MARK DRUGS ROSELLE
Better Health and Care, Not Just Healthcare!

www.markdrugs.com
www.mdnorthshore.com
Roselle
Ph: 630 529-3400
Fax: 630 529-3429
Deerfield
Ph: 847 419-9898
Fax: 847 419-9899

8-11-18

1. Pfizer Stops Sales of Injectable Opioids to Veterinarians
AstraZeneca, Pfizer, Roche, and Johnson & Johnson Being Investigated of Bribing Iraqi Terrorists to Win Contracts

2. Gauging the Efficacy of Pharmacologic Agents for Female Sexual Dysfunction

A New Endocrine Agent for ER+/HER2− Breast Cancer

3. Acupuncture for Joint Pain Associated with Aromatase Inhibitors for Breast Cancer

4. Safety of Anti–Tumor Necrosis Factor Use for IBD During Pregnancy

Advanced Technologies for Treating Large Bile Duct Stones Are Comparably Effective

5. Finally, Actual Data for the FDA-Approved Biomarkers of Traumatic Brain Injury

6. New marijuana-based epilepsy treatment to cost $32,500 a year
Behind Schedule — Reconciling Federal and State Marijuana Policy
8. Parenteral Opioid Shortage — Treating Pain during the Opioid-Overdose Epidemic

Pfizer Stops Sales of Injectable Opioids to Veterinarians

Dogs, cats, and other animals are now without Pfizer's injectable opioids. The company has halted sales of the painkillers to veterinarians until sometime next year. It said it won't resume sales for animal use until the shortage at hospitals and surgical facilities has been resolved, which is not expected before the second quarter of 2019.
https://www.fiercepharma.com/pharma/pfizer-halts-injectable-opioid-sales-to-veterinarians-as-shortages-persist
****

AstraZeneca, Pfizer, Roche, and Johnson & Johnson Being Investigated of Bribing Iraqi Terrorists to Win Contracts

Alleging that certain drug companies paid bribes to terrorists that "openly controlled the Iraqi ministry in charge of importing medical goods," veterans and family member sued the following drug companies last year:

- AstraZeneca,
- Pfizer,
- Roche, and

- Johnson & Johnson.

The plaintiffs contend that the drug companies "obtained lucrative contracts from that ministry by making corrupt payments to the terrorists who ran it."
https://www.fiercepharma.com/pharma/doj-probes-astrazeneca-over-allegations-corruption-iraq

https://www.fiercepharma.com/pharma/roche-johnson-johnson-also-under-justice-department-probe-alleged-terrorist-bribes

****

Obstet Gynecol 2018 Aug; 132:453

Gauging the Efficacy of Pharmacologic Agents for Female Sexual Dysfunction

A meta-analysis finds that much of the benefit seen in trials may represent a placebo effect.

Clinical trials of pharmacologic agents to treat female sexual dysfunction (FSD), which encompasses hypoactive sexual desire, arousal, orgasmic, and sexual pain disorders, have often observed a substantial placebo effect. To assess the extent of this effect, investigators conducted a systematic review and meta-analysis of randomized, controlled trials that used the Female Sexual Function Index (FSI; scored from 0 to 36, with scores below 26.6 indicating dysfunction) as an outcome. The placebo effect on the FSI was compared with each study's treatment effect.

Eight eligible trials included 3,959 women who received placebo or one of the following agents: flibanserin, bupropion, onabotulinum toxin A, intravaginal prasterone, intranasal oxytocin, ospemifene, or bremelanotide. The FSI score improved by 3.62 among women assigned to placebo and 5.35 among women assigned to active treatment, indicating that about two thirds of the improvement noted in these trials represented a placebo effect.

COMMENT: Although female sexual dysfunction is widely prevalent, few pharmacologic treatments are available. The observation that most of the improvement noted in clinical trials is due to a placebo effect may be frustrating for women, clinicians, and researchers looking for effective pharmacologic treatments; it may also illustrate the shortcomings of attempting to treat a multifactorial entity with a single approach. On a more positive note, nonpharmacologic measures — including education, self-monitoring, and counseling — are available and may be of therapeutic value in addressing FSD.

