benefit from our well-meaning interventions. It could serve as a constant admonition that as researchers we must better understand the pathogenesis of disease, and as clinicians we should maximise clinical acumen, so that our treatments may become ever selectively targeted. Patients too might benefit from this knowledge. Thus empowered, some might decide to forego the benefits we have generally taken for granted on their behalf.

In the table below the NNT for selected interventions from the literature are presented and their corresponding NTN and ITI are presented.

Intervention	NNT	NTN	ITI
Statin treatment for 3 to 5 years for the primary prevention of 1 myocardial infarction or stroke.	71 ³	70	98.6%
Alendronate (Fosamax) treatment for 4 years in women with low bone mineral density but without vertebral fractures to prevent the first vertebral deformity.	60 ⁴	59	98.3%
Finasteride (Proscar) treatment for 4 years to prevent 1 surgery for benign prostatic hyperplasia.	19 ⁵	18	94.7%
Clopidogrel (Plavix) treatment versus aspirin for 1.9 years to prevent one episode of the combined outcome of ischemic stroke, myocardial infarction, or vascular death.	196 ⁶	195	99.5%

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**COMMENTARY
ARE SAFETY AND EFFICACY
DATA CONFIDENTIAL
COMMERCIAL
INFORMATION?**

In early July, the Food and Drug Administration (FDA) posted information on its Web site concerning a higher than expected rate of suicide attempts observed in open-label extensions of controlled studies of duloxetine (Cymbalta) for stress urinary incontinence (SUI) in adult women.¹ Eli Lilly, duloxetine's manufacturer, withdrew its application for SUI in January 2005. The drug is approved by the FDA for major depressive disorder and diabetic peripheral neuropathic pain.

The Wall Street Journal reported that Lilly "raised legal issues including our use of confidential commercial data" with the FDA when it posted the duloxetine in SUI safety information.²

The FDA's practice has been to consider all information submitted by a manufacturer as part of the drug approval process as confidential commercial information under the

Freedom of Information Act (FOIA) until the drug receives final approval. This policy has extended to failed New Drug Applications (NDAs) and to indications denied approval for drugs approved by the agency for other uses.

There are several examples of the FDA having in its possession important safety information that was not made public in a timely manner. For example, the results of a study using valdecoxib (Bextra) in coronary artery bypass graft patients that showed an increased risk of cardiovascular events with the use of the drug. Valdecoxib was denied approval for an acute pain indication on the basis of this study. The drug was removed from the market on April 7, 2005 because of safety concerns, including cardiovascular risk.

The recent revelations about the possible harm associated with the use of antidepressants and the risk of suicide in children and adolescents when the agency had access to data raised the ire of both the public and Congress.

There are two views of the legality of the FDA releasing safety and efficacy data to the public. The first is that the agency is over interpreting FOIA. Manufacturers report to the financial community the existence of new drug submissions and in some cases the positive results of pre-approval clinical trials. Pre-approval clinical trials may also be openly presented at scientific meetings. The fact that a manufacturer has publically

disclosed such information should preclude it from being considered confidential commercial information and the FDA should be free to release all information about the safety and efficacy of drugs, and new indications, to the public whether or not they were approved or disapproved.

This may have been the FDA's thinking with duloxetine and the findings from SUI trials.

The other view is that FOIA prevents the FDA from releasing any safety and efficacy information about a drug, or new indication, unless, and until, it is approved. This is the position that Lilly may be taking with duloxetine and the release of what the company thinks is confidential commercial information.

Unfortunately, there is nothing in FOIA that recognizes a compelling public need to have information about the safety and efficacy of drugs. Trade secret information about the synthesis and manufacturing of drugs should remain protected. However, in situations involving safety and efficacy Congress should step in and give the FDA clear legal authority to release this information. Both patients and prescribers cannot make fully informed decisions without it.

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