

Drugs and Devices from 2008 – 2009

That Might Affect Your Practice

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More than 20 New Molecular Entities have been approved by the US Food and Drug Administration in each of the last two years. While not all of them will be prescribed by practicing emergency physicians, several will be in common enough usage that the emergency medicine practitioner needs to know at least something about them. This essay is one person's attempt to present the available literature in an understandable format, with some special comments thrown in. I have absolutely no conflict of interest, apparent or hidden, as I own no stock in drug or device manufacturing concerns. In other words, I don't stand a chance to make a penny from this essay.

Flector® Patch (diclofenac epolamine 1.3%): a patch containing a nonsteroidal anti-inflammatory agent

Diclofenac has been around since 1973, and used as a medication since 1979.¹ The generic name derives from the chemical formula, 2-(2,6-**dichloranilino**) **phenylacetic acid**. Probably the best-known commercially available product in the United States is Voltaren®, but worldwide there are dozens of generic versions available,² and over the counter (OTC) use is approved in some countries for treating minor aches and pains or fever associated with common infections. While the biggest side effects in human beings seem related to the gastrointestinal track, diclofenac is implicated in the near-extinction of several vulture species in India. These flying scavengers who fed on carcasses of domestic cattle and used for traditional Tibetan “sky burials” were dying of kidney failure.³ Since the substitution of miloxicam for diclofenac in Asian veterinary medicine, there has been a mild resurgence in these endangered vulture populations.⁴ (See Sidebar 1)

Flector® Patch is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions, and is supplied in resealable envelopes of five patches each. Each patch contains 180 mg of diclofenac epolamine. Because of direct absorption through the skin into tissues of the joints, serum concentrations achieved with diclofenac is less than 5% of the serum concentrations achieved with orally administered NSAIDs, but concentrations in meniscus and cartilage are generally four to seven times higher than after oral administration, and concentrations in tendon sheath are several hundred times greater than plasma concentrations.⁵

Despite the impressive percentages of tissue drug concentration, these are disease-oriented endpoints rather than patient-oriented. Studies that examine the amount of pain relief offered by topical diclofenac are less optimistic: topical NSAID formulations generally reduce pain scores by 50% at two weeks in about one in five patients with chronic pain like osteoarthritis, and are comparable in efficacy to oral NSAIDs.⁶ But this effect appears not to be sustained beyond two weeks; long-term studies of topical NSAIDs show them to be less efficacious than oral NSAIDs when used beyond two weeks in patients with osteoarthritis.⁷

Sidebar 1: Unintended consequences

The reduced vulture population on the Indian subcontinent poses a potential threat to human health. In many places, populations of feral dogs have replaced Gyps vultures as the main scavengers of wild and domestic ungulate carcasses. With the rise in dog numbers, there is an increased rate of rabies, and casualties now top 50,000 people.* In addition, the loss of vultures has had a social impact on the Indian Zoroastrian Parsi community, who traditionally use vultures to dispose of human corpses in Towers of Silence (“sky burials”)⁺, but are now compelled to seek alternate methods of disposal.[#]

*http://www.newscientist.com/article/mg19926684.400-rabies-tragedy-follows-loss-of-indias-vultures.html?DCMP=ILC-hmts&nsref=news10_head_mg19926684.400, accessed 13 August 2009

#Swan G, Naidoo V, Cuthbert R, et al. Removing the threat of diclofenac to critically endangered Asian vultures. *PLoS Biol.* 2006 Mar;4(3):e66.

+For a photo essay on Tibetan Sky Burials, see <http://www.stewpig.com/weird/viewer-discretion-advised-tibetan-burial-not-for-weak-of-heart-61-photos/2009/09/15/>

Early adaptors of Flector® patches are complaining that the adhesive easily fails and the patches fall off after a brief time, especially when placed over a mobile joint like the ankle or knee, or when the patient sweats profusely. Other people have reported good luck using them on flatter surfaces, such as the pretibial region (for shin splints) or the low back (for acute musculoskeletal strains).

Based on available data, topical NSAIDs seem unlikely to be associated with an increased risk of GI bleeding⁸ or renal failure,⁹ but there is no definitive proof that they are safer than oral NSAIDs. The FDA labeling for Flector® Patch includes the standard NSAID warnings and precautions.¹⁰ I suppose they're worth a try in patients who need some local pain relief and are at risk for the renal and GI side effects of NSAIDs.