CITATION(S): Weinberger JM et al. Female sexual dysfunction and the placebo effect: A meta-analysis. Obstet Gynecol 2018 Aug; 132:453. (https://doi.org/10.1097/AOG.0000000000002733)

****

Clin Cancer Res 2018 Feb 13; 24:3510

A New Endocrine Agent for ER+/HER2− Breast Cancer

The oral selective estrogen receptor degrader AZD9496 demonstrated activity in heavily pretreated patients.

Whereas recent approaches to hormone receptor–positive breast cancer have focused on combining endocrine therapy with targeted therapies such as CDK4/6 inhibitors and mTOR inhibitors, development of new endocrine agents has been lacking. Preclinical work has shown that AZD9496 — an oral, nonsteroidal, small-molecule inhibitor of ERα — is a selective antagonist and degrader of estrogen receptor (ER) α that decreases expression of the progesterone receptor in models with *ESR1* mutations and causes tumor regression in animal models.

Now, investigators have conducted an industry-sponsored, first-in-human, phase I, dose-escalation, dose-expansion study to test the safety and efficacy of AZD9496 (20 mg 4 times daily, escalated to 600 twice daily) in 45 patients with advanced, ER+/HER2− breast cancer who experienced disease progression after at least 6 months of endocrine therapy (median endocrine treatments, 3). More than half of patients (56%) had received prior treatment with the one approved selective estrogen receptor degrader, fulvestrant, with which the optimal dose necessary to degrade all ER is unachievable owing to the agent's intramuscular administration.

The common causally related adverse events (AEs) were diarrhea (36%), fatigue (31%), and nausea (22%); 7 patients had grade ≥3 AEs. Three patients experienced a dose-limiting toxicity: one each at 150 mg twice daily (abnormal hepatic function), 400 mg twice daily (diarrhea and elevated liver function tests), and 600 mg twice daily (diarrhea), all of which were reversible. One patient achieved a partial response, and four had stable disease at 12 months.

COMMENT: Most patients with breast cancer have ER+ disease. For those who develop metastasis, multiple endocrine options exist, but progression of disease is inevitable. New endocrine agents that are effective and tolerable and that have the potential to confer clinical benefit when drug resistance develops are urgently needed for this large group of breast cancer patients. AZD9496 has shown activity in heavily pretreated patients with ER+ disease, including those who have received fulvestrant. Development of AZD9496 is ongoing.

CITATION(S): Hamilton EP et al. A first-in-human study of the new oral selective estrogen receptor degrader AZD9496 for ER+/HER2− advanced breast cancer. Clin Cancer Res 2018 Feb 13; 24:3510. (https://doi.org/10.1158/1078-0432.CCR-17-3102)

Jordan VC. Tamoxifen resistance trumped and oral selective estrogen receptor degraders arrive. Clin Cancer Res 2018 Apr 19; 24:3480. (https://doi.org/10.1158/1078-0432.CCR-18-0759)

****

JAMA 2018 Jul 10; 320:167

Acupuncture for Joint Pain Associated with Aromatase Inhibitors for Breast Cancer

This nonpharmacologic intervention helped control joint pain.

Aromatase inhibitors (AIs) increase disease-free survival in menopausal women with hormone–receptor-positive breast cancer, but half of such women experience AI-associated musculoskeletal pain that leads to discontinuation of therapy. Does acupuncture reduce joint pain associated with AIs? U.S. investigators at 11 academic sites conducted a blinded trial in which 226 postmenopausal women receiving an AI for early-stage breast cancer who reported pain scores of ≥3 (out of 10) were randomized to true acupuncture, sham acupuncture (shallow needling at non–acupuncture points), or waitlist control (no intervention). Both acupuncture groups received 6 weeks of biweekly acupuncture followed by 6 weeks of once-weekly sessions.

Between baseline and 6 weeks, true acupuncture lowered joint-pain scores more than sham acupuncture (rates of clinically significant 2-point reductions in pain scores, 58% vs. 33%; *P*=0.02) or waitlist control (31%; *P*=0.01). At 12-week follow up, recipients of true acupuncture reported less pain than waitlist controls, but no differences compared with sham acupuncture recipients.

COMMENT: Although these investigators do not say whether acupuncture increased adherence to AIs, their elegant study adds to the scientific literature supporting the benefits of this intervention for pain control. Managing chronic pain remains a clinical challenge; thus, health insurance plans are increasingly covering acupuncture. Given the limited benefits and known risks of narcotics, I often encourage patients with chronic pain to consider trying acupuncture.

