

SOME DRUGS FROM 2010 THAT MIGHT CHANGE YOUR PRACTICE

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Although more than a dozen New Molecular Entities (NMEs) were approved by the FDA in 2010, most of them will have little impact on the practice of emergency physicians. Nonetheless, many will affect our patients. While I don't expect you to prescribe Pradaxa®, Exalgo®, or Vivitrol®, you need to be aware of their indications, possible adverse effects, and maybe even the potential consequences of overdose. Some of these drugs are already being promoted to emergency practitioners as “the latest and greatest.” Here's my take on several of them.

Pradaxa® (dabigatran etexilate mesylate) – for risk reduction of stroke and embolism due to atrial fibrillation

Warfarin has been around for more than 60 years. It derives its name from the Wisconsin Alumni Research Foundation where much of the original research was done; its –arin ending is from coumarin, a plant molecule that produces dicoumarol.¹ In the early 1920s, there was an outbreak of a previously unrecognized cattle disease in the northern United States and Canada. Cattle were bleeding to death after minor procedures (dehorning, castration), and on some occasions, spontaneously. Frank Schofield, a Canadian veterinary pathologist, determined in 1921 that the affected cattle were ingesting moldy silage made from sweet clover.² Only spoiled sweet clover hay produced the condition. In 1929, North Dakota veterinarian L.M. Roderick demonstrated that the condition was due to a lack of functioning prothrombin.³ In 1933 Karl Paul Link and his lab of chemists at the University of Wisconsin set out to isolate and characterize the hemorrhagic agent from the spoiled hay. They determined that the anticoagulant was 3,3'-methylenebis-(4-hydroxycoumarin), which they named dicoumarol.⁴ They confirmed their results by synthesizing dicoumarol and proving that it was identical to the naturally occurring agent. It was introduced as a rat poison in 1948, but approved for therapeutic human use in

1954; one of its first recipients was President Dwight Eisenhower, as he recovered from a heart attack in 1955.⁵

Warfarin is best suited to prevent clots in areas of slowly-running blood, such as veins or blood pooled behind artificial and natural valves, or in dysfunctional cardiac atria. It is far less effective at preventing new thromboses in arteries, where antiplatelet drugs work much better (warfarin normally has no effect on platelet function).⁶ For a list of currently available and investigational antiplatelet drugs, anticoagulant drugs, and fibrinolytic drugs, see Table 1.

Table 1: Antithrombotic Agents Available in the US

Antiplatelet drugs	Glycoprotein IIb/IIIa inhibitors	abciximab (ReoPro®), tirofiban (Aggrastat®), eptifibatide (Integrilin®)	
	ADP receptor / P2Y12 inhibitors	<i>Thienopyridines</i> : clopidogrel (Plavix®), prasugrel (Effient®), ticlopidine (Ticlid®)	
	Prostaglandin analogue (PGI2)	beraprost, prostacyclin, iloprost (Ventavis®), treprostinil (Tyvaso®)	
	COX inhibitors	aspirin, aloxiprin, carbasalate, indobufen, triflusal	
	Thromboxane inhibitors	<i>Thromboxane synthase inhibitors</i> : dipyridamole (Persantine®), picotamide <i>Thromboxane receptor antagonist</i> : terutroban	
	Phosphodiesterase inhibitors	Cilostazol (Pletal®), dipyridamole (Persantine®), triflusal	
Anticoagulants	Vitamin K antagonists (inhibit II, VII, IX, X)	<i>Coumarins</i> : acenocoumarol, coumatetralyl, dicoumarol, ethyl biscoumacetate, phenprocoumon, warfarin (Coumadin®) <i>1,3-indandiones</i> : clorindione, diphenadione, phenindione	
	Factor Xa inhibitors	Heparin group	<i>Low molecular weight heparin</i> : bemiparin, certoparin, dalteparin (Fragmin®), enoxaparin (Lovenox®), nadroparin, parnaparin, reviparin, tinzaparin (Innohep®) Heparin, unfractionated <i>Oligosaccharides</i> : fondaparinux (Arixtra®), idraparinux <i>Heparinoid</i> : danaparoid (Orgaron®), sulodexide, dermatan sulfate
		Direct Xa inhibitors	<i>Xabans</i> : apixaban, betrixaban, edoxaban, otamixaban, rivaroxaban (Xarelto®)
	Direct thrombin (II) inhibitors	<i>Bivalent</i> : hirudin (bivalirudin (Angiomax®), lepirudin (Refludan®), desirudin) <i>Univalent</i> : argatroban, dabigatran	
	Other	REG1, defibrotide, ramatroban, antithrombin III, activated protein C (drotrecogin alfa [Xigris®])	
Fibrinolytics / thrombolytics	<i>Plasminogen activators</i> : r-tPA (Alteplase®, Reteplase®, Tenecteplase®), UPA (Urokinase®, Saruplase®), streptokinase, anistreplase, monteplase		
	<i>Other serine endopeptidases</i> : anicrod (Viprinex®), fibrinolysin		
Non-medicinal	citrate, EDTA, oxalate		