Patches cost around \$170 for a one-month supply, about the same as Voltaren® tablets at a dose of 150 mg/day.¹¹

Nucynta™ (tapentadol): an oral analgesic

The July 2009 edition of Emergency Medical Abstracts had an interesting comment in the last few minutes by Jerry Hoffman. He and Rick Bukata were discussing the recent FDA brouhaha (see sidebar 2) over “acetaminophen toxicity,”¹² and the worry that people would overreact and stop taking this drug because of concerns about its safety. Hoffman said, “...the thing that I’m really worried about is...there’s some new analgesic out there that’s going to come on the market in two months (and) this is all in preparation...” What he didn’t know is that it’s already been here for almost a year.

Tapentadol (trade name Nucynta™) is a centrally-acting analgesic approved in 2008 by the FDA. It works as an agonist at the mu-opioid receptor¹³ and as a selective norepinephrine reuptake inhibitor (SNRI).¹⁴ While this dual action may

seem unusual, the SNRI duloxetine (Cymbalta, Yentreve) has long been used as an adjunct in treating chronic pain¹⁵ and the opioid levorphanol (Levo-Dromoran) is well known to have SNRI effects.¹⁶ But the double-receptor

mechanism also means you may have to deal with the side effects of two different medication types. For instance, tapentadol has a theoretical risk of serotonin syndrome and should not be combined with an SSRI (fluoxetine, etc), another SNRI (venlafaxine, etc), or a triptan (sumatriptan, etc).

Tapentadol is being promoted as a novel pain reliever with efficacy somewhere between tramadol and morphine – in other words, for moderate to severe pain. While the website has some very impressive illustrations demonstrating both ascending and descending pathway involvement,¹⁷ it also says that “...(t)he exact mechanism of action of NUCYNTA™ is unknown.”

The FDA approved tapentadol based on results from two randomized, double-blind, placebo and active-controlled clinical trials of patients suffering from moderate to severe pain as a result of first metatarsal bunionectomy or end-stage degenerative joint disease. In the studies, patients treated with tapentadol 50mg, 75mg, or 100mg every four to six hours were found to have significantly greater reduction in pain compared to placebo.¹⁸

Sidebar 2: APAP Black Box??

On 29 and 30 June 2009, the FDA held an advisory committee meeting about how to address the “problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription products.” Acetaminophen is found in many common brand name OTC products such as Tylenol, as well as prescription products such as Vicodin and Percocet. Its effectiveness in relieving pain and fever is widely known. This drug is generally considered safe when used according to the directions on its labeling. But taking more than the recommended amount can cause liver damage, ranging from abnormalities in liver function blood tests, to acute liver failure, and even death. Data from the FDA’s Adverse Event Reporting System (AERS) show that the median daily dose of acetaminophen related to liver injury was 5 to 7.5 grams/day, very near the current maximum daily dose of 4 grams/day. While these occurrences are rare, APAP toxicity has been shown to be the number one cause of liver transplants in the US.*

Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005 Dec;42(6):1364-72.

Table 1: Drug	Dosage	Adverse Events
Tapentadol	25mg	51%
	50mg	82%
	75mg	60%
	100mg	73%
	200mg	92%
Morphine sulfate	60mg	84%
Ibuprofen	400mg	37%
Placebo		49%

Several other clinical trials have also found the efficacy of tapentadol to be noninferior to oxycodone IR 10 mg or 15 mg with a lower potential for gastrointestinal side effects.¹⁹

Late in 2009, a study was published comparing single, oral doses of tapentadol (25, 50, 75, 100, or 200mg), morphine sulfate (60mg), ibuprofen (400mg), or placebo in patients undergoing mandibular 3rd molar (wisdom tooth) extraction.²⁰ While we certainly see many, many people with dental pain, I am not sure that our population is the same as the one studied. There were ~50 patients in each of the 8 study groups. In the five tapentadol groups, the higher doses of tapentadol gave quicker pain relief and more noticeable pain relief than lower doses, but there was also a rise dose-related side effects. The ibuprofen 400mg worked just as well and just as quickly as all doses of tapentadol. At least 1 adverse event was reported for 66% of patients in the study, but most were considered mild or moderate in intensity. I found it interesting (see Table 1) that fewer patients had side effects from ibuprofen 400mg (37%) than with placebo (49%) – a 12% absolute reduction of side effects!! Also, the use of a single dose of pain medicine does not match what we generally do in the emergency department.