CITATION(S): Hershman DL et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: A randomized clinical trial. JAMA 2018 Jul 10; 320:167. (https://doi.org/10.1001/jama.2018.8907)

****

Am J Gastroenterol 2018 Jul 2

Safety of Anti–Tumor Necrosis Factor Use for IBD During Pregnancy

Retrospective data show excess infection risk among pregnant anti-TNF users but not their infants exposed in utero.

The continued use of anti–tumor necrosis factor (TNF) therapy during pregnancy for treatment of inflammatory bowel disease (IBD) is debated, as data on risks are conflicting. In a retrospective cohort study, researchers examined data from approximately 11,000 pregnancies in 8700 women with IBD receiving care under the French national health insurance system. They found that mothers exposed to an anti-TNF agent had a higher risk for infection during pregnancy compared with nonexposed women (adjusted odds ratio, 1.3). In an adjusted subgroup analysis, stopping anti-TNF therapy before the 24th week of amenorrhea was associated with doubled risk for disease relapse compared with continuing therapy beyond that point. No elevated risk for infection was seen in exposed infants at 1 year of age.

COMMENT: Women want to know the risks of IBD therapy on their infants' birth outcomes but also on the pregnancy course itself. That anti-TNFs are relatively safe in children exposed in utero is becoming more evident as outcomes in larger populations are studied. However, maternal health is key to a healthy pregnancy outcome, and this study's finding of elevated maternal infection risk during pregnancy with

continued anti-TNF use is important. This risk needs to be balanced with the increased risk for disease activity with therapy cessation. The infections found were mostly self-limited and community-acquired, and less than half required antibiotics. Given the relatively higher risk for active disease than for infection, and the lack of observed effect on infants, the benefits of continued use of an anti-TNF seem to outweigh the risks.

CITATION(S): Luu M et al. Continuous anti-TNFα use throughout pregnancy: Possible complications for the mother but not for the fetus. A retrospective cohort on the French national health insurance database (EVASION). Am J Gastroenterol 2018 Jul 2; [e-pub]. (https://doi.org/10.1038/s41395-018-0176-7)

****

Endoscopy 2018 Jul 10

Advanced Technologies for Treating Large Bile Duct Stones Are Comparably Effective

Laser lithotripsy had the edge in clinical efficacy, but electrohydraulic and extracorporeal shock wave lithotripsy also performed well.

Approximately 90% of bile duct stones can be removed during endoscopic retrograde cholangiopancreatography via simple biliary sphincterotomy and balloon extraction. The other 10% are typically characterized as “difficult” bile duct stones, usually owing to large size, unusual shape, presence above a biliary stricture, or a combination of these factors. In a recent systematic review and meta-analysis, researchers compared three advanced techniques for removing difficult bile duct stones — electrohydraulic lithotripsy, laser lithotripsy, and extracorporeal shock wave lithotripsy (ESWL).

Based on data from 32 studies (none randomized) comprising nearly 2000 patients, laser lithotripsy had a higher duct clearance rate (95%) compared with electrohydraulic lithotripsy and ESWL (88% and 85%, respectively). Electrohydraulic lithotripsy had the highest postprocedural complication rate at 14% compared with 10% for laser lithotripsy and 8% for ESWL.

COMMENT: Although these findings suggest that laser lithotripsy may be the clinically superior advanced tool for removal of difficult bile duct stones, it is far more expensive to obtain, and few endoscopy labs have ready access to a laser lithotripter. Electrohydraulic lithotripsy is by far the cheapest and most accessible of these three technologies and as such is the most widely used. I find it curious that ESWL was included in this study as it is a nonendoscopic technique, suggesting that, at least to some extent, the authors are comparing apples to oranges. Overall, given that all three techniques had high efficacy, endoscopists should choose a technique based on accessibility and their comfort level in using it.

CITATION(S): Veld JV et al. A systematic review of advanced endoscopy-assisted lithotripsy for retained biliary tract stones: Laser, electrohydraulic or extracorporeal shock wave. Endoscopy 2018 Jul 10; [e-pub]. (https://doi.org/10.1055/a-0637-8806)

****

MARK DRUGS ROSELLE
Better Health and Care, Not Just Healthcare!

www.markdrugs.com
www.mdnorthshore.com
Roselle
Ph: 630 529-3400
Fax: 630 529-3429
Deerfield
Ph: 847 419-9898
Fax: 847 419-9899

Lancet Neurol 2018 Jul 24

Finally, Actual Data for the FDA-Approved Biomarkers of Traumatic Brain Injury

The numbers don't support the hype.