Anticoagulation with warfarin is known to prevent strokes in patients who are diagnosed with atrial fibrillation, but in clinical practice only 51% of eligible patients receive warfarin.⁷ Fewer than half of those are controlled within the narrow therapeutic range.⁸

For years, the pharmaceutical industry has been looking for the “holy grail” – a drug that prevents strokes but which sidesteps the inconveniences and safety issues of warfarin, with its narrow therapeutic window. In 2006, the drug ximelagatran (Exanta®), another direct thrombin inhibitor set to displace warfarin, had its application for approval withdrawn by AstraZeneca after reports of hepatotoxicity during trials. It was also taken off the market in countries where it had already been approved and was in use, including Germany, Portugal, Sweden, Finland, Norway, Iceland, Austria, Denmark, France, Switzerland, Argentina and Brazil.⁹

Dabigatran, pronounced da BIG a tran, (Pradaxa® in Europe and USA, Pradax® in Canada) is a “direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.”

The hype for Pradaxa® started long before the drug was approved, as manufacturer Boehringer-Ingelheim ran “informational” commercials about atrial fibrillation before the drug hit the shelves of pharmacies. In Canada, which approved use of the drug shortly after the US approval, atrial fibrillation guidelines already recommend its use instead of warfarin.¹⁰

What you will hear quoted is the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.¹¹ It was a huge study of more than 18,000 atrial fibrillation patients (mean age 71 years) followed for a median of two years. Dabigatran in doses of 110 or 150 mg twice daily was compared with adjusted-dose warfarin once daily to achieve an INR between 2 and 3. The primary outcome was stroke (hemorrhagic or ischemic) or systemic embolism. Results are shown in Table 2.

Table 2			
Two-year events	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
Stroke / systemic embolism	1.71%	1.54%	1.11%
Hemorrhagic stroke	0.38%	0.12%	0.10%
Major bleeding	3.57%	2.87%	3.32%
Myocardial Infarction	0.64%	0.82%	0.81%

Notice that the number needed to treat (NNT) to prevent one stroke in two years is 167 ($1.71 - 1.11 = 0.6$. $100\% / 0.6 = 167$). We do not know if dabigatran use beyond two years prevents more strokes...or causes more bleeds. The NNT to avoid one hemorrhagic stroke is 357.

Dabigatran etexilate is rapidly absorbed and converted to the active form dabigatran, reaching a serum peak in about 1 hour after oral administration. Steady state is reached after only 2 or 3 days of therapy. It is excreted mainly in the urine, with a half-life of 12 to 17 hours. Unlike warfarin, there is no effective antidote in case of bleeding or emergency surgery, but it is dialyzable.¹² Dyspepsia and gastritis were the most common reasons for drug discontinuation.

One potentially big downside is that dabigatran deteriorates when exposed to air; the expiration date for tablets is 30 days after the bottle is first opened. The manufacturer recommends that the tablets remain in the bottle, rather than being placed in “pill containers” used by so many patients. Warfarin is not so fragile. This inability to keep dabigatran with other medications may affect compliance.

Also unlike warfarin, dabigatran does not require dose adjustment or close monitoring. Interestingly, RE-LY used doses of 110 mg and 150 mg, but the only approved doses in the US are 75 mg and 150 mg. Both are to be taken twice daily, with the lower dose reserved for patients with $\text{CrCl} > 30 \text{ mL/min}$. You will hear arguments that despite the higher cost (US\$6.50 for the daily two 150-mg capsules of dabigatran), use of this drug will save money because it requires no careful monitoring of blood levels. But the cost of warfarin + monthly INR monitoring is only US\$60.

So far, dabigatran is approved only for prevention of thromboembolic stroke in patients with non-valvular atrial fibrillation. There will no doubt be many off-label uses suggested. Several studies have already shown dabigatran to be non-inferior to low-molecular weight heparin in post-hip and knee replacement DVT prophylaxis.¹³ If you're a believer in tissue plasminogen activator use for acute ischemic stroke, you better think twice if the patient takes dabigatran – there are no data to suggest either efficacy or safety.

Is it a good thing or a bad thing that we can't check a level? I don't know; we can't check levels on blood pressure meds, psychotropic meds, and many many others categories of drugs. I do know that since my neurology colleagues have started switching their seizure patients from drugs we can measure (phenytoin, carbamazepine, divalproex) to drugs we cannot

measure [levetiracetam (Keppra®), lacosamide (Vimpat®)], I am limited in my options when a patient presents to the ED after experiencing a seizure. They are obviously subtherapeutic, but what are my choices? I don't have an answer. What if a patient purportedly taking dabigatran presents with a swollen leg or breathlessness? I not only have no way to confirm that they are appropriately anticoagulated, I don't even have a way to prove they are taking the medication.