In addition, the drug is trying to position itself in the market as a “longer acting, safer tramadol” – and yet no direct comparison to tramadol has yet been published. And tramadol is a non-scheduled drug, meaning that the FDA does not consider it to have potential for addiction and misuse. (see **Table 2**)

When the drug company Johnson & Johnson received approval for this drug in November 2008, it did not even have a brand name (proprietary name) ready for this drug – Nucynta™ was only announced in April 2009. In addition, the company hoped for at least a Schedule III listing, meaning that a prescriber could write, phone, or fax a prescription, making it more convenient to be used. Instead, the FDA approved tapentadol for Schedule II, meaning that a written prescription must be presented to the dispensing agent before the drug can be dispensed.²¹

Personally, I don't see any reason to prescribe this drug. It offers no benefits over currently-available non-opioid analgesics, has a horrible side-effect profile, and will initially cost US\$3 – 4 per tablet.²²

Table 2

- * **Schedule I:** Illegal drugs such as LSD and heroin
- * **Schedule II:** Drugs with significant addictive potential, including narcotics such as oxycodone and meperidine
- * **Schedule III:** Drugs which have some potential for abuse, such as hydrocodone
- * **Schedule IV:** Drugs which have low potential for abuse but may lead to physical or psychological dependence, including the benzodiazepines
- * **Schedule V:** Drugs that have been determined to have low abuse potential, and have been designated for regulation by individual states or localities, such as buprenorphine

Massachusetts designates an additional category of controlled substances. This sixth category includes all prescription medications that are not already covered in Federal Schedules I – V:

- * **Schedule VI:** Medications such as penicillin, cimetidine, and ibuprofen

Relistor® (methylnaltrexone): an injection for opioid-induced constipation

More and more patients are getting aggressive end-of-life care in order to keep them in a comfortable home environment and out of hospital. This may involve use of opioid pain medicine to manage the pain of cancer, end-stage cardiomyopathy, or other terminal illnesses. A common side effect – and a common reason for visiting the Emergency Department – for these patients is constipation and the discomfort that goes along with it.

Opioids induce bowel dysfunction through several expected effects: blockade of propulsive peristalsis, inhibition of the secretion of intestinal fluids, and an increase in intestinal fluid absorption. Opioids decrease the activity of both excitatory and inhibitory neurons in the myenteric plexus. In addition, they increase smooth muscle tone and inhibit the coordinated peristalsis required for propulsion, leading to disordered, nonpropulsive contractile activity, which contributes to nausea and vomiting as well as constipation.^{23,24,25}

Methylnaltrexone is a mu-opioid-receptor antagonist similar to the opioid antagonist naltrexone. It binds to the same receptors in the gut that the opioid painkillers bind to, preventing the opioid-induced constipation described in the previous paragraph. However, the analgesic effects of opioids mostly occur in the brain and are unaffected, as the methyl branch does not allow substantial crossing of the blood-brain barrier.

Methylnaltrexone is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. It is administered as a subcutaneous injection every other day, and is moderately successful in maintaining laxation. But, as an off-label indication, it may be useful in the patient who presents to the Emergency Department with severe opioid-induced constipation. You won't know right away whether it is going to work, although the median time to response in those on whom it did work was four hours.²⁶ (see Table 3).

Time to laxation	Placebo n = 52	Methylalntrexone 0.15 mg/kg (n = 47)	Methylalntrexone 0.30 mg/kg (n = 55)
Within 4 hours	15%	62%	58%
Within 24 hours	33%	68%	64%
Median time	>24 hours	70 minutes	45 minutes

Caldolor® (ibuprofen): an injectable NSAID for pain and fever relief

While the rest of the world has had access to numerous parenteral forms of non-steroidal anti-inflammatory drugs (NSAID) for years, an injectable form of ibuprofen was first approved in the US only in 2009, and the full-page advertisements are already blossoming in many Emergency Medicine journals. Before you jump on the bandwagon, take a close look: the indications for using this drug are incredibly small, and may be nonexistent.

The publications supporting this drug are incredibly unimpressive. One study²⁷ of 406 patients undergoing elective single-site orthopedic or abdominal surgery who were on Patient Controlled Analgesia (PCA) and who received ibuprofen 800 mg, ibuprofen 400 mg, or placebo. The primary end-point was “morphine use in the first 24 hours after surgery.” Pain reduction was a secondary endpoint. I was puzzled by this lack of a patient-oriented outcome until one of my residents pointed out that “to find out if the patient has less pain you actually have to see and talk with the patient; morphine doses can be copied from a chart.” Of course.

