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Help! My Patient Needs Opioids, or Do They?

Introduction

The national epidemic of substance abuse naturally imparts uncertainty and fear in the decision-making process regarding the prescribing of opioids for patients in pain. Statistics alone substantiate the need to validate our decisions with a documented plan of care. The burden of deciphering which patients are appropriate for ongoing opioid management typically falls to the primary care provider. How best can we manage our patients safely and ethically? A descriptive step-by-step approach to making the decision to prescribe opioids and managing your patients on opioids will be presented.

Background

Statistics released by the Drug Abuse Warning Network (DAWN) tout the drastic upswing in the abuse of prescription opioids and the related deaths.[1] Emergency departments (ED) in the United States reported a 156% increase in the non-medical use of opioids from 2004-2010. (*See Table 1.*) In 2010, the misuse or abuse of drugs accounted for 46.8% of all ED visits related to adverse drug events. The most common drugs of abuse included oxycodone, with a 255% increase, and hydrocodone, with a 149% increase. During the same time period, benzodiazepine abuse increased 139%.

The Centers for Disease Control and Prevention (CDC) has reported equally disturbing data. In the United States, 100 people a day die in the United States from drug overdoses, a rate of death that has tripled since 1990.[2] For every four deaths that occur due to prescription drugs, three are related to prescription opioids. The 2009 National Youth Risk Behavior Survey revealed that one in five high school students have taken a prescription drug that has not been prescribed for them,[3] while one in 20 people ages 12 and older have admitted to using a prescription opioid within the past year for purely recreational reasons.[4] A reported 12 million people in the United States use prescription opioids for the euphoric effect vs pain relief. The abuse of methamphetamines, marijuana, cocaine, steroids, and even alcohol has shown a decline in the time period from 1999-2009.[5]

While our nation battles the abuse of prescription opioids, the prescribing of these medications has drastically increased. As the population lives longer, with coexisting aging issues related to pain, the demand for analgesic medications increases. The rise in obesity also contributes to the development of chronic pain related to stress on joints and the back. According to the CDC, in the last 15 years, the prescribing of opioids has increased tenfold.[6] In 2010, there were enough opioids prescribed to medicate "every American adult around the clock for one month."[7] History reveals that an increase in the availability of a drug increases the risk for abuse.[8] Responsible prescribing of opioids, coupled with risk mitigation strategies, has never been more paramount.

Opioid demand has increased as the number of patients with chronic pain has become more prevalent; in fact chronic pain has reached epidemic proportions.

Executive Summary

- The most rapidly increasing drugs of abuse are prescription opioids.
- Twenty-six percent of the U.S. population over the age of 20 experiences chronic pain,[10] increasing the demand for prescription opioids.
- The decision to initiate opioids for longer than 3 months should include screening for abuse potential, initiation of an opioid treatment contract, checking available prescription databases, and a risk/benefit discussion with the patient.
- An opioid "trial" for pain control should be followed up with frequent monitoring for plan adherence, aberrant behaviors, random urine drug testing, and measurement of functional improvement.

Table 1: Drugs with Increasing Involvement in Emergency Department (ED) Visits for Drug Misuse or Abuse: 2004-2010

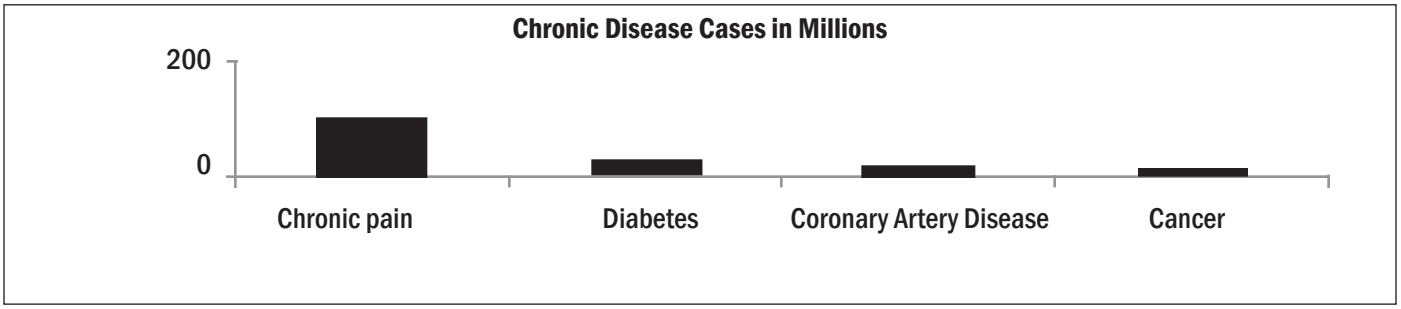
Drug	ED Visits, 2004	ED Visits, 2010	Percent Change 2004 to 2010*
Illicit Drugs	**991,640**	**1,171,024**	**NC**
Marijuana	281,619	461,028	64%
MDMA (Ecstasy)	10,227	21,836	114%
Pharmaceuticals	**626,472**	**1,345,645**	**115%**
Anti-anxiety and Insomnia Drugs	210,711	472,769	124%
Benzodiazepines	170,471	408,021	139%
Antipsychotics	41,930	69,149	65%
CNS Stimulants (e.g., ADHD Drugs)	10,656	31,507	196%
Muscle Relaxants	29,014	58,783	103%
Pain Relievers	282,275	659,969	134%
Narcotic Pain Relievers	166,338	425,247	156%
Hydrocodone Products	46,536	115,739	149%
Oxycodone Products	51,418	182,748	255%