In February, the FDA approved the first blood biomarker test for diagnosis of traumatic brain injury (TBI); it measures ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP). Data submitted to the FDA have now been published.

The prospective industry-funded study enrolled adults at emergency departments in the U.S. and Europe who had a head computed tomography (CT) scan for suspected TBI, initial Glasgow coma scale (GCS) score of 9–15, and blood obtained within 12 hours of injury. CT evidence of injury included intracranial injuries, but also skull and facial fractures, or even scalp injury alone. The biomarker test was considered positive if levels of one or both proteins were above prespecified thresholds.

Of 1959 patients, 125 (6%) had CT evidence of injury but only 8 had injuries the authors considered eligible for surgical intervention. Only 39 patients had GCS scores of 9–13, and 31% of these had injuries. Among all participants, 66% tested biomarker positive. The test had a sensitivity of 97.6% and negative predictive value of 99.6% for injury. The positive predictive value **(PPV)** among patients with GCS 14–15 was only 8.8%.

COMMENT: The authors don't report whether these biomarkers improved the ability to predict injury beyond a validated clinical prediction rule, such as the Canadian Head CT rule. The test had a very low PPV, even though inclusion of extra-cranial injuries, like scalp swelling, would inflate the PPV. The high rate of injuries in patients with GCS scores of 9–13 strongly suggests these patients need immediate head CT and clinicians shouldn't wait for biomarker results. With all this in mind, I recommend using a clinical prediction rule for now and avoiding these biomarkers until we have evidence they can decrease CT use beyond prediction rules alone.

CITATION(S): Bazarian JJ et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): A multicentre observational study. Lancet Neurol 2018 Jul 24; [e-pub]. (https://doi.org/10.1016/S1474-4422(18)30231-X)

Maas AIR and Lingsma HF. ALERT-TBI study on biomarkers for TBI: Has science suffered? Lancet Neurol 2018 Jul 24; [e-pub]. (https://doi.org/10.1016/S1474-4422(18)30275-8)

****

New marijuana-based epilepsy treatment to cost $32,500 a year

Wall Street Journal (08/08/18) Loftus, Peter

GW Pharmaceuticals, the manufacturer of a new marijuana-based treatment for rare types of epilepsy, said Wednesday it will charge approximately $32,500 per patient annually in the United States. The drug, cannabidiol (Epidiolex), received FDA approval in June to treat seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients aged 2 years and older. FDA

has stated that GW Pharmaceuticals' drug does not cause the euphoria that comes from tetrahydrocannabinol, the main psychoactive component of marijuana. According to company CEO Justin Gover, the drug's price was set to be in line with other brand-name epilepsy medications. "We wanted to make sure we were pricing Epidiolex in such a way where the means to access this medication would be consistent with branded epilepsy drugs these patients already use," he said. Julian Gangolli, president of the drug company's North American unit, said in a conference call with analysts that patients' out-of-pocket costs for Epidiolex could be $5-$10 monthly for those in state Medicaid programs, or up to $200 a month for some private insurance plans. Individuals without insurance may be able to obtain the drug free of charge. GW Pharmaceuticals said it plans to make Epidiolex available after DEA assigns it a controlled-substance classification.
https://www.wsj.com/articles/new-marijuana-based-epilepsy-treatment-to-cost-32-500-a-year-1533761758
****

Behind Schedule — Reconciling Federal and State Marijuana Policy

R.L. Haffajee, R.J. MacCoun, and M.M. Mello
N Engl J Med 2018;379:501-504 | Published Online July 11, 2018

The long-standing chasm between federal and state marijuana policy recently widened when U.S. Attorney General Jeff Sessions rescinded Obama-era guidance indicating that the Justice Department would not make it a priority to prosecute federal marijuana crimes in states where the activities are legal. At present, a budgetary amendment is the only legal barrier to Justice Department enforcement of the Controlled Substances Act (CSA) against users and sellers of medical marijuana in the 30 states that have legalized it. Nothing prevents federal prosecution of recreational marijuana activities in jurisdictions where they are legal. However, spurred by Sessions's policy, Senator Elizabeth Warren (D-MA) introduced a bipartisan bill in June 2018 (S.3032) that would exempt most marijuana-related activities from CSA application when they're allowed under state or tribal law — legislation that President Donald Trump says he will support. As the marijuana-policy terrain shifts, it's important to consider the potential public health benefits of closing the federal–state divide.