Despite this bizarre endpoint and despite trying to baffle the reader with off-putting sentences like “(t)he assumptions of ANCOVA were assessed for the Box-Cox-transformed data, and it was determined, based on the Kolmogrov-Smirnov test for normality, that the data violated the assumption of normality,” the final outcomes weren’t terribly impressive. Median, but not mean, morphine dose was reduced in patients receiving 800mg of intravenous ibuprofen. And instead of using the standard Visual Analog Scale (VAS) of 0 to 10, they used a “VAS AUC,” or Area Under the Curve, scale. So “pain with movement” in the first 24 hours after surgery was 111.9 ± 40.7 for the morphine + 400 mg ibuprofen group, 106.3 ± 43.9 for the morphine + 800 mg ibuprofen group, and 123.3 ± 46.0 for the morphine plus placebo group. I don’t have the faintest idea what that means, but it’s statistically significant.

I see no reason to use Caldolor® in the Emergency Department. Oral ibuprofen works fine for most patients, both for pain relief and for antipyresis, with a ceiling analgesic dose of 400 mg.^{28,29} (See sidebar 4) Parenteral ketorolac has been shown in several studies to offer no benefits over oral ibuprofen,^{30,31,32} and tends to be used in doses far higher than the apparent ceiling of 10 mg.³³ There are intriguing studies that show rectal absorption of ibuprofen leads to excellent bioavailability, but for now there are no convenient delivery systems.³⁴

Sidebar 4: Ceiling Doses of Analgesics

The analgesic ceiling effect of a drug refers to the dose beyond which there is no additional analgesic effect. Higher doses do not provide any additional pain relief but may increase the likelihood of side effects as well as the cost of treatment. This concept, often disregarded in the treatment of pain in the emergency department, should be carefully considered when using common analgesics such as acetaminophen, ibuprofen, and other NSAIDs. For an essay on this topic, see Motov SM, Ast T. Is There a Limit to the Analgesic Effect of Pain Medications? www.medscape.com/viewarticle/574279, accessed 28 Jan 2010.

Effient® (prasugrel): a platelet inhibitor for acute coronary syndrome

Prasugrel is a prodrug hydrolyzed in the intestine to an active metabolite that inhibits platelet action by binding irreversibly to one of the platelet ADP receptors. It is indicated, along with aspirin, to prevent cardiovascular events post-PCI in acute coronary syndrome patients.

The TRITON-TIMI 38 study compared prasugrel 60 mg, followed by a 10 mg once daily maintenance dose, with clopidogrel 300 mg followed by a 75 mg once daily maintenance dose in 13,000 patients with acute coronary syndrome undergoing PCI.³⁵ Patients also took aspirin 75 mg to 325 mg once daily and could receive heparin or a glycoprotein IIb/IIIa inhibitor, but not warfarin, NSAIDs, and other antiplatelet agents. Prasugrel was started anytime from randomization to within one hour of leaving the cardiac catheterization laboratory, and patients were followed for 15 months. The primary outcome was a composite of cardiovascular death, heart attack, and stroke.

About 2% fewer prasugrel patients met the primary outcome measure (relative risk reduction 19%). (See Table 4) Similar to clopidogrel, the benefit was mainly due to fewer non-fatal MIs (9.7% for clopidogrel vs. 7.4% for prasugrel. Absolute reduction 2.3%, number needed to treat = 43, very similar to the NNT with clopidogrel in

CURE). For every 1000 patients treated, there were 23 fewer MIs with prasugrel compared to clopidogrel; but six more cases of major bleeding.

Another advantage of prasugrel over clopidogrel is the lack of significant drug interactions. While proton pump inhibitors such as omeprazole reduce clopidogrel’s antiplatelet effect by blocking its conversion to its active metabolite, prasugrel’s conversion to its active metabolite does not seem to be affected by pharmacogenetics.³⁶

We may be asked to give this drug to patients going to the cardiac catheterization laboratory but, like clopidogrel, it should NOT be given to patients who will undergo open heart surgery in the next seven days. Patients in TRITON–TIMI 38 were having planned PCIs, but a small number went on to undergo coronary-artery bypass grafting (CABG). Among these, the rate of major bleeding in the prasugrel group was more than four times that in the clopidogrel group (13.4% vs. 3.2%). Cardiac surgeons who have been reluctant to operate on patients receiving clopidogrel will probably find prasugrel even more objectionable.³⁷

Table 4: The Balance of Efficacy and Safety in Selective Subgroups (Note: the percentages printed in the NEJM article ³⁵ are incorrect)				
End Point	Prasugrel	Clopidogrel	Hazard Ratio	P value
History of Stroke or MI				
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke	47/262 (17.9%)	35/256 (13.7%)	1.37 (0.89-2.13)	0.15
Non-CABG-related TIMI major bleeding	14/257 (5.4%)	6/252 (2.4%)	2.46 (0.94-6.42)	0.06
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	57/262 (21.8%)	39/256 (15.2%)	1.54 (1.02-2.32)	0.04
No History of Stroke or MI				
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke	596/6551 (9.1%)	746/6539 (11.4%)	0.79 (0.71-0.88)	<0.001
Non-CABG-related TIMI major bleeding	132/6484 (2.0%)	105/6464 (1.6%)	1.26 (0.97-1.62)	0.08
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	727/6551 (11.1%)	854/6539 (13.1%)	0.84 (0.76-0.93)	<0.001