We do know that at recommended therapeutic doses, dabigatran prolongs the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and thrombin time (TT). ECT is most reliable, but generally unavailable. With an oral dose of 150 mg twice daily the median peak aPTT is approximately 2x control, but there is poor linear relationship between drug dose and aPTT. Twelve hours after the last dose the median aPTT is 1.5x control, with less than 10% of patients exceeding 2x control. In the RE-LY trial, the median (10th to 90th percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds. The median (10th to 90th percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds. The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients taking dabigatran.

Exalgo® - hydromorphone extended release tablet for patients with opioid-tolerant pain

Hydromorphone is the common synonym for dihydromorphinone and dimorphone. It is a potent centrally-acting opioid analgesic on mu receptors, derived from morphine as a hydrogenated ketone. In medical terms, it is an opioid analgesic; in legal terms, a narcotic.

Hydromorphone was synthesized and researched in Germany in 1924 and introduced to the mass market in 1926

under the brand name Dilaudid, indicating its derivation and degree of similarity to morphine

Sidebar 1: Hydrocodone (Vicodin®, whose name is derived from the Roman Numeral VI, since it is six times more potent than codeine – 5mg hydrocodone = 30mg codeine) is converted to hydromorphone by the same hepatic cytochrome P450 enzyme CYP2D6 that converts codeine to morphine. CYP2D6 poor metabolizers (~10% of the Caucasian population) have a reduced capacity for this metabolic pathway, and so might receive a reduced analgesic benefit from the drug. However, the pharmacodynamic profile of the drug in these individuals indicates that the effects of hydrocodone are largely independent of its conversion to hydromorphone.

(laudanum, aka tincture of opium). It is prescribed around the world under many trade names: Dilaudid, Hydral, Sophidone, Hydrostat Hydromorfan, Hydromorphan, Laudicon, Hymorphan, Opidol, and others. An extended-release version of hydromorphone called Palladone® was available for a short time in the US before being voluntarily withdrawn from the market after a July 2005 FDA advisory warned of a high overdose potential when it was taken with alcohol.¹⁴ A “dose dumping” effect caused patients to get up to six times the intended dose, with concomitant respiratory depression and even death.

Like Palladone®, Exalgo® is an extended-release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time.^{15, 16} Patients are considered opioid tolerant if they take at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg of oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg of oral oxymorphone/day or an equianalgesic dose of another opioid, for a week or longer.

The tablet uses OROS® (Osmotic-controlled Release Oral delivery System) technology¹⁷ to slowly release the drug over 24 hours. A semi-permeable membrane allows water to get into the tablet as it passes through the gastrointestinal tract, changing the drug to a gel suspension which is slowly pushed through a laser-drilled hole on the other side of the tablet as the osmotic layer expands. This constant release allows for once-daily dosing,¹⁸ but requires that the tablet be swallowed whole in order to prevent a potentially fatal overdose. The tablet itself is not actually dissolved, so the patient may see a “ghost tablet” in the stool.¹⁹ Simultaneous ingestion with alcohol causes an increase of serum hydromorphone levels of ~30%, but this does not appear to be clinically significant.

Exalgo® is one of a handful of opioids that require a Medication Guide. These MedGuides are part of the larger Risk Evaluation and Mitigation Strategy (REMS) that the FDA began implementing

Sidebar 2: On 13 November 2009, the Director of the Ohio Department of Rehabilitation and Correction outlined changes applied to the execution process in Ohio. A press release (www.drc.ohio.gov/public/press/press342.htm), explains the new policy:

“The previous method of execution included a three-drug protocol applied intravenously. The first change to the execution procedure includes the adoption of a one-drug protocol, using thiopental sodium alone, applied intravenously. Pancuronium bromide and potassium chloride will no longer be used as a part of the process. *In the event that an IV site cannot be established or maintained, then I have authorized the use of an intramuscular injection of midazolam and hydromorphone as a back-up means of carrying out the execution.*” (Emphasis mine)

in 2007 to ensure that the benefits of a drug outweigh its risks.²⁰ A new formulation of OxyContin was recently approved and will also require a MedGuide to ensure safe use of the product.

Depending on the dose, Exalgo® costs about US\$15 per day, compared to ~US\$2.25 for an equivalent dose of immediate-release hydromorphone. Fentanyl patches average US\$11 per day, oxycodone ER averages US\$9 per day, and MS Contin is about US\$10 per day.

ella® - ulipristal acetate, a non-hormonal emergency post-coital contraceptive

Emergency contraception is intended for occasional use, when primary means of contraception fail. They are drugs that act both to prevent ovulation or fertilization and possibly post-fertilization implantation of an embryo. They are distinct from medical abortion methods that act after implantation.

