



## Health Matters March 2009; Volume 3, Issue 6

### FDA Approves 21 New Drugs in 2008 by Jennifer Wagner

The Food and Drug Administration (FDA) approved 21 new molecular entities in 2008. A complete listing of these new molecular entities is included in the table below:

New Molecular Entities		
Brand	Generic	Indication/Use
	degarelix*	Advanced prostate cancer (gonadotropin-releasing hormone receptor antagonist)
	tapentadol*	Relief of moderate to severe acute pain
<i>AdreView</i>	iobenguane I 123	Detection of primary or metastatic pheochromocytoma or neuroblastoma
<i>Banzel</i>	rufinamide	Seizures associated with Lennox-Gastaut syndrome
<i>Cleviprex</i>	clevidipine	Hypertension (calcium channel blocker)
<i>Durezol</i>	difluprednate	Post-operative ocular inflammation and pain (corticosteroid)
<i>Entereg</i>	alvimopan	Prevention of post-op ileus after partial bowel resection surgery (peripherally-acting opioid antagonist)
<i>Eovist</i>	gadoxetate	Contrast agent for MRI of the liver
<i>Intence</i>	etravirine	Advance HIV infection (non-nucleoside reverse transcriptase inhibitor)
<i>Lexiscan</i>	regadenoson	Pharmacologic stress agent for patients unable to undergo an exercise stress test
<i>Lusedra</i>	fospropofol	Induce anesthesia (sedative/hypnotic)
<i>Mozobil</i>	plerixafor	Hematopoietic stem cell mobilizer to be used prior to stem cell transplantation
<i>Pristiq</i>	desvenlafaxine	Depression (serotonin-norepinephrine reuptake inhibitor)
<i>Promacta</i>	eltrombopag	Idiopathic thrombocytopenic purpura (thrombopoietin receptor agonist)
<i>Rapaflo</i>	silodosin	Benign prostatic hyperplasia (alpha-blocker)
<i>Relistor</i>	methylnaltrexone	Severe opioid induced constipation (peripherally-acting opioid antagonist)
<i>Toviaz</i>	fesoterodine	Overactive bladder (antimuscarinic)
<i>Treanda</i>	bendamustine	Chronic lymphocytic leukemia and a certain type of non-Hodgkin's lymphoma (alkylating agent)
<i>Vasovist</i>	gadofosveset	Contrast imaging agent for use with magnetic resonance angiography
<i>Vimpat</i>	lacosamide	Partial onset seizures
<i>Xenazine</i>	tetrabenazine	Huntington's disease (monoamine depletor)
* Brand name pending		

In addition to these new molecular entities, 10 new biologicals and several new dosage forms were approved in 2008. Included in the new biologicals group were some notable vaccines including *Kinrix* (diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus), *Pentacel* (diphtheria and tetanus toxoids, acellular pertussis adsorbed, inactivated poliovirus and haemophilus b) and *Rotarix* (rotavirus, live, oral). For more information on the drugs and biologicals approved in 2008, please contact the Center for Drug Information and Evidence Based Practice at (402) 280-5100 or [druginfo@creighton.edu](mailto:druginfo@creighton.edu).

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U.S. Food and Drug Administration Center for Drug Evaluation and Research. Accessed at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed January 20, 2009. New Drug Approved by the FDA in 2008. Pharmacist's Letter/Prescriber's Letter 2008.

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## Do antioxidant supplements interfere with cancer chemotherapy? by Danielle Robley

The role of antioxidant supplement use during chemotherapy treatment in cancer patients has been a controversial topic for many years. Conflicting clinical trials and data have been observed, yielding insufficient conclusions.<sup>1,2</sup>

Chemotherapy agents produce their anti-cancer effects through several different mechanisms. Some classes of chemotherapy rely on the creation of reactive oxygen species (ROS) to exert their therapeutic effect.<sup>2</sup> These include platinum-containing compounds (eg, cisplatin, carboplatin); alkylating agents (eg, cyclophosphamide, ifosfamide); and mitomycin C.<sup>1,2</sup> Anthracyclines (eg, doxorubicin) and bleomycin create ROS, but this reaction may not be their primary means for producing antineoplastic activity. DNA, proteins, and lipids can be severely damaged due to high or sustained levels of ROS.<sup>2</sup>