Other bleeding risk factors include weight less than 60 kg, bleeding predisposition, or use of other medications that increase bleeding risk. Prasugrel carries a “black box” warning regarding bleeding risk, as life-threatening bleeding occurred in 1.3% of patients in TRITON TIMI 38. Fatal bleeding occurred in 0.3% of patients, and major or minor bleeding occurred in 4.5% of patients, and for each death from cardiovascular causes prevented by the use of prasugrel as compared with clopidogrel, approximately one additional episode of fatal bleeding was caused by prasugrel.

So it doesn’t save lives, but it does help prevent the next heart attack in a small number of patients undergoing percutaneous coronary interventions.

Prasugrel is probably best-suited for patients at relatively low risk of bleeding, relatively high risk of cardiovascular events, and/or who take a CYP2C19 inhibitor (e.g., a proton pump inhibitor). Average cost of prasugrel to wholesalers is \$5.45 per tablet, vs \$4.62 for clopidogrel.

Ulesfia® (benzyl alcohol lotion 5%): a treatment for head lice

Yes, I am scratching as I write this. There’s a tendency to do so whenever writing about this topic, or for a brief period after diagnosing a patient with head or body lice. We have several products already on the market to treat this infestation, and now there’s Ulesfia®.

I learned a lot about lice when preparing this essay. For instance, the timing of treatments must take into account head lice maturation; the maximum time as an egg is 12 days, and the shortest possible time of maturing from newly hatched nymph to egg-laying adult is 8.5 days.³⁸ Thus, unless the treatment is ovicidal, a second (and sometimes a third) treatment is necessary in order to kill the newly-emerging nits. Human-to-human transmission occurs through direct contact, as the lice cannot jump or fly. Head lice have plagued humanity since the beginning of recorded time, and many methods of cure have been proposed, from direct removal (“nit picking”) to slathering the scalp and hair with mayonnaise, butter, olive oil, or Vaseline. Chemicals are also used.

Pyrethrin is an extract made from the dried flower heads of *Chrysanthemum cinerariifolium* and *Chrysanthemum coccineum*; it is neurotoxic to lice, but – as eggs have no nervous system – not to eggs; hence, the patient must repeat therapy after all the eggs have ostensibly hatched. Pyrethrum has been used as an insecticide as long ago as 400 B.C. in Persia. Kenya has been the main producer of pyrethrum since 1945.³⁹

Permethrin is a synthetic compound based on the insecticidal components of natural pyrethrins, only more active and less allergenic. It is heat-stable and light-stable and has residual activity for 2 weeks or more. Permethrin is toxic to cats; many have died after being given flea treatments intended for dogs, or through contact with dogs that have recently been treated with permethrin.⁴⁰ Recent studies have linked permethrin exposure to Parkinson's disease, including very small exposures.⁴¹

Malathion is an irreversible cholinesterase inhibitor, and the only preparation currently on the market which is ovicidal.⁴² So far, there is no resistance reported in the US or Canada; in other countries, lice have become resistant. Despite its bad reputation, it is a safe drug in this concentration, even in children 6 or older. But many patients find it objectionable due to its odor,⁴³ prolonged (8 to 12 hour) application time and especially its flammability (no hair dryer or curling iron for several hours after applying it). Its cost makes it prohibitive for use by some patients.

Lindane is an organochlorine insecticide (as is DDT) which is stored in adipose and nerve tissue of humans and other mammals; it is banned for use in California⁴⁴ due to concerns about contamination of drinking water, rivers, lakes, fish and wildlife from the rinse-off of head lice treatment,⁴⁵ and the FDA has issued a public health advisory on its safety due to the occurrence of neurotoxicity including seizures.⁴⁶

Ivermectin is approved for treating onchocerciasis (river blindness) and strongyloidiasis, but has been used off-label for treating head lice when all other therapies have failed. It is not ovicidal. No controlled studies have been published, but anecdotal reports indicate that it is effective and resistance has not been reported. A topical ivermectin is being studied,⁴⁷ but is not yet approved for usage.