Until now, most post-coital pregnancy prophylaxis was managed with hormonal therapy. The progestin-only method uses levonorgestrel 1.5 mg, either as two 750µg doses 12 hours apart, or more recently as a single dose. In the USA, Canada and Honduras it is known as Plan B; in Great Britain, Australia, and other countries as Levonelle; in South Africa as Escapelle, in 44 other countries as NorLevo; and in 44 more countries as Postinor-2. In general, a woman is fertile during a limited time period, from about five days before ovulation to about one day after ovulation. Levonorgestrel inhibits pregnancy by altering ovulation. If given 48 hours prior to the leuteinizing hormone surge, it delays or inhibits ovulation.²¹ Once levels of leuteinizing hormone have begun to increase, levonorgestrel has no inhibitory effect. Levonorgestrel does not appear to affect the endometrium or the fallopian tubes. This pill typically works up to 72 hours after intercourse. When taken within 24 hours of sexual intercourse, levonorgestrel prevented 95% of expected pregnancies. This effectiveness dropped to 85% at 25 to 48 hours, and 58% when taken within 49 to 72 hours.²²

The combined or Yuzpe regimen uses large doses of both estrogen and progestin, taken as two doses at a 12-hour interval. This method is believed less effective and less well-tolerated than the progestin-only method. The same dosage of hormones and the same effect can be

achieved by taking several regular combined oral contraceptive pills. The United States Food and Drug Administration approved this off-label use of certain brands of regular combined oral contraceptive pills in 1997.²³

Ulipristal acetate (ella® in the USA, ellaOne in the European Union) is a selective progesterone receptor modulator (SPRM) for emergency contraception up to 120 hours (5 days) after an unprotected intercourse or contraceptive failure.²⁴ Ulipristal is effective even when administered immediately before ovulation when leuteinizing hormone has started to rise. When given prior to the leuteinizing hormone surge, ulipristal inhibits 100% of follicular rupture, thereby leading to inhibition or delay of ovulation. When given after leuteinizing hormone has begun to increase, follicular rupture failed to occur within five to six days after treatment in 44% to 59% of patients. When administered on the day at which leuteinizing hormone has peaked, ulipristal has been shown to delay ovulation by 24 to 48 hours. Bottom line: women who have unprotected intercourse have about 1 chance in 20 of becoming pregnant; Plan B® within 3 days reduces this to 1 in 40, and ella® within 5 days reduced it to 1 in 50.

It's a chemical cousin to mifepristone (RU-486, Mifeprex®), leading some people to incorrectly label it an “abortion pill.” In the USA, high-dose mifepristone combined with misoprostol (Cytotec®) is used for the medical termination of pregnancy; the dose equivalent of ulipristal acetate in ella® is one-twentieth that of mifepristone. In China, low doses of mifepristone are used as an emergency contraceptive.

Unlike levonorgestrel, but like mifepristone, ulipristal acetate is embryotoxic in animal studies, so pregnancy must be ruled out before taking the drug. Of the 29 study women who became pregnant despite taking ulipristal acetate, 16 had induced abortions, six had spontaneous abortions, six continued the pregnancies, and one was lost to follow-up.²⁵

After taking ulipristal acetate, the most common side effects are headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%), and dizziness (5%). If the patient vomits the tablet within three hours of ingestion, she should get another dose.²⁶

You have to let the patient know that ulipristal will probably change her menstrual cycle, and that menses may occur either a few days earlier or later than expected. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than seven days earlier than expected,

and 19% reported a delay of more than seven days. If there is a delay in the onset of expected menses beyond one week, suggest testing for pregnancy.²⁷

Teflaro® - ceftaroline, a “fifth generation” cephalosporin antibiotic

Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu,²⁸ but the first agent cephalothin (Keflin®) was not launched until 1964.

Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls, which is important for cell wall integrity. Hence, they are bactericidal and have the same mode of action as other beta-lactam antibiotics like penicillins, but are less susceptible to penicillinases.

The 1st generation cephalosporins have activity against penicillinase-producing, methicillin-susceptible staphylococci and streptococci, but no activity against methicillin-resistant *Staphylococcus aureus* (MRSA) or enterococci. Their Gram negative activity is limited to *Proteus mirabilis*, some *Escherichia coli*, and *Klebsiella pneumoniae* ("PEcK"); they have no activity against *Bacteroides fragilis*, Pseudomonas, Acinetobacter, Enterobacter, indole-positive Proteus, or Serratia.

Successive generations of cephalosporins have increased activity against Gram negative organisms, but frequently at the expense of Gram positive coverage (See Table 3). In general, all cephalosporins cover all penicillin-sensitive organisms with the exception of Listeria and Pasteurella. Coverage for group B streptococci is better with penicillin than with cephalosporins.