*Percent change is measured as difference in the estimated number of visits between 2004 and 2010. Reported changes are significant at the .05 level; "NC" signifies no significant change.
Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

The American Chronic Pain Association describes chronic pain as "… ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, and which adversely affects the individual's well-being."[9] Chronic pain affects approximately 100 million adults in the United States, costing an average of $2000 for every U.S. resident.[10] The National Center for Health Statistics reported 26% of adults over the age of 20 experience chronic pain.[11] Chronic pain is four times more prevalent than diabetes,[12] nearly six times more prevalent than coronary heart disease,[13] and eight times more prevalent than cancer.[14] (*See Table 2.*)

According to the Institutes of Medicine, the most common chronic pain treated is low back pain (28.1%), followed by knee pain (19.5%) and migraine or headache pain (16.1%).[10] Chronic pain historically has been managed poorly. In the 2006 "Voices of Chronic Pain" survey, respondents revealed that they felt little control over their pain (51%), and that breakthrough pain experienced on a daily basis greatly impacted their quality of life (60%).[15] Sadly, 50-75% of cancer patients, at the time of death, have moderate-to-severe pain.[16] Clearly, the increase in opioid prescribing has not been effective in alleviating chronic pain. When do these chronic conditions that are frequently evaluated and

Table 2: Incidence of Chronic Diseases in the United States



treated by the primary care physician warrant opioid prescribing?

Management of the Crisis

Government representatives have proposed legislation in an attempt to help mitigate the addiction crisis. Congressman Vern Buchanan (R-FL) proposed federal legislation, H.R. 1065: Pill Mill Crackdown Act of 2011, and Senator Joe Manchin (D-WV) proposed S. 1760: Pill Mill Crackdown Act of 2011 to increase fines and prison terms to individuals who prescribe opioids for monetary gain by running "pill mills."[17] Although the bills are still in committee, it is likely that some federal legislation will be forthcoming. Many state medical boards have enacted legislation regarding rules for the prescribing of scheduled substances, while state legislators have enacted additional monitoring, fines, and imprisonment for illegal prescribing. Thirty-seven states have instituted prescription monitoring systems to help physicians, pharmacists, and law enforcement track the patterns of individuals obtaining controlled substances via prescriptions, while 11 additional states are in the legislative process for implementation.[18] Linkage of information among states in nearby geographical locations is being planned in some regions to better monitor those individuals who cross state lines to hide prescription abuse. Primary care physicians have a responsibility to link into their state resources for monitoring prescriptions and to validate or invalidate patient behaviors that are suspicious of substance abuse. The Alliance of States with Prescription Monitoring Programs (www.pmpalliance.org) provides a list for available programs in your state.

Resources from pharmaceutical companies that manufacture and distribute potent opioids are readily available in the form of Risk Evaluation and Mitigation Strategies (REMS) and patient education tools. The FDA began requiring REMS in 2007 for extended-release and long-acting (ER/LA) opioid analgesics.[19] General requirements of the manufacturer are to provide patient education materials with clear product labeling regarding the dangers and prescriber education with guidelines for patient monitoring. Prescribers are responsible for implementing the REMS strategies associated with particular medications that they are prescribing for their patients.

Available Tools and Resources

Screening Tools for Abuse Potential. Several easy-to-use assessment tools are available for screening patients for possible substance abuse. For an office-based practice, a tool that is simple to use, reliable, valid, and can be completed fairly quickly would be practical. Tools that aid in predicting abuse potential prior to prescribing include NIDA Drug Use Screening Tool, Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain (SOAPP/SOAPP-R), and Diagnosis Intractability Risk Efficacy Tool (DIRE). Many other tools have been studied minimally or are currently being studied; however, all of the tools developed to date are susceptible to deception.

The National Institute on Drug Abuse (NIDA) offers a quick screen via interview that is followed by a more in-depth interview with the NIDA-Modified Assist Tool.[20] Since the tool requires an interviewer, it may be more cumbersome for a busy practice. The ORT may be self-administered, has only five questions, can be completed fairly quickly, and shows more sensitivity to low-risk patients than the SOAPP.[21] It has been commonly used in the office setting. The SOAPP involves 5-24 questions, is self-administered, and takes a little longer to complete if all 24 questions are administered.[22] A newer version, the SOAPP-R, was developed to offer a more subtle approach to questioning, and still has 24 questions.[23] Both tools are considered reliable and valid and could be considered if the patient has adequate time to complete the documentation. Finally, the DIRE is seven questions administered by patient interview and is used to screen for appropriateness of placing the patient on opioid therapy.[24] Again, the patient must be interviewed so self-administered tools may be more desirable.