And now we have Ulesfia,[®] which uses the mayonnaise / olive oil principle of smothering the lice. Benzyl alcohol in low concentration is used in intravenous medications as a bacteriostatic preservative. In healthy individuals, it is oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. High concentrations can cause respiratory failure, vasodilation, hypotension, convulsions, and paralysis. Newborns, especially if critically ill, may not metabolize benzyl alcohol as readily as adults.

Ulesfia[®] is benzyl alcohol as a 5% solution in lotion. The benzyl alcohol prevents the lice from closing their respiratory spiracles: the spiracles become blocked with the other products in the lotion, and the lice asphyxiate. In fact, the company is using a cartoon of an asphyxiating louse as its logo. The lotion does not work against louse eggs, so a second application a week or so after the first is necessary. It appears to be effective about 75% of the time. One concern is its high price – up to US\$31 per bottle – and the need for several bottles depending on the length of a patient's hair. For hair more than 22 inches long, 6 bottles are recommended, with two separate treatments, for a total cost of more than US\$350. There's a lot of chatter on the Pharmaceutical Representative blogs about how the drug should be called "Useless" instead of Ulesfia,⁴⁸ but at least one state is convinced that it's a safe, effective, viable alternative to the products already on the market, and they have approved its payment by state Medicaid office.⁴⁹

See Table 5 for a comparison of pediculicides currently approved in the US.

Table 5: Drug	Ovicidal	Resistance	Dosage	Cost
Benzyl alcohol lotion 5%: Ulesfia [®]	No	No	Apply to dry hair for 10 min then rinse; repeat 7 days later	\$31 per bottle; hair 22 inches long may require 6 bottles
Pyrethrins w/ piperonyl butoxide shampoo	No	Yes	Apply to dry hair for 10 min, then repeat 7-10 days later	Rid: \$6 A-200: \$5 Pronto Plus: \$6
Permethrin 1% creme rinse	No	Yes	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	Generic: \$8 Nix: \$9
Malathion 0.5% lotion	Yes	Not in US	Apply to dry hair for 8-12 hrs, then shampoo; repeat 7-9 days later if necessary	Generic: \$150 Ovide: \$160
Lindane 1% shampoo	No	Yes	Apply to dry hair for 4 min, then rinse; do not repeat	Generic: \$137
Ivermectin tablets	No	No	200-400 mcg/kg PO once	Stromectal: \$11

Uloric® (febuxostat): a treatment for gout

Gout is known as “the disease of kings” or “rich man’s disease.” It affects about 1% of Western populations at some point in their life, with an estimated 3,000,000 to 5,000,000 cases in the US. Attacks cause acute inflammatory arthritis with a red, tender, hot, swollen joint. For acute gout, an NSAID or colchicine is first-line therapy. If the patient cannot take or tolerate NSAIDs or colchicine, then corticosteroids are recommended.⁵⁰ Nonpharmacological interventions such as changing diet, reducing alcohol intake, and losing weight should also be implemented. Thiazide diuretics, long accepted as a risk factor, are now being questioned and may not play the role once thought.⁵¹

Traditionally, allopurinol (Zyloprim®) has been used chronically to lower serum uric acid levels, but side effects (GI intolerance, rash) sometimes limit its usefulness. Physicians are reluctant to prescribe doses greater than 300 mg daily, although the FDA has approved allopurinol in doses up to 800 mg daily.⁵² A recent study shows that patients who do not respond to the 300 mg daily dose can be accelerated to 600 mg daily without fear of harmful side effects.⁵³ Dose adjustments due to renal insufficiency can result in inadequate control of uric acid levels.⁵⁴

Some of the sensitivity reactions seen with allopurinol are attributed to the purine structure of both the parent and the active metabolite, oxypurinol.⁵⁵ Uloric (febuxostat) is a nonpurine selective inhibitor of xanthine oxidase, and has a completely different structure from allopurinol. It is the first new drug to be approved for treating gout in more than 40 years.⁵⁶ In large studies, febuxostat 40 mg daily is comparable to allopurinol 300 mg daily and febuxostat 80 mg daily is more effective than allopurinol 300 mg daily in reducing uric acid levels to the goal level of <6 mg/dL.⁵⁷ Note that the studies used only a 300 mg dose of allopurinol, which has drawn criticism in several commentaries.^{58,59,60}

Astonishingly, the studies show no difference in a patient-oriented endpoint such as number of gout flares or reduction of pain; rather, they use the surrogate endpoint of uric acid reduction as a primary outcome. Gout flare reduction has not been an end point in any trials comparing allopurinol and febuxostat.