Controversy over marijuana policy originates from the 1970 federal decision to classify marijuana as a Schedule I substance under the CSA. Schedule I drugs are deemed to have high potential for abuse and no accepted medical use. Crimes involving such drugs can result in penalties of thousands to millions of dollars and substantial prison time. Marijuana's Schedule I classification has been repeatedly challenged in all branches of the federal government (see timeline), but although synthesized versions of some marijuana components, including the psychoactive compound tetrahydrocannabinol (THC), have been rescheduled and approved by the Food and Drug Administration (FDA), the plant as a whole has not. The FDA did recently approve a plant-based product, cannabidiol (CBD; Epidiolex), for the treatment of certain seizures in children.[1] The Drug Enforcement Administration is expected to reschedule CBD so that Epidiolex can be sold legally.

Although the Obama administration did not support rescheduling of marijuana, it signaled in a series of Justice Department memos that it would ease federal marijuana-crime enforcement in some circumstances. This guidance culminated in the 2013 Cole Memorandum, which deprioritized marijuana prosecutions in states where use was legal, indicating that states could proceed with carefully regulating and taxing marijuana. The Rohrabacher–Blumenauer Amendment (previously the Rohrabacher–Farr Amendment), adopted by Congress the following year and currently renewed through September 2018, went further, prohibiting the use of federal funds to prosecute medical marijuana activities.

Encouraged by these developments, states have moved toward marijuana legalization, which more than 6 in 10 Americans now favor, according to a survey by the Pew Research Center. Starting with California in 1996, more than half the states have legalized medical marijuana, and at least three are currently considering doing so. This year, at least six more states are poised to follow the nine states and District of Columbia that have legalized recreational marijuana.

As state legal restrictions have eased and evidence concerning marijuana's medical benefits has accumulated, marijuana use has increased: about 9% of Americans 12 years of age or older used marijuana in 2016, according to the National Survey on Drug Use and Health. Marijuana sales in states where they are legal topped $8 billion in 2017 and are projected to grow to $24 billion by 2025.[2] State revenues from taxes and permits — totaling $745 million in 2017 and used for budget shortfalls, schools, public heath, and law-enforcement programs — are expected to reach $4.3 billion in 2020.[2] In short, state marijuana legalization and industry growth show no signs of slowing.

Sessions's about-face in January introduced new uncertainty. Although marijuana taxes typically account for at most 1% of state general-fund revenues, states' reliance on this money may increase as sales grow. Marijuana businesses face difficulty obtaining federally regulated credit and other banking services because of their precarious legal status.[3]

Such effects could jeopardize the continuity of the medical marijuana supply. In some states, dispensaries are licensed to supply to both recreational and medical users, so action against them or their suppliers shrinks access for all. For patients using marijuana in lieu of potentially riskier alternatives such as opioids, supply reductions could worsen health outcomes. Furthermore, marijuana's Schedule I status is a known hindrance to conducting the research required to secure FDA approval of medical marijuana products; federal funding for such research has been meager, and the federal government has a monopoly on supplying marijuana for clinical trials.

Another threat to medical users is the possibility that Congress will not renew the Rohrabacher–Blumenauer Amendment, leaving prescribers, dispensers, and patients vulnerable to federal criminal enforcement. Ultimately, individual U.S. attorneys' offices will have to decide how to prioritize prosecution of federal marijuana offenses in light of competing demands on their resources — which will exacerbate the unpredictability of marijuana markets. U.S. attorneys have considerable discretion, and though the social climate for prosecuting medical users in particular is not favorable, there are no longer any guarantees.

In addition, the absence of a sensible, stable federal marijuana policy affects the safety of marijuana products and physicians' comfort in recommending or prescribing them. Although the FDA has an approval track for botanicals, only one purified plant-based marijuana product is currently regulated by the FDA.[1] Inconsistency in marijuana regulation from state to state can allow inappropriate marketing, formulation, and packaging practices to persist — making THC content across samples unpredictable, for instance, or permitting marketing of edibles that appeal to children.[4] Without FDA approval, a lack of information about efficacy, dosing, adverse effects, and availability of marijuana products deters providers from recommending them.