Table 3: Some Cephalosporins Commonly Used in the United States

Generation	Some Common Names	Gram positive coverage	Gram negative coverage
1 st	Cefadroxil (Duricef) Cephalexin (Keflex) Cephalothin (Keflin) Cefazolin (Ancef, Kefzol)	Methicillin-susceptible staphylococci and streptococci	PEcK <i>Proteus mirabilis</i> , some <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i>
2 nd	Cefaclor (Ceclor) Cefuroxime (Zinacef) Cefotetan (Cefotan) Cefoxitin (Mefoxin) Loracarbef (Lorabid)	Less than first generation, but generally adequate	HEN <i>Haemophilus influenzae</i> , <i>Enterobacter aerogenes</i> some Neisseria + PEcK as above
3 rd	No anti-pseudomonal activity Cefdinir (Omnicef)	• Less than 1 st generation, but	• Increased activity against

	Cefixime (Suprax) Cefotaxime (Claforan) Ceftriaxone (Rocephin) Antipseudomonal activity Cefoperazone (Cefobid) Ceftazidime (Fortaz)	generally adequate <ul style="list-style-type: none"> • Oral forms and those with anti-pseudomonal activity have decreased activity against Gram positive organisms. • Can penetrate blood-brain barrier: useful for pneumococcal and <i>H. influenzae</i> meningitis. 	Gram-negative organisms. <ul style="list-style-type: none"> • Can penetrate blood-brain barrier: useful against meningitis caused by meningococci, susceptible <i>E. coli</i>, Klebsiella, and penicillin-resistant <i>N. gonorrhoeae</i> • Since 2007, ceftriaxone and cefixime only recommended treatment for gonorrhea in the United States.
4 th	Antipseudomonal activity Cefepime (Maxipime) Cefpirome (Cefrom)	Similar to 1 st generation	<ul style="list-style-type: none"> • Greater resistance to beta-lactamases than 3rd generation • Many can cross blood-brain barrier • Useful against <i>Pseudomonas aeruginosa</i>.
5 th	Ceftaroline (Teflaro)	Skin and soft tissue: Methicillin-resistant <i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i> <i>Klebsiella oxytoca</i> <i>E. coli</i>

While the classification of cephalosporins into “generations” is common, it is imprecise. In Japan, cefaclor is a 1st generation cephalosporin, but in the United States it is 2nd generation. The 4th generation of cephalosporins is not recognized as such in Japan, but cefoxitin is classed as 3rd generation. In practice, the usefulness of this organization system is of limited clinical relevance.²⁹

Ceftaroline³⁰ is the first so-called 5th generation cephalosporin released in the US. In its intravenous form, it is approved for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI).

The Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients (FOCUS 1 and 2) studied patients hospitalized (but not admitted to an intensive care unit) with Pneumonia Outcomes Research Team (PORT) risk class III or IV. They were randomized to ceftaroline 600 mg every 12 hours or ceftriaxone 1 gram every 24 hours for 5–7 days. Patients in FOCUS 1 also received two doses of oral clarithromycin 500 mg every 12 hours on day 1. A responder was defined as a patient who on Day 4 of therapy had normalized vital signs and improved from baseline on at least one respiratory symptom (cough, dyspnea, pleuritic chest pain, or sputum production) while not worsening on any of these four respiratory symptoms. In FOCUS I, the 4 day response rate for Teflaro-treated patients was 69.6%, compared with 58.3% for ceftriaxone-treated patients. In addition, clinical cure rates at

the test of cure (TOC; 8-15 days after end of therapy) were 86.6% in the ceftaroline group compared with 78.2% in ceftriaxone-treated patients.³¹ Their conclusion was that the new, twice a day, expensive drug is non-inferior to a familiar, once daily, inexpensive drug.

I find the inclusion and exclusion criteria very interesting. To be included in the study, you had to show ≥ 3 clinical signs or symptoms of lower respiratory tract infection [new or increased cough, purulent sputum or change in sputum character, auscultatory findings consistent with pneumonia (eg, rales, egophony, findings of consolidation), dyspnea, tachypnea, or hypoxemia (O_2 saturation $\leq 90\%$ on room air or $pO_2 \leq 60$ mm Hg)], temperature $\geq 38^\circ C$ or $\leq 35^\circ C$, WBC count $\geq 10,000$ cells/ mm^3 or ≤ 4500 cells/ mm^3 , $\geq 15\%$ immature neutrophils (bands) irrespective of WBC count. Notice that “positive chest x-ray finding of pneumonia” was NOT an inclusion requirement. Also note that a WBC count $\geq 10,000$ cells/ mm^3 was high enough to get you included in the study (at my hospital, this is a normal white count), as was a temperature $\geq 38^\circ C$ (PORT requires $\geq 39.9^\circ C$).

Also interesting were exclusion criteria. It was a “Goldilocks” study:³² a PORT Score of III or IV was required to be included. If you weren’t sick enough (PORT I or II) or you were too sick (PORT V), you were excluded. You were also excluded if you were admitted to the ICU, or had empyema, or had any of numerous concomitant comorbidities.

And while ceftaroline is approved for treating ABSSSI caused by suspected MRSA, it is NOT approved for suspected pneumonias caused by the same organism. I have not yet seen a cost, but I can’t see it costing less than ceftriaxone (IV piggyback premixes cost about \$36 for a 1 gram dose).