Once the patient has been placed on opioids, the Current Opioid Misuse Measure (COMM) could be administered. The COMM helps determine if patients already on opioids are abusing their prescription.[25] It includes 17 questions, is self-administered, and will lead to a positive or negative result, thereby lending itself to some false positives. The COMM has been found to

Table 3: Screening Tool Samples for Clinical Use – Websites

Screening Tool	Website
NIDA	http://www.drugabuse.gov/nmassist/
ORT	http://www.partnersagainstpain.com/printouts/Opioid_Risk_Tool.pdf
SOAPP	http://www.algosresearch.org/PracticeTools/DxTestForms/SOAPPTest.pdf
DIRE	http://www.jfponline.com/Pages.asp?AID=8949
COMM	http://nationalpaincentre.mcmaster.ca/documents/comm_sample_watermarked.pdf

be reliable and valid.[26] Table 3 lists websites at which the tools can be accessed for clinical use.

Toxicology Screening. Random toxicology screening is recommended for any patient prescribed opioids longer than 3 months. The American Pain Society (APS) guidelines for screening include testing every 3-6 months for low-risk patients and up to weekly for patients at high risk of aberrant behaviors.[27] Patients should be made aware that random screening will occur if they are maintained on an opioid regimen. Urine is the most common method of screening in an office setting, but saliva, hair, blood, or stomach contents also may be screened. Provisions should be made to ensure that the patient's own urine is what is tested.

Laboratories may vary regarding which medications are routinely included in their screens, so the prescriber should be familiar with the standard inclusions in the random screen. If unsure, the specific drug(s) that the provider is looking for should be identified on the order. In general, "ordering and interpreting urine drug screenings requires an understanding of the different testing modalities, the detection times for specific drugs, and the common reasons for false-positive and false-negative test results."[28] A good reference on urine drug screening, including false positives, timeframe for reliability, and other variables, usually can be provided by the laboratory that is contracted for screening.

Opioid Agreements. An opioid agreement should delineate specific rules that the patient must follow while being prescribed opioids. According to APS and American Academy of Pain Medicine (AAPM) clinical guidelines,[29] the following components should be included:

- A discussion of the risks and benefits of opioid therapy.
- The types of common side effects and risks of adverse effects including abuse, addiction, and overdose.
- The risk of hyperalgesia, sexual, and endocrine dysfunction.
- Goals of opioid therapy.
- How the opioids should be taken; scheduled vs as needed, and frequency with guidelines for tapering and weaning. Patient should be informed when they might need to discontinue the medication, including signs of aberrant behavior.
- Expectations for office follow-up, refill process, pill counts, and random drug screening.
- Use of one prescriber and one pharmacy for opioid therapy.
- Guidance on safe storage of prescriptions to guard against theft and policy on theft replacement.
- How to properly dispose of opioids.
- Alternatives to opioid therapy.

Informed consent and a sample opioid agreement can be found in Appendix 6 and 7 at www.jpain.org/article/S1526-5900(08)00831-6/fulltext#appseca6.

Equianalgesic Dosing Charts. Equianalgesic dosing charts provide dosing guidelines when switching from one opioid to another. (*See Table 4.*) Calculating an accurate conversion more likely provides a safe dose with analgesic efficacy. Making a switch in opioids without a calculation may cause oversedation or respiratory depression, or on the other end of the spectrum, inadequate analgesia. Dose conversions are most easily calculated by totaling the past 24-hour usage of all opioids into a morphine equivalent. The sum can then be used to convert to an equianalgesic amount of the newly prescribed opioid. Most references suggest using a one-third to one-half total reduction in the sum before conversion, due to the patient's incomplete cross tolerance, resulting in an unpredictable response.[29] Additionally, most references caution against initiating methadone unless experienced in its use, such as a pain specialist or palliative care specialist. The long half-life of methadone, with the cumulative effect, and the unpredictability of equianalgesic conversions, can be dangerous. Patients maintained on a stable dose for pain management could be managed by a primary care provider; special licensing to prescribe methadone only applies to opioid detoxification or rehabilitation maintenance programs.[30]

Managing Pain with Opioids

The first step in prescribing opioids is the decision to initiate the therapy. Some decision-making steps have already been described, including the

Table 4: Equianalgesic Opioid Table (mg)