Antioxidants are agents that bind to ROS and are widely used as preventive agents for diseases such as cancer. Some patients turn to antioxidants for use during chemotherapy to help prevent chemotherapy side effects. It is thought that antioxidants might protect tissues and cells from oxidative damage through scavenging free radicals and therefore reduce side effects. However, through the same mechanism, there has been concern that antioxidants could potentially reduce the effectiveness of chemotherapy, particularly those agents that work primarily through generation of ROS.<sup>1</sup>

Two systematic reviews were identified that evaluated studies relevant to the topic. In the review by Lawenda et al., 16 randomized clinical trials regarding the use of antioxidants along with chemotherapy were evaluated.<sup>1</sup> In the systematic review by Simone et al., 14 randomized clinical trials regarding the use of antioxidant along with chemotherapy were evaluated.<sup>3</sup> These two reviews evaluated 19 distinct studies that evaluated the impact of antioxidants on cancer progression and/or survival in patients receiving chemotherapy.

Nine of these clinical trials revealed no statistically significant results relating to cancer progression and/or survival in patients receiving antioxidants and chemotherapy. However, some of these studies may have been underpowered to determine a statistical difference. In the trials, many different cancer types were studied, and different chemotherapeutic regimens, different antioxidants, and different doses were used, making it very difficult to compare these studies for analysis.

Four of the reviewed studies revealed significant results. Three studies used melatonin 20mg by mouth, while the fourth administered glutathione 30mg/kg IV.<sup>1</sup> Investigators found that the antioxidant group had increased stable disease rate ( $p < 0.01$ ) and increased tumor regression rate ( $p < 0.05$ ) compared to those not receiving antioxidants ( $p < 0.01$ ).<sup>1,4</sup> Researchers also found that the antioxidant group compared to those not receiving antioxidants were more likely to achieve a significant complete response rate ( $p < 0.02$ ), partial response rate ( $p < 0.01$ ), and complete and partial tumor regression rate ( $p < 0.001$ ).<sup>1,5</sup> There was also an increased overall survival in the antioxidant group compared to those not receiving them ( $p < 0.05$ ). Cerea et al. found that those receiving antioxidants had an increased number of stable disease ( $p < 0.05$ ).<sup>1,6</sup> Fujimoto et al. found that patients with Stage 3-4 gastric cancer taking antioxidants had a higher survival rate than placebo ( $p < 0.025$  at 3, 4, & 5 years).<sup>1,7</sup>

Overall, it is difficult to make an analysis due to the different types and doses of chemotherapy and antioxidants used and the different cancer types in the studies evaluated. Some studies evaluated a primary outcome of side effects, while outcomes relating to disease progression and survival were secondary, and may not have been designed to evaluate the outcomes. Nine of the studies reviewed had fewer than 50 participants. Thus, larger studies need to be performed.

After reviewing the data, it appears there is insufficient information regarding the role of antioxidants in chemotherapy and their use in high-doses should be discouraged during cancer chemotherapy until further studies can be completed.<sup>1,2</sup>

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## Fosamax may have Osteonecrosis Risk Similar to Other Bisphosphonates by Mike Zadina

Bisphosphonates have received attention in the popular press recently due to their association with osteonecrosis of the jaw (ONJ). Bisphosphonates are commonly used to treat osteoporosis, but can also be used to treat Paget's disease, hypercalcemia associated with malignancy, osteolytic lesions associated with metastatic bone disease, and multiple myeloma.<sup>1</sup> Bisphosphonates work by binding to the bone matrix and slowing down osteoclastic activity, thereby facilitating osteoblastic effectiveness.<sup>1</sup> These drugs also have novel antiangiogenic effects which could, in theory, lead to ONJ.<sup>1</sup>

Bisphosphonates have half-lives that last for many years. For example, alendronate's half-life is 12 years.<sup>1</sup> The bisphosphonate group of drugs includes the following agents: alendronate (Fosamax), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa). Ibandronate (Boniva), pamidronate (Aredia), and zoledronic acid (Reclast, Zometa) are currently available in intravenous dosage forms.<sup>1</sup>