Ceftaroline versus Vancomycin in Skin and Skin-Structure Infection (CANVAS I and CANVAS II) trials evaluated ceftaroline monotherapy versus vancomycin plus aztreonam in adult patients with complicated skin and skin structure infections caused by Gram-positive and Gram-negative bacteria. Included were ABSSSI patients with either a major abscess with ≥ 5 cm of surrounding erythema, wound infection, or deep/extensive cellulitis requiring treatment with IV antimicrobials; a responder was defined as a patient who on Day 3 achieved both cessation of lesion spread and absence of fever. Ceftaroline-treated patients had a response rate of 74% compared with a response rate of 64.6% for vancomycin plus aztreonam-treated patients. Using predetermined test of cure protocols at 8-15 days after the end of therapy, ceftaroline-treated

patients had a clinical cure rate of 91.1% compared with a rate of 93.3% in vancomycin / aztreonam-treated patients.³³

I do not foresee a major shift in the drugs I use to treat CABP and ABSSSI. While it may be an alternative treatment for patients who cannot tolerate one of the standard therapies, I do not recommend a change in practice. If you can find your copy of December 2010 ACEP News, check out the “news article” on page 27. It is essentially a press release for ceftaroline. Interestingly, there’s a full-page ad for the drug earlier in the issue.

Can we use a 5th generation cephalosporin in a patient who states he’s allergic to penicillin? As far as the so-called “10% cross reactivity between penicillin and cephalosporin,” I think that rumor has been debunked. Because of emerging resistance to broad-spectrum antibiotics, this is an important question. If we can use cephalosporins for appropriate infection, we can reduce the use of vancomycin by up to 95% and fluoroquinolones by up to 96%.³⁴

The literature is pretty clear that less than 10% of people who say they are allergic to penicillin actually are allergic. In one study 132 patients who gave a history of immediate reaction to penicillin and were tested by radio-allergosorbent test (RAST) and only four were found to be truly allergic. The other 128 patients were given an oral penicillin challenge without ill effect.³⁵

The recent classic study by Apter et al.³⁶ showed that if you were allergic to penicillin there was a 1.1% of having an allergic event after exposure to cephalosporin, BUT there was a 1.6% chance of having an allergic event after exposure to a sulfonamide. In other words, people who are allergic to things tend to be allergic to other things, but there seems to be no cross-reactivity between penicillin and the cephalosporins.

Ofirmev® - injectable acetaminophen preparation

This one is a bit of a head scratcher. Intravenous preparations of acetaminophen (APAP) have been available in virtually every part of the world for almost a decade, except for the United States. The Ofirmev® approval comes eight years after the first approval of IV APAP in France, which was followed by other European countries; more than 80 countries have approved the formulation since its introduction. In Europe, under brand name Perfalgan®, it has become the market and unit share leader among injectable analgesics, with approximately 90 million units

sold, or approximately \$250 million in product sales, in 2008. This corresponds to an estimated European market share of 20% of all injectable analgesic units, and an estimated 45% market share of all injectable analgesic dollar sales.³⁷

Cadence Pharmaceuticals quietly got their product approved by the FDA in late 2010, but it was so low-key that many ER docs, including me, initially missed it. It is approved for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever, just like its oral counterpart.

N-acetyl-para-aminophenol serves as the source for the common abbreviation APAP. The chemical name para-acetylamino-phenol gives the origin for other common names (para-ACETylAMINOPHENol – para-aceTYLaminophENOL – PARA-aCETylAMinophenOL). APAP is lethal to snakes³⁸ and extremely toxic to cats (which lack glucuronyl transferase enzymes),³⁹ but only mildly toxic to dogs.⁴⁰

The World Health Organization (WHO) recommends that APAP be given to children with fever higher than 38.5°C (101.3 °F). While it is probably subject for an essay in itself, the first question is “Why treat fever?” Fever appears to have developed as an adaptive response with net benefit to the febrile host.⁴¹ Studies nearly 40 years old showed that survival from Gram-negative sepsis was directly related to the height of patient temperature on the day that sepsis was diagnosed.⁴² Children infected with varicella who received antipyretics take longer for the primary lesions to crust over.⁴³ Numerous other articles demonstrate limited, if any, benefit to treating fever, although most clinicians agree that an afebrile patient feels better. And, no, antipyretic therapy does not prevent febrile seizure.⁴⁴

Assuming that there are times we want to treat a fever, but we are concerned about oral absorption, the rectal route seems to work just fine. In children, a rectal APAP loading dose of 40 mg/kg followed by 20 mg/kg every 6 hours maintains serum concentrations in the target range of 10-20 mcg/ml, with no evidence of toxic accumulation.⁴⁵ In adults, there is surprisingly little data, but a suggestion of lower bioavailability requiring higher doses.⁴⁶ For this reason, it is my practice to “double dose” with suppositories, giving 1300mg, although I have no articles to back this choice.