Opioid Agonist Available dosage forms	Approximate equianalgesic dose[1] (The shortest time interval is listed)		Recommended Starting Dose for Moderate-to-Severe Pain (adults and children ≥ 50 kg body weight)[2]	
	Oral	Parenteral	Oral	Parenteral
Morphine 15 mg tablet; 10 mg/2.5 mL oral liquid; 2 mg, 4 mg, 8 mg, 10 mg, 15 mg syringes; PCA	30 mg q 3 hrs (around the clock dosing) 60 mg q 3 hrs (single or intermittent dosing)	10 mg q 3 hrs	10 mg q 3 hrs	5 mg q 3 hrs
MS Contin (Morphine, controlled release) 15 mg, 30 mg, 100 mg tablets	90 mg q 12 hrs	Not available	30 mg q 12 hrs	Not available
Codeine 15 mg tablet; 60 mg syringe	180 mg q 3 hrs	130 mg q 3 hrs	60 mg q 3 hrs[3]	60 mg q 2 hrs (IM/SQ)
Fentanyl patch (Fentanyl Transdermal) 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr patch	25 mcg/hr transdermal fentanyl = 12 mg/day parenteral morphine = 36 mg/day oral morphine. Most patients are adequately maintained with q 72 hr transdermal fentanyl.[4]		Transdermal fentanyl is NOT appropriate for acute pain. It should ONLY be used in patients already receiving opioid therapy and who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to 25 mcg/hr transdermal fentanyl.[5]	
Actiq (Fentanyl Transmucosal) 400 mcg, 600 mcg, 800 mcg troche	Not available		Patients should not be on Actiq unless opiate tolerant to a minimum of 25 mcg of transdermal fentanyl or 60 mg of oral morphine per day.	
Sublimaze (Fentanyl) IV, PCA	Not available	0.1 mg	Not available	25 mcg q 2 hrs
Hydrocodone (in Lortab, Norco, Vicodin) Only in combination	30 mg q 3 hrs	Not available	10 mg q 3 hrs	Not available
OxyContin (Oxycodone, controlled release) 10 mg, 20 mg tablet	60 mg q 12 hrs	Not available	10 mg q 12 hrs	Not available
Dilaudid (Hydromorphone) 2 mg tablet; 2 mg/mL injection	7.5 mg q 3 hrs	1.5 mg q 3 hrs	2 mg q 3 hrs	1 mg q 3 hrs
Dolophine (Methadone) 5 mg, 10 mg tablet; 40 mg dispersible tablet, 10 mg/mL oral liquid; 10 mg/mL injection	10 mg q 6 hrs	5 mg q 6 hrs	5 mg q 6 hrs	2.5 mg q 6 hrs
Roxicodone (Oxycodone, also in Percocet, others) 5 mg, 7.5 mg, 10 mg; 5 mg/5 mL oral liquid	20 mg q 3 hrs	Not available	5 mg q 3 hrs	Not available
Ultram (Tramadol) 50 mg	1 tablet has comparable analgesia to 1 Tylenol #3		50 mg q 6 hrs	Not available

[1]Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical responses is necessary. Because there is a not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response.

[2]Recommended doses do not apply for adult patients with body weight less than 50 kg. Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics.

[3]Codeine doses > 65 mg often are not appropriate because of diminishing incremental analgesia with increasing nausea, constipation, and other side effects.

[4]Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic of transdermal fentanyl cannot be made before 24 hours of wearing. The initial transdermal fentanyl dosage may be increased after 3 days. During the initial application of transdermal fentanyl, patients should use short-acting analgesics as needed until analgesic efficacy with transdermal fentanyl is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for "breakthrough" pain.

[5]Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

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use of a screening tool and checking prescription history via a state website. Other assessment questions that have demonstrated predictive value may be utilized. Past or current use or abuse of tobacco, alcohol, or other illicit drugs all have been shown to increase the risks for future abuse, while existence of addictive behaviors, such as gambling, sex addiction, Internet addiction, kleptomania, or other impulse control disorders, are directly correlated with an increased risk of substance abuse.[31,32,33] According to Grant, gamblers have been shown to have a tenfold increase in risk of substance abuse as compared with the normal population.[31] Other addiction disorders demonstrate similar behaviors to substance abuse including uncontrolled use despite harm and diminished self-control due to cravings.[31] Neurobiologists believe that the similarities of addictive disorders are attributable to abnormalities in serotonin production and availability.[31] A discussion regarding past or current abuse behaviors should be included as part of the risk stratification for routine screening prior to opioid initiation.

Other predictors may include mental health disorders or a history of physical or sexual abuse as a child.[32,33] Substance abusers report high rates of major depression and anxiety (23.5%) as well as high rates of sexual abuse (25.4%).[34] As the incidence of anxiety disorders, mood disorders, or behavior disorders increases, there is a direct linear correlation with an increase in substance abuse.[35] As the addiction develops, unemployment or frequent job changes, failed relationships or marital problems, involvement in litigation, seeing multiple medical providers, or "doctor shopping" may emerge.[33] Successful recovery from addiction results most often from strong social and family relationships, ongoing employment with possible vocational training, and development of leisure activities.[36] Without these variables present at the initiation of opioid therapy, the patient may be more vulnerable to misuse.