ONJ was once thought to be more common with the IV formulations of the drug when used for treating cancer. It has been reported that anywhere from 1.3% to 7% of cancer patients being treated with an IV bisphosphonate develop ONJ.<sup>2</sup> Originally, the makers of Fosamax reported the incidence of ONJ in alendronate patients as low as 0.7 cases per 100,000 person-years exposed.<sup>3</sup> However, ONJ has recently been seen more frequently with oral bisphosphonates to be used to treat osteoporosis.<sup>3</sup>

In a recent inquiry performed by Sedghizadeh et al., a higher risk of ONJ was revealed with alendronate.<sup>3</sup> Researchers looked at the of USC School of Dentistry's electronic medical record system to determine the number of patients with a history of alendronate use and how many of those patients were also receiving treatment for ONJ. The investigators identified 208 patients with a history of alendronate use. Of these, 9 (approximately 4%) had active ONJ.<sup>3</sup> All of the ONJ cases occurred after simple tooth extraction or denture trauma.<sup>3</sup> The patients were between 63 and 80 years old, and were all women who received alendronate for osteoporosis. It should be noted that type 2 diabetes, hypertension, hypercholesterolemia, steroid therapy, and chemotherapy were common among these patients, some of which are compounding risk factors for developing ONJ. The researchers also identified 13,522 patients with a history of alendronate use, of which 32.4% underwent dental extraction. No cases of ONJ were observed in this group of patients.<sup>3</sup>

A similar survey was performed in Australia.<sup>4</sup> The researchers found that frequency of ONJ in osteoporotic patients, most of whom were being treated with once weekly alendronate, was 0.01% to 0.04%.<sup>4</sup> If extractions were carried out, the calculated frequency increased to 0.09% to 0.34%.<sup>4</sup>

These studies are not randomized, placebo-controlled trials. They contained homogenous populations and did not have controls in place for other comorbid conditions. More investigations need to be done before a definite link between alendronate and ONJ can be identified.

Because the risk of ONJ appears highest following dental extractions, practitioners may want to consider performing alternative dental procedures or delaying the initiation of bisphosphonate therapy until all necessary dental work has been performed. If a patient on a bisphosphonate requires a dental procedure, they should be reminded to maintain excellent oral hygiene. Holding the bisphosphonate prior to the procedure will not help, due to the extremely long half-lives of these agents.

Patients should be reassured that the risk of ONJ while on a bisphosphonate is extremely low, but they need to report any signs and symptoms such as pain, swelling, numbness, loose teeth, and dramatic gum loss to their healthcare provider immediately.

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## Acid Suppressing Therapy for Patients Taking Low-dose Aspirin by Jessie Leonard

The use of low-dose aspirin for primary and secondary prevention of cardiovascular and cerebrovascular events is a widely accepted practice. It has been estimated that 50 million Americans use low-dose aspirin for cardio-prophylaxis on a regular basis. The use of low-dose aspirin is associated with a two- to four-fold increased risk for upper gastrointestinal events. Aspirin directly irritates the intestinal mucosa and indirectly damages the intestinal mucosa by inhibition of prostaglandin synthesis.<sup>1,2</sup> It has been hypothesized that use of acid suppressant therapy with low-dose aspirin will decrease the risk of developing gastrointestinal hemorrhage.<sup>2</sup>

A systematic search for studies that assessed the use of low-dose aspirin along with acid suppressant therapy returned four studies. In three of the four studies, all patients had at least one additional risk factor for developing a gastrointestinal hemorrhage. Risk factors include history of peptic ulcer, history of gastrointestinal bleed, history of *H. pylori* infection, age >60 years, and/or concomitant use of drugs known to cause gastrointestinal hemorrhage.<sup>1</sup> Many drugs are associated with increased risk of gastrointestinal hemorrhage, including (but not limited to) corticosteroids, NSAIDs, and anticoagulants.<sup>1</sup>



Occurrence of gastrointestinal hemorrhage and gastrointestinal bleeding rate were the primary endpoints of the four studies identified and overall, the studies produced similar results. The primary outcome was significantly improved in all studies when acid suppression therapy was combined with aspirin. Acid suppressants were dosed once daily and included lansoprazole 15mg, lansoprazole 30mg, omeprazole 20mg, and ranitidine 150mg. Based on the evidence provided, it can not be determined if one proton pump inhibitor or H<sub>2</sub>-receptor antagonists is superior to another.<sup>3,4,5,6</sup> However, similar pharmacology is seen among the agents in these therapeutic classes, and class effect can be assumed. Similar outcomes would be expected when agents in the same therapeutic classes are utilized.