Ofirmev® is being promoted, mostly to anesthesiologists, as a safe, effective post-operative antipyretic and pain medication.⁴⁷ It appears to have a very rapid onset, reaching a clinical analgesic effect within five minutes of administration.⁴⁸ It also seems to have a faster

onset of temperature reduction than acetaminophen administered orally.⁴⁹ IV APAP has also been shown to achieve higher maximum concentration (C_{max}) and earlier time to maximum concentration (T_{max}) than bioequivalent oral or rectal formulations with less intrasubject variability.⁵⁰ At no time does the C_{max} approach the accepted toxic level of 150 mcg/ml.

Regardless of route of delivery, the terminal elimination half-life of APAP is approximately 2 to 4 hours in children, adolescents, and adults. It is slightly longer in infants and neonates and is longer still in premature neonates.⁵¹ APAP is metabolized by the liver via glucuronidation (~85%), sulfation, and oxidation; this metabolism is not dependent on the route of administration.⁵²

Adverse reactions are rare (<1 in 10,000), and are usually mild and transient. The safety profile is similar to that of placebo.⁵³

Should we use this new intravenous APAP? Ask yourself honestly: how many times have you said, “Gee, I wish I had an intravenous formulation of acetaminophen.” It does not appear that cost will be prohibitive, although comparison with the European market may be misleading. In 2008, the average selling price in Europe was ~US\$2.85 per vial of intravenous APAP, but this is largely driven by government-controlled reference pricing in those markets. In Scandinavian countries with less restrictive pricing controls, the average Perfalgan selling price is as high as US\$10.42 per vial. For comparison, ketorolac prior to generic competitors was approximately US\$7.00 per vial. Intravenous ibuprofen (Caldolor®) was US\$10.50 per 800 mg vial at launch in 2009.⁵⁴

Despite the company’s optimistic projections, I do not see this becoming a blockbuster. And if you figure out where they came up with the name Ofermev®, please let me know.

SPRIX™ (ketorolac tromethamine) – nasal spray for short-term treatment of pain

So now that we’ve got oral, rectal, and intravenous pain medicines covered, let’s talk about the nose. All non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-inflammatory, and antipyretic activities, but each agent has its own efficacy and safety profile; some NSAIDs are predominantly analgesics, while others have stronger anti-inflammatory

effects. Ketorolac tromethamine is a potent analgesic, but only a moderately effective anti-inflammatory drug. It was approved for intramuscular and intravenous use in the US in 1989, and is used primarily for symptomatic relief of moderate-to-severe pain.

Concerns over a high incidence of reported side effects led to its withdrawal in several countries, while in others its permitted dosage and maximum duration of treatment were reduced. From 1990 to 1993, at least 97 fatal outcomes were reported worldwide from ketorolac due to allergic reactions, acute renal failure, gastrointestinal bleeds, and other side effects.⁵⁵ Despite its availability in 30mg and 60mg vials, the maximum pain relief seems to be reached with a parenteral dose of 10mg.^{56,57}

Use of intranasal ketorolac has been studied for at least 17 years,⁵⁸ but a product did not reach market until 2010. In recent years, the intranasal route has been used for delivery of many molecules, both small (dihydroergotamine, metoclopramide, butorphanol tartrate, sumatriptan succinate) and large (vitamin B12, vasopressin, calcitonin). Delivery of intranasal drugs is limited by local tissue irritation, rapid removal from the site of absorption, and pathologic conditions (cold, allergies) that may alter the nasal bioavailability. While potentially more irritating, powder formulations usually have several advantages over liquid formulation. The chemical stability of a drug is increased in powders; preservatives may not be required; and larger amounts of the drug and excipients can be administered.⁵⁹ In the case of ketorolac, a liquid preparation of ketorolac tromethamine in microcrystalline cellulose at pH 5.95 was best absorbed, with a bioavailability of 91% and a time to maximum concentration (T_{max}) of 30 minutes (compared to 100% absorption with T_{max} 5 minutes for the intravenous formulation.)⁶⁰

Side effects are the same as oral and parenteral preparations: GI distress, bleeding, renal impairment, increased risk of cardiac and cerebral thrombotic events, and the rare case of anaphylaxis.

Now here's where it gets weird. SPRIX™ comes in a 1.7 g bottle that contains 8 doses of 15.75 mg per 100 µL spray. Maximal dose over 24 hours is 126 mg; that's two 15.75 mg spritzes in each nostril every 6. And if you feel better after one dose and don't need any more, that's too bad, because the manufacturer recommends you discard the bottle within 24 hours of taking the first dose, even if it still contains some medication. Cut the dose in half for patients older than 65 or with impaired renal function. The dose for children is unknown.

This drug was approved in 2010, but has not yet been released to the public and I am unable to find the cost. If the cost is reasonable, there might be a rare occasion when I would prescribe this inhalational pain med, but I would need to see a few post marketing studies before I changed my practice.