The present state of conflicting laws seems unstable and suboptimal for rational drug control. Federal regulation that accommodates and reinforces state medical marijuana regulatory regimes would result in a safer, more reliable, more accessible supply of marijuana products. Congress, because it answers to the people and represents the states, appears the most likely branch to move on marijuana policy; it could even be encouraged to act by Canada's recent legalization of recreational marijuana. Federal courts are increasingly hearing challenges to marijuana's Schedule I status but have so far been unwilling to deem Congress's scheduling determination irrational and therefore unconstitutional.

In Congress, rescheduling marijuana by amending the CSA is one attractive option. The executive branch, too, can reschedule CSA substances,[3] but the mechanisms are time consuming and unlikely to attract interest within the current administration. Because considerable evidence now supports marijuana's therapeutic benefits in reducing chronic pain,

nausea, and vomiting in patients with cancer, as well as multiple sclerosis–related muscle spasms,[5] there is a compelling argument that marijuana is more appropriately designated as a Schedule II or Schedule III drug. Rescheduling would facilitate further study of products for FDA approval, but would not automatically change the severity of penalties for marijuana crimes or alter international treaty obligations, enshrined in the CSA, to ensure that all psychoactive substances are used only for legitimate medical and scientific purposes.[3]
Congress could also remove marijuana from the CSA schedules altogether. This dramatic action could be coupled with legislation authorizing FDA oversight of marijuana products. Whether marijuana's psychoactive effects preclude this move away from regulation as a controlled substance would provoke considerable debate. Subjecting marijuana products to FDA approval would hinder access initially but ultimately foster a robust system for regulation and research. FDA oversight of marketing would also improve product safety and consistent promotion across states.[3]

The Warren legislation represents a third option designed to respect states' rights — codifying the approach articulated in the Cole Memorandum by amending the CSA to exempt marijuana activities that are lawful in the jurisdiction where they occur. This solution would be more permanent than attorney-general guidance or agreements between states and the attorney general regarding enforcement, which shift with the political winds, and would therefore promote stability for medical users and suppliers. But it would not facilitate research into marijuana harms and benefits, bring products within the FDA's purview to ensure safety and efficacy, alleviate interstate health risks, or address potential conflicts with international treaty obligations.

We think this third option, which addresses some pressing conflict-of-law concerns such as unpredictable criminal enforcement, is preferable to the current blurred vision of the future of marijuana policy. Ultimately, a more comprehensive federal regime that perhaps resembles Canada's recent legalization of recreational marijuana could affirmatively promote health and safety through research and regulation.

https://www.nejm.org/doi/full/10.1056/NEJMp1804408?query=TOC
****

Parenteral Opioid Shortage — Treating Pain during the Opioid-Overdose Epidemic

Eduardo Bruera, M.D.

https://www.nejm.org/doi/full/10.1056/NEJMp1807117?query=psychiatry

The opioid-overdose epidemic now causes more than 30,000 deaths per year in the United States. In response to the increasing death toll, many measures have recently been implemented, including reclassification of hydrocodone as a Schedule II opioid and new requirements for physician review of prescription drug monitoring program (PDMP) databases in most states. Guidelines for opioid prescribing have been issued by multiple organizations, including the Centers for Disease Control and Prevention (CDC),[1] and the Surgeon General sent a letter with recommendations to all U.S. physicians. These and other educational and regulatory measures have resulted in a reduction in the quantity of opioids prescribed,[2] but there have been unintended consequences.
Although guidelines from most organizations, such as the CDC, exempt patients with cancer-related pain, the median daily equivalent opioid dose of morphine prescribed by cancer specialists before referral of patients to supportive and palliative care programs decreased from 78 mg per day in 2010 to 40 mg per day in 2015.[3] The types of opioids being

prescribed have also changed, with a significant decrease in the use of Schedule II opioids such as hydrocodone and transdermal fentanyl and an increase in the use of Schedule IV opioids such as tramadol.[3]