While febuxostat is a more selective xanthine oxidase inhibitor than allopurinol, it’s still not known if it will offer more effective control of gout flares. Cost of the two agents also differs significantly: Uloric 40 mg and 80 mg cost about \$160.00 per month, while generic allopurinol costs less than \$16.00 for a month’s supply of 300 mg tablets. For now, you can consider febuxostat for patients who don’t tolerate or respond to allopurinol, but there’s no way it should be a first-line agent.

Vibativ® (telavancin) – an antibiotic with Gram positive activity

The prevalence of vancomycin-resistant enterococcus (VRE) has increased to around 25% of enterococcal isolates over the past 20 or so years since it was first isolated.⁶¹ Increasing vancomycin resistance of MRSA (methicillin-resistant *Staphylococcus aureus*) is also an evolving problem.⁶²

The past ten years has seen the development of several drugs to fight this emerging resistance, and I’ve mentioned them all in previous editions of this essay: quinupristin / dalfopristin (Synercid® - apparently no longer available), linezolid (Zyvox® - www.Zyvox.com), daptomycin (Cubicin® - see www.cubicin.com), and tigecycline (Tygacil® - www.Tygacil.com). The bad news is resistance to all has been reported.

Now we have telavancin, the first lipoglycopeptide approved in the US, for the treatment of skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including methicillin susceptible and –

Sidebar 4: Vitamin C and Gout

Vitamin C is thought to decrease uric acid reabsorption in the kidney’s proximal tubule. A recent prospective cohort study evaluated vitamin C intake and risk of gout in 46,994 men over a 20 year period by using validated questionnaires every four years. Compared with men whose vitamin C intake was less than 250 mg per day, absolute risk reductions of gout incidence associated with doses of vitamin C 500 mg to 999 mg, 1000 mg to 1499 mg, and 1500 mg per day or more were 27, 51, and 69 cases per 10,000 persons per year, respectively.* Vitamin C doses should be limited to 2000 mg per day with adequate fluid intake, as high doses of vitamin C may lead to an increased risk of osmotic diarrhea and gastrointestinal upset and kidney stone formation in patients with renal impairment or history of kidney stones.

* Choi HK, Gao X, Curham G. Vitamin C intake and the risk of gout in men. *Arch Intern Med* 2009;169:502-7.

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resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, or *Enterococcus faecalis* (vancomycin-susceptible isolates only). It inhibits bacterial wall synthesis and disrupts bacterial cell membrane function.

Telavancin is highly protein bound (93%), has a large volume of distribution (115 mL/kg) and a half-life of approximately eight hours, so once daily treatment is adequate.⁶³ It is eliminated renally, and a dosage reduction is required in renally impaired patients.⁶⁴ It binds to a reagent used in anticoagulation testing and can cause a false increase in prothrombin time, INR, activated partial thromboplastin time, activated clotting time, and coagulation based factor Xa tests, but does not affect actual coagulation. Blood samples for these tests should be collected right before a dose of telavancin is given, when blood levels are lowest, to minimize interference.⁶⁵

Adverse effects include metallic taste, nausea, vomiting, headache, foamy urine, Q-Tc-interval prolongation, hypokalemia, and serum creatinine increases. Although there are no data on human pregnancies after exposure to telavancin, it has caused reduced fetal weights and fetal malformations (phocomelia) in animals and is therefore Pregnancy Category C. A black box warning advises that all women of childbearing potential have a serum pregnancy test prior to administration of telavancin, and that telavancin be avoided in pregnant patients unless the benefit to the mother outweighs the risk to the fetus. There is a pregnancy registry (phone 888-658-4228) for telavancin to monitor outcomes of women exposed during pregnancy. There is no data as to the presence of telavancin in breast milk.

Telavancin will be useful when limitations of other drugs or resistance to other drugs comes into play. For instance, linezolid can cause bone marrow suppression and has some important drug interactions (i.e., MAOIs and serotonergic agents, etc).⁶⁶ Daptomycin can cause myopathy⁶⁷ or neuropathy. Tigecycline has activity against gram-negative organisms and might provide broader coverage than desired for some infections.

As with its cousin vancomycin, telavancin can cause the “red man syndrome” – upper body flushing, urticaria, pruritus, or other rash – when infused rapidly.⁶⁸ While not a true IgE-mediated allergic reaction, “red man syndrome” can be disturbing to the patient and treating physician alike.⁶⁹ Telavancin costs about the same as daptomycin, linezolid, or tigecycline, about \$150 to \$200 a day average wholesale price.