After the decision is made to initiate opioids, careful monitoring of the patient must ensue. An opioid agreement should be reviewed with the patient and signed with a copy included on the chart and a copy given to the patient. The prescriber should be alert to any developing signs of addiction. Patients with undermanaged pain may develop pseudoaddictive behaviors, which can be difficult to differentiate from addictive behaviors. Although both behaviors are not 100% consistent with each category, a comparision of the most likely categorized addictive and pseudoaddictive behaviors is included in Table 5.[37]

If aberrant behaviors develop that are more indicative of addiction, the prescriber should follow the guidelines issued by the Association of Healthcare Research and Quality (AHRQ) and AAPM described later in this article, and refer the patient to an addictionologist. Patients who have altered prescriptions or sold their prescriptions have committed a felony. They should be reported to law enforcement and immediately discharged from your practice.

Referral to a pain specialist should be considered when the current medical provider becomes uncomfortable with the opioid dosing, is not seeing functional improvement with the analgesic regimen and/or intolerable side effects, and is unsure of the next steps for optimal safe care of the patient. The referral should be made with a direct phone call to the receiving pain specialist with the following information: the expectations for the referral, whether it is confirmation of the current regimen, suggestions for improvement in the regimen, further diagnostics, interventional strategies that the current provider does not offer, and the current plan.[38] Frequent communication between the pain specialist and the referring physician is the key to a successful outcome.

Several organizations have provided guidelines on how to manage the non-cancer patient on long-term opioid therapy based on clinical guidelines published by Chou in 2009.[39] A summary of those guidelines is listed in Table 6.

Managing the Palliative Care Patient on Opioids

Managing the pain of a terminally ill patient seems an obvious ethical responsibility, yet > 50-90% of cancer patients report moderate-to-severe pain at end of life.[40] As many as 75% of heart failure patients in the last 6 months of life and 50% of AIDS patients describe pain related to the disease itself, comorbities, or related treatment.[40] A large study conducted from 1994-2006 concluded that about 26% of patients in the last 2 years of life experienced "clinically significant" or moderate pain on a regular basis, which increased to 46% in the last month of life.[41] The American Medical Association Code of Ethics is clear by stating, "Physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care. This includes providing effective palliative treatment even though it may foreseeably hasten death."

There are many myths surrounding pain management at the end of life, including saving strong analgesics until near death.[42] The reality is that strong analgesics may be needed early in diagnosis to enhance the patient's quality of life until death.

The World Health Organization published an analgesic ladder for cancer pain, familiar to most clinicians, suggesting initiation of therapy with an oral non-opioid with adjuvant for mild pain, progressing to opioids with non-opioids (nonsteroidal anti-inflammatory drugs [NSAIDS] or acetaminophen) and adjuvants for severe pain.[43] Delay in aggressive pain therapy may occur if the patient's pain is severe, and the clinician conservatively begins treatment at the base of the ladder. In an article written by Fine in 2012, it was noted that 20% of patients with advanced disease are not adequately managed with the analgesic ladder.[44] Since the undertreatment of pain is widely published, related to the palliative population, multimodal therapies

Table 5: Addiction vs Pseudoaddiction

Addiction	Pseudoaddiction
Losing prescriptions. Asking for opioid replacements.	May use other available drugs to treat symptoms; excessive acetaminophen or NSAID use, burns from heating pads, benadryl to sleep, etc.
Calling at night or on weekend for refills/additional meds — wants to get medical provider partner who doesn't know them; may call office to ask who is on for the weekend.	Typically calls during office hours, but could have pain exacerbate on off hours.
Sense of urgency — calls office multiple times in a day > 2 times. May show up at office.	Aggressive complaining about needing more drugs, but typically will only call office 1-2 times.
Obtaining opioids/benzodiazepines from multiple providers (won't tell you) — check state prescription report at initial visit.	May have several providers but WILL tell you who is prescribing what medication for what purpose.
Multiple allergies — explore, can skin test.	Requesting specific drugs — just knows what works from past exposure.
Refuses additional testing for pain complaints.	May be resistant to testing that has been done in past but ultimately will comply; may ask for additional testing.
Caught selling prescription drugs to get drug of choice, or forging prescriptions — changing "n" on prescription. Stealing drugs.	May borrow drugs from family members but will tell prescriber. Will not steal or forge prescription drugs.
Using drug by unprescribed route — snorting or injecting, chewing long-acting agents.	May be anxious about changes in medications or route for fear of being back in pain.
Concurrent abuse of other drugs will show up on tox screen. Other addictions present.	Tox screen negative for other illicit drugs.
Repeatedly escalating dose despite warnings.	Occasionally escalates drug dose but will let you know.
Frequent ED visits WITHOUT telling prescriber.	May visit ED but WILL tell doctor to convince him/her that problems exist.
Making up or embellishing chronic diagnoses; reluctant to give the previous physician's name or number.	Willingly provides paperwork and physician name for other diagnoses.
Exhibits work, family, social deterioration. Unemployed or frequent job changes.	May temporarily not be working unless disabled, but often employed.

including neuropathic agents and opioids should be employed.