These findings are not surprising. Physicians already burdened by frequent and time-consuming denials of payment and preauthorization requirements for opioids from insurers now face the extra burdens of universal screening of patients for risk for nonmedical use of opioids, PDMP database review, more frequent monitoring of opioid use, and sometimes ordering and interpreting of urinary opioid screening tests. Many have opted to use nonopioid agents or Schedule IV opioids, or to refer patients requiring opioids to palliative care or pain specialists.
Against this worrisome background, on February 8, 2018, our cancer-center pharmacy announced that there were severe and immediate shortages of the three most commonly used parenteral opioids: morphine, hydromorphone, and fentanyl. Similar shortages were reported in the vast majority of cancer centers and hospitals in the United States.[4] These shortages resulted from a series of events related to the tightening of government regulations and controls in response to the opioid-overdose epidemic, such as a Drug Enforcement Administration proposal to reduce opioid manufacturing for 2018 by 20%, as well as manufacturing problems in several pharmaceutical companies, including violations in manufacturing practices discovered by the Food and Drug Administration.[4] The opioid shortage is not expected to be resolved in the near future, so hospitals will need to implement mitigation strategies.[4]

The shortage has serious consequences for patients and physicians. Parenteral opioids provide fast and reliable analgesia for patients admitted to the hospital with poorly controlled pain, patients who have undergone painful procedures such as major surgery, and those who were previously on oral opioid regimens but are unable to continue treatment by mouth. Shortages of the three best-known parenteral opioids may increase the risk for medication errors when it becomes necessary to switch a patient to a less familiar drug or to use opioid-sparing drug combinations. Opioids are already among the drugs most frequently involved in medication errors in hospitals. There are also increased risks of delayed time to analgesia and of side effects resulting in unnecessary patient suffering and delayed hospital discharge.

Physicians' burden and stress increase when they are forced to make sudden changes in practice. Pharmacies currently send regular e-mail updates notifying prescribers about which of the three parenteral opioids are or will be unavailable over the next few days. Even for those of us who prescribe opioids daily, it is hard to read and remember all these e-mails. Usually, after a physician orders parenteral opioids (sometimes hours later), the pharmacy will notify the physician that the requested opioid is not available. The physician must then access the patient's medical record, calculate the opioid dose ratio and adjustments for switching to an alternative opioid, try to notify the patient, and write new orders. This process is time consuming and stressful and will further discourage physicians other than palliative care and pain specialists from prescribing opioids.

Most hospitalized patients and almost all patients with cancer need opioids, either on a temporary basis after surgery or painful treatments such as stem-cell transplantation, or longer for cancer-related pain or dyspnea. It is impossible to appropriately treat such a large number of patients unless most physicians are able and willing to prescribe opioids. There were not enough palliative care and pain specialists to meet patient needs before the shortages began, and universal referral of patients who need parenteral opioids will therefore only result in more undertreated pain.
There are some possible clinical alternatives. A series of measures to address the consequences of the opioid shortage for patient care are summarized in the table. The electronic health record (EHR) might help by notifying physicians immediately when the opioid is in shortage and providing information on alternative available opioids and the recommended dose ratio. But all these proposed measures will, at best, be only partially effective in achieving analgesia, and some will result in increased complexity of care and physician burden.

What U.S. patients need is access to parenteral morphine, hydromorphone, and fentanyl. These opioids are 80 to 220 years old, are inexpensive, and can be manufactured with minimal technology. Perhaps for these reasons they are unattractive to manufacturers.

What are some longer-term solutions? The dependence on unreliable manufacturers and an unreliable regulatory environment compromise patients' access to parenteral opioids. Like the strategic oil reserve designed to maintain a national supply, a strategic opioid reserve in all hospital pharmacies and health networks could mitigate the impact of similar episodes in the future.
With minimal regulatory changes, pharmacies in most health care facilities could successfully prepare parenteral opioids from powder. Some midsize Canadian hospitals have successfully prepared solutions of most opioids for decades, at much lower cost than buying them from drug companies.[5]

Unfortunately, the leaders of universities and funding agencies have largely failed to establish and support academic structures aimed at alleviating pain and suffering. Well-supported teams of clinical and translational researchers will probably ultimately discover better pharmacologic and nonpharmacologic therapies to replace centuries-old opioids. Until they do so, however, we can make it a clinical and ethical priority to secure the availability of parenteral opioids for U.S. patients who are in pain.

****
***