Multaq® (dronedaron) – a new anti-dysrhythmic agent to prevent atrial fibrillation

There are three objectives when managing patients with atrial fibrillation: rate control, rhythm control, and prevention of thromboembolism.⁷⁰ According to the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, there is no difference in mortality or stroke rate between patients assigned to rate control or rhythm control.⁷¹ The RACE (Rate Control vs. Electrical cardioversion for persistent atrial fibrillation) trial found rate control noninferior to rhythm control for prevention of death and morbidity.⁷² Treatment decisions for the management of atrial fibrillation should be made based on patient characteristics and symptoms. If the initially chosen strategy is unsuccessful at improving patient symptoms, the alternate strategy is then adopted.

Dronedaron is a new anti-dysrhythmic agent with a very narrow target audience. The FDA approved it for reducing the risk of cardiovascular hospitalization in patients with a history of paroxysmal or persistent atrial fibrillation or atrial flutter, and with a recent episode of atrial fibrillation or flutter and associated cardiovascular risk factors (e.g., age >70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter >50 mm or left ventricular ejection fraction [LVEF] <40). It is to be used in patients who are currently in sinus rhythm or will be cardioverted⁷³ and is not approved to convert someone from atrial fibrillation or flutter.

Like its older cousin amiodarone, dronedaron has anti-dysrhythmic properties of all four Vaughan-Williams classes (Class I - sodium channel blockade; Class II - beta-blockade; Class III - potassium channel blockade; Class IV - calcium channel blockade), but the contribution of each of these properties to its clinical effect is unknown.

The new drug application (NDA) for dronedaron was originally submitted to the FDA in 2005, but was rejected due to an increased mortality rate found in patients with heart failure. The ANDROMEDA⁷⁴ trial (Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease) was a randomized, placebo controlled study of more than 600 patients with a depressed left ventricular ejection fraction (LVEF <35%) and decompensated heart failure (NYHA Class II-IV). About 40% of the patients also had atrial fibrillation. The study was terminated early as a result of the doubling death rate in the dronedaron group compared to placebo (8.1% vs. 3.8%).⁷⁵

Next came the ATHENA trial (A Trial to assess the efficacy of dronedaron 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter), which included more than 4000 patients in normal sinus rhythm and recent history of atrial fibrillation or flutter within the

last six months. Patients were randomized to receive either dronedarone 400 mg twice daily or placebo for 30 months.⁷⁶ ATHENA⁷⁷ showed that dronedarone reduced the combined endpoint of cardiovascular hospitalization or death from any cause from 39.2% to 31.6%, so 13 patients had to be treated with dronedarone to prevent one case of cardiovascular hospitalization over 21 +/-5 months,⁷⁸ but there was no evidence that dronedarone reduced mortality.

Finally, DIONYSOS⁷⁹ (Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) pitted dronedarone head-to-head against amiodarone in more than 500 patients looking at both safety and efficacy. Compared to amiodarone, dronedarone was less effective for maintenance of sinus rhythm but was better tolerated, associated with significantly less adverse effects, and less prone to premature discontinuation. The composite primary endpoint of recurrent atrial fibrillation or withdrawal due to intolerance or lack of efficacy at 12 months was 75.1% in the dronedarone group and 58.8% in the amiodarone group.⁸⁰ Patients treated with dronedarone had significantly fewer thyroid adverse events (1.2% vs. 7.8%) and neurological adverse events (1.2% vs. 9.4%) compared to amiodarone. Amiodarone caused more QT prolongation (20.5% vs. 10.9%) and bradycardia than dronedarone. There were more reports of GI distress (diarrhea, nausea) in patients taking dronedarone.⁸¹

Not that you will prescribe dronedarone, but it costs about four times as much as amiodarone – US\$200 monthly vs. US\$50 monthly. Its exclusionary criteria make it far less useful than you might anticipate, but certainly safer than amiodarone.

The Barf Bib®

This is one of those brilliant ideas, like the Zerowet®⁸² splash shield that makes me smack my forehead that I didn't come up with it first. I'll bet First Responders all over the world will jump on using this – a one-gallon virtually indestructible plastic bag that slips over the neck of the vomiting patient and keep stomach contents of the wall, floors, equipment, and personnel. The cost is reasonable – US\$20 for 10 bags, and worth every penny in the proper situation. They're not a big presence yet, but check out their website at www.thebarfbibcompany.com/ (with pictures!!).

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¹² <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm168830.htm> - accessed 15 August 2009.

¹³ The prototypical mu receptor agonist is the opium alkaloid morphine.

¹⁴ A norepinephrine reuptake inhibitor is also known as an adrenergic reuptake inhibitor. It blocks the action of the norepinephrine transporter (NET), leading to increased extracellular concentrations of norepinephrine and epinephrine and therefore an increase in adrenergic neurotransmission.

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