The American College of Physicians (ACP) published practice guidelines for end-of-life care in 2008 and recommended a combination of radiotherapy/radiopharmacology, opioids, NSAIDs, adjuvant medications, and particularly biophosphonates for bone cancer from breast cancer or myeloma.[45] Clinical guidelines developed regarding opioids for palliative care still recommend morphine as the primary mainstay of opioid therapy.[46] A long-acting version of morphine for sustained pain, along with breakthrough dosing of a short-acting agent, is recommended. As with all opioid therapy, individual variances may require use of another opioid such as oxycodone or hydromorphone, particulary if the patient has renal dysfunction. Transdermal fentanyl preparations are not recommended for initial therapy as a level of opioid tolerance should be established prior to initiating. If the patient cannot tolerate oral therapy, subcutaneous injection of opioid should be considered.[46] Fear of respiratory depression from potent opioids should not outweigh the benefit of effective analgesia.[47] Many states

Table 6: Clinical Guidelines for the Use of Opioid Therapy in Chronic Non-Cancer Pain

Guideline	Criteria
Patient Selection with Risk Stratification	1. Physical exam with appropriate testing for anatomical area of pain. 2. Assess risk of substance abuse, misuse, or addiction. 3. Initiate a trial of opioid if: • Moderate to severe pain • Adverse impact on quality of life and functionality • Therapeutic benefits are expected to outweigh risks
Informed Consent and Opioid Treatment Plan	1. Review risks, benefits, and potential adverse effects of opioid therapy including addiction and overdose. 2. Review opioid contract with provider and patient expectations. 3. Have patient sign both documents with a copy to the patient and a copy on the chart.
Initiation and Titration	1. Consider as "trial" when discussing with patient. 2. Base opioid selection on the following: • Patient's health status • Prior exposure to opioids • Therapeutic goal • "Predicted or observed harms"
Methadone	Should only be initiated and titrated by experienced clinicians who are familiar with the risks and safe use of the drug
Monitoring	Schedule follow-up visits with assessment and documentation of the following: • Pain intensity • Functional level • Progress toward goals • Any adverse events or side effects • Adherance to the prescribed therapy • If patient has history of aberrant drug behaviors or is high risk for abuse, obtain random urine drug screens and /or pill counts regularly. If not high risk, consider occasional random urine drug screens. • If patient has addiction history or mental health history, consider referral to mental health specialist or addictionologist to help manage patient while on opioids
Dose Escalations/High-dose Opioid Therapy/Opioid Rotation/ Indications to Discontinue	Actions if the following behaviors are exhibited: • Repeated escalations — re-evaluate therapy • High doses — more frequent follow-up visits, monitor for adverse effects, monitor health status, monitor for adherence • Poor analgesia or increased side effects — consider opioid rotation to plan • Aberrant behaviors or lack of progression toward goals — titrate opioid down and wean off
Adverse Effects	Actively treat side effects of the opioids, proactively planning for constipation.
Psychotherapeutic Co-interventions	Use psychotherapeutic interventions (behavioral), functional restoration (PT/ OT), interdisciplinary therapies, and non-opioid adjuvant medications.
Driving and Work	Caution about driving or working if feeling "impaired."
Identify Medical Home	One primary physician should coordinate care of consultants AND prescriptions.
Breakthrough Pain	As-needed opioids should be considered on the basis of a risk/benefit decision.
Opioids while Pregnant	A risk/benefit decision should be made with potential harm to the fetus discussed.
Opioid Policy Recommendations	Follow all federal laws, state laws, regulatory guidelines from State Boards of Medicine and Pharmacy, and any policy statements that guide opioid therapy for non-malignant pain.

have compassionate care laws in place that protect the physician from litigation for treating the dying patient.

The emotional component of the experience of dying cannot be ignored when managing the pain of a palliative care patient. Multiple literature sources cite depression as a major component at end of life.[48] Clearly undermanaged emotional distress can exacerbate physical pain. Therapies recommended based on systematic review of the literature include treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), in combination with psychosocial therapies.[48] Interdisciplinary management of the patient is paramount for optimizing pain control. The ACP clinical guidelines include the following recommendations (summarized)[45]:

- Pain, dyspnea, and depression should be regularly reassessed.
- Pain therapies utilized at end of life should be clinically proven; for cancer pain this includes the use of NSAIDs, opioids, and biophosphonates.
- Dyspnea should be actively managed with opioids and oxygen.
- Depression should be treated with tricyclic antidepressants, SSRIs, and psychosocial support.
- Advance care planning, including completion of Advance Directives, should be completed.