Vivitrol® - Extended-release naltrexone injection for treatment of opioid dependence

Since The Joint Commission made pain management a standard in 2001, the use of opioids in the United States has gone up 20-fold, and drug overdose deaths have gone up more than five times.⁶¹ During 2008, 4.6% of people over 18 admitted to taking a prescription pain reliever for non-medical use.⁶²

Naltrexone is the N-cyclopropylmethyl derivative of oxymorphone (Numorphan). It reversibly blocks or attenuates the effects of opioids at mu- and kappa-opioid receptors.⁶³ This is the basis behind its action in the management of opioid dependence, and it is used to prevent backsliding by people who have been addicted to opioids but have withdrawn and wish to avoid recidivism. Plasma half-life of oral naltrexone is about 4 hours, but is 13 hours for its major metabolite 6-β-naltrexol. Hence it requires dosing 2 or 3 times daily.

Since 1992, it is also known to be effective for the treatment of alcoholism; a number of studies have confirmed its efficacy in reducing frequency and severity of relapse to drinking.⁶⁴ Although “plausible pseudoscience” dictates that it should be very successful in helping people stay away from addictive substances, the success rate is a disappointingly low 20% to 30% over six months.⁶⁵ It is most effective for those in whom there is an external incentive to stay clean, such as health care professionals, business executives, or probation referrals, where success rates are higher than 80%.⁶⁶

Vivitrol® is a long-acting naltrexone preparation available in a single-use carton containing a 380 mg vial of naltrexone microsphere powder, syringe, and needles. In 2006 it had been approved for treatment of alcohol dependence. In 2010, the FDA approved its use in treating opioid-dependent patients. It can't be started until the patient has been detoxed from

opioids (including tramadol) for seven to ten days from their last opioid dose.⁶⁷ Withdrawal can occur if there are opioids in the patient's system when the drug is started.

Vivitrol joins Suboxone®, Subutex®, ReVia®, and methadone as another option for treating opioid dependence. It costs ~US\$1100 per month, compared to oral naltrexone (~US\$100 per month), Suboxone (~US\$430 per month), and methadone (~US\$60). Another drawback is that patients must be opioid-free prior to initiation, which can be a huge challenge for many.

If a patient who takes Vivitrol® suffers a traumatic injury, treating the associated pain will be a challenge, since the antagonistic effects precludes the usual use of opioids. Alternative medications may include NSAIDs (injectable ketorolac or ibuprofen), local anesthesia, or regional analgesia;⁶⁸ and don't forget about ketamine.⁶⁹

Table 4: Some other new drugs you may encounter in your patients

Proprietary	Generic Name	Indication
Atelvia	Risedronate	Delayed-release bisphosphonate taken AFTER breakfast.
Axiron	Testosterone	Topical solution formulation for underarm application.
Beyaz	Drospirenone / ethinyl estradiol / levomefolate	Oral contraceptive (similar to YAZ) which also contains folate.
Butrans	Buprenorphine	Transdermal patch for moderate to severe chronic pain.
Dulera	Mometasone / formoterol	Combination steroid / long acting beta-agonist inhaler for asthma.
Jalyn	Dutasteride / tamsulosin	Combination of a 5-alpha-reductase inhibitor and an alpha-blocker for treatment of benign prostatic hyperplasia (BPH).
Kombiglyze XR	Sitagliptin / metformin	Combination product for treatment of type 2 diabetes.
Krystexxa	Pegloticase	Uric acid-specific enzyme for chronic refractory gout.
Latuda	Lurasidone	Atypical antipsychotic for schizophrenia.
Menveo	Meningococcal vaccine	Vaccine to prevent meningococcal disease caused by <i>Neisseria meningitidis</i> serogroups A, C, Y, and W-135 in persons 11 to 55
Oravig	Miconazole	Buccal tablet formulation for oropharyngeal candidiasis.
Prenar 13	Pneumococcal 13-valent conjugate vaccine	Vaccine to prevent <i>Streptococcus pneumoniae</i> -related infections in children 6 weeks through 5 years.
Staxyn	Vardenafil	Orally disintegrating tablet formulation for erectile dysfunction.
Suprep	Sodium / potassium / magnesium sulfate	Osmotic laxative bowel prep kit for colon cleansing prior to colonoscopy.
Tekamlo	Aliskiren / amlodipine	Combination renin inhibitor / calcium channel blocker
Tribenzor	Olmesartan / amlodipine / hydrochlorothiazide	Combination ARB, calcium channel blocker, and diuretic
Victoza	Liraglutide	GLP-1 agonist to improve glucose control in type 2 diabetes.
Vimovo	Naproxen / esomeprazole	NSAID/PPI combination for arthritis patients at risk of NSAID-associated gastric ulcers.
Zortress	Everolimus	Immunosuppressant for prevention of organ rejection (kidney)
Zuplenz	Ondansetron	Oral soluble film formulation for prevention of nausea and vomiting.
Zymaxid	Gatifloxacin	0.5% ophthalmic solution for bacterial conjunctivitis.

As always, I welcome your comments and suggestions: Joseph.Lex@TUHS.Temple.edu.

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