There are a few limitations to the studies evaluated. All had a short-term duration and the effect of long-term acid suppression therapy with low-dose aspirin has not been evaluated. There are a limited number of studies evaluating low-dose aspirin and acid suppression. Only two proton pump inhibitors and one H<sub>2</sub>-receptor antagonist have been reviewed.<sup>3,4,5,6</sup>

In conclusion, acid suppressant therapy can decrease the risk of gastrointestinal hemorrhage in patients at high-risk for developing gastrointestinal hemorrhage. High-risk patients are those with one or more risk factors listed above. Acid suppressant therapy with either a proton pump inhibitor or an H<sub>2</sub>-receptor antagonist at standard dosing should be used for prevention of gastrointestinal hemorrhage in patients at high risk.<sup>3,4,5,6</sup>

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## Study Finds Antidepressants Less Effective in Children with Mild Depression by Jamie Redman

Placebo pills were able to help 48% of depressed children feel better, compared to 59% of children being treated with antidepressants. How can this be explained? A new article from the American Journal of Psychiatry attempts to make sense of this placebo effect. In a meta-analysis done by Bridge et al, the authors compiled the results from all relevant available published and unpublished trial reports (12 in total). After seeing such a high response to placebo in these studies, their goal was to identify factors that could predict placebo response in a pediatric population.<sup>1</sup>

The investigators looked at many potential factors including age, sex, race, number of patients undergoing randomization, number of study sites in a trial, average number of trial participants, duration of treatment, location of study, duration of depressive episode, episode history and severity of illness. Of all these possible predictors, number of study sites, severity of illness and age were correlated with a higher placebo response.<sup>1</sup>

Children enrolled in trials with greater numbers of study sites were more likely to respond to placebo than children enrolled in smaller trials. There was also a correlation between the numbers of sites and severity of illness.<sup>2</sup> This indicates that studies with multiple sites included more patients with mild depression, who would more likely respond to placebo. Another finding was that younger children (<12 years) were more likely to respond to placebo. The authors discovered this after excluding one fluoxetine trial that covered a wide age range and had a small placebo response.<sup>1</sup>

There are some limitations to the study that the authors point out. Since there were a small number of studies, the meta-analysis may have been underpowered to detect a significant difference. Also, the authors were not able to examine factors such as family history of psychiatric disorder and prior non-response to an SSRI. In spite of this, the results still give meaningful information that future trials can build upon.

The authors concluded that placebo response in pediatric depression is correlated with the number of study sites. If trial sites can be restricted to just a few, this can allow for careful selection and screening of participants. Many of the placebo responders were children with less severe or mild depression. This suggests that starting treatment early with an antidepressant might not outweigh the risks involved. These children might benefit from behavioral or psychotherapy instead. Bridge and colleagues say that “since many young patients with an episode of mild depression may respond to brief supportive therapy, future work should aim to identify the level of clinical severity at which first-line treatments with medications, psychotherapy or combination are warranted.”<sup>1</sup>

According to the American Academy of Child & Adolescent Psychiatry, psychotherapy refers to techniques used to help children that have difficulties with emotions or behavior. There are different types of therapy, but all revolve around communication as a base to help children change their behaviors or emotions. Psychotherapy sessions can be just one child, many children, a family or multiple families together. There is communication during sessions, but there could also be child interaction and playing, drawing or pretending. Different strategies can help these children use the therapy in a meaningful way.<sup>3</sup>

Psychotherapy is beneficial because these children learn to understand their feelings, how to deal with problems, and receive support from family or others involved. Psychotherapy benefits children with mild depression because if they can understand their depression and why they feel the way they do, they might not need medication therapy. If this therapy is not effective, medications can always be added at a later time.<sup>3</sup>

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