Risks of addiction in the palliative care population in patients who have no previous history of addiction is extremely rare.[49] Presenting signs of aberrant behaviors in terminal patients are often manifestations of pseudoaddiction and undertreated pain.[49] Patients who have a prior history of substance abuse will need to be monitored more closely, just as any patient with an addiction history. Since substance abuse lends itself to a higher risk of chronic disease and cancer, patients should be actively screened regardless of terminal diagnosis.

Summary

The decision to prescribe opioids for a patient with non-cancer pain is a difficult and calculated one. Patients with a substance abuse or mental health history should not be denied opioids when experiencing a co-existing pain condition that is affecting their quality of life. Careful screening with a pre-determined pain management plan is imperative for optimal management of all patients, including palliative care. When viewed as a "trial," the patient is informed with initiation, that the use of opioids requires ongoing monitoring and follow-up. The use of available screening tools and opioid prescribing guidelines are recommended to enhance safe, quality patient outcomes. The complete text for the clinical guidelines for prescribing is available at http://www.painmed.org/Library/Clinical_Guidelines.aspx.

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Primary Care Reports CME Objectives

Upon completion of this activity, participants should be able to:

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. For patients maintained on opioids, urine drug screening should occur:
   a. at each office appointment.
   b. once a month if high risk.
   c. every 2 months if low risk.
   d. on a random basis depending on level of risk.
2. The acronym "REMS" refers to:
   a. random evaluation medication screening.
   b. risk evaluation medication screening.
   c. risk evaluation mitigation strategies.
   d. random education medication schooling.
3. Your patient reports his opioid prescription was stolen while vacationing in Florida. You should:
   a. replace the prescription.
   b. follow the guideline on your opioid treatment agreement.
   c. ask for a police report before replacing the opioid.
   d. prescribe a non-opioid replacement.
4. The new patient in your office today checks "gambling" as a past addiction on her history. If prescribing opioids for this patient you should:
   a. place her in the "high risk" category for potential overuse/abuse.
   b. treat her as you would any other patient.
   c. obtain random drug screening regularly.
   d. Both a and c
   e. All of the above
5. Your patient on opioids has had three visits to the emergency department in the past 2 weeks due to uncontrolled pain. He has called your office each time, prior to the visit. You should:
   a. trial an opioid rotation.
   b. revise the opioid agreement to keep the patient out of the ED.
   c. place the patient in a "high risk" category.
   d. suspect that the patient is developing addiction.
6. Responsible opioid prescribing includes:
   a. use of a screening tool to ascertain risk for aberrant behaviors.
   b. use of an opioid treatment agreement.
   c. checking the state prescription database for patient history (if available).
   d. All of the above

In Future Issues: Dyspepsia

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AHC Media

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 18, NUMBER 2 PAGES 3-4 FEBRUARY 2013

Does Screening for Type 2 Diabetes Pay Off?

Source: Simmons RK, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): A cluster-randomised controlled trial. *Lancet* 2012;380:1741-1748.

IT IS EASY TO ENVISION THAT EARLIER DIAGnosis of type 2 diabetes (DM2) might lead to an opportunity for earlier, intensified interventions that might translate into improved outcomes. So far, however, we only *think* that, we don't actually *know* it. Simmons et al followed patients from general practices in England (n = 11,737) who enrolled in pathways of 1) screening for DM2 plus intensive multifactorial interventions, 2) screening for DM2 plus routine care, and 3) a "no screening" population. The mean age of the population was 58 years.

The practices in which multifactorial intervention groups were enrolled received educational and logistical support for attaining glucose, blood pressure, and lipid goals. Recent data in the United States suggest that currently fewer than 15% of type 2 diabetics are achieving simultaneous goal attainment in all three of these.

Over an interval of approximately 10 years' follow-up, there were no significant differences seen between unscreened vs screened subjects in regards to all-cause mortality, cardiovascular mortality, cancer mortality, or diabetes-related death.

Explanations for failure to reduce risk include the following: 1) screening for diabetes became more routine in the non-screened group over time; 2) routine care is improving, such that intensive intervention may not be as dramatically different than routine care, and 3) the duration of follow-up was insufficient. ■

Surgical Treatment of Diabetes

Source: Vetter ML, et al. Comparison of bariatric surgical procedures for diabetes remission: Efficacy and mechanisms. *Diabetes Spectrum* 2012;25:200-210.

THE LINK BETWEEN OBESITY AND TYPE 2 diabetes (DM2) is widely acknowledged. Certainly, weight gain is associated with increased incidence of DM2, and weight loss improves insulin sensitivity, as well as other cardiovascular risk factors. Surgery produces prompt and dramatic reductions in excess body weight, yet it appears that rebalancing of the disturbed metabolic homeostasis seen in DM2 varies among the different bariatric surgical interventions. Additionally, it appears that weight loss alone cannot fully explain the metabolic restorations seen post-surgically. Favorable metabolic changes are especially prompt, intensive, and durable when surgery involves bypassing or elimination of much of the small intestine from the digestive path.

In their review of the DM2 bariatric surgery trials, Vetter et al conclude that the primary driving force for DM2 remission appears to be weight loss. Since diversionary procedures are associated with greater and more durable weight loss, they would be anticipated to produce greater benefits for DM2 and they do. Overall adjustable gastric bypass is reported to result in remission in 57% vs 95% in biliopancreatic diversion surgery. The long-term relapse rate is not insubstantial: One very long follow-up of diversionary surgery (up to 16 years) noted relapse in 43%.

There are distinct hormonal changes that differ between the surgical interventions. For instance, gastric banding does not affect incretin activity, but bypass surgeries are associated with increased secretion of incretins. Evidence continues to accumulate that corroborates the efficacy, safety, and durability of bariatric surgical intervention for DM2. ■

Benefits and Consequences of Aldosterone Antagonists for HF

Source: Hernandez AF, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA* 2012;308: 2097-2107.

CLINICAL TRIAL DATA HAVE CONCLUSIVELY demonstrated improved mortality and cardiovascular outcomes in chronic heart failure (CHF) patients who receive aldosterone blockade (ALD) with spironolactone or eplerenone in addition to standard of care treatment. Clinical trial populations, however, are different from practice settings in which patients may not enjoy the same risk:benefit balance as the often highly selected subjects who enroll in clinical trials.

To evaluate outcomes among patients

with newly administered ALD *not* enrolled in a clinical trial, Hernandez et al reviewed 2005-2010 Medicare data on older (mean age, 78 years) patients who had received a new ALD prescription on discharge from the hospital for CHF (n = 5887). They looked at all-cause mortality, cardiovascular readmission, heart failure readmission, and hyperkalemia.

Although there was no difference in total mortality, the addition of ALD to the treatment regimen was associated with lower heart failure readmission. On the other hand, patients treated with ALD were statistically significantly more likely to be readmitted with hyperkalemia over the next year (1.5-2.5 times more likely). ALD treatment offers some positive outcomes, but clinicians must be vigilant for hyperkalemia when ALD treatment is chosen. ■

Long-term Prevention of Recurrent DVT

Source: Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; 367:1979-1987.

Current guidelines for management of venous thrombosis (e.g., the Antithrombotic 9 guideline published by the American College of Chest Physicians in 2012) suggest that after an initial episode of unprovoked deep venous thrombosis (DVT), it is reasonable to provide at least a 3-month course of anticoagulation, with consideration of a longer interval on a case-by-case basis. Usually, anticoagulation is not continued long-term. But the risk of DVT recurrence after cessation of coumadin is not insignificant.

Aspirin (ASA) is easy to administer and has a generally favorable risk profile. After cessation of coumadin, Brighton et al compared DVT patients treated with aspirin vs placebo for approximately 3 years. Although numerically fewer recurrent DVT episodes occurred in the ASA group, the numbers did not achieve statistical significance (4.8%/yr vs 6.5%/yr; P = 0.09). On the other hand, ASA produced a reduction in secondary composite outcomes, which included myocardial infarction, stroke, and cardiovascular death. Hence, even though ASA did not produce a statistically significant reduction in DVT, the potential reduction in other cardiovascular adversities might tip the balance toward benefit. Because the primary endpoint of the trial was not met, secondary endpoints, however, must be considered hypothesis generating rather than conclusive. ■

Marijuana and the Risk of Schizophrenia

Source: Evins AE. The effect of marijuana use on the risk for schizophrenia. *J Clin Psychiatry* 2012;73:1463-1468.

The recent legalization of marijuana in two states has brought the discussion of potential toxicity to the fore. Although it is unclear what impact legalization will have on epidemiology of marijuana use, most experts agree that more widespread and heavier marijuana use would not be at all surprising. The psychiatry community has particular concern about marijuana use because observational data suggest that early (during adolescence) marijuana use is associated with an increased risk for an earlier onset of schizophrenia.

Most schizophrenia is genetic in origin (80%). Hence, if marijuana is a contributor to schizophrenia, it occurs in a minority of cases. On the other hand, some genetic predilection for development of schizophrenia can be seen in carriers of the Met allele of the COMT gene, who appear especially likely to develop psychosis subsequent to cannabis use in adolescence.

At the current time, experts suggest advising parents that marijuana use in adolescence, especially heavy use, may increase the risk of future schizophrenia, and for persons with existing psychosis, may make symptoms worse. ■

Losartan Improves Erectile Function in Diabetics

Source: Chen Y, et al. Losartan improves erectile dysfunction in diabetic patients: A clinical trial. *Internat J Impot Res* 2012; 24:217-220.

Animal studies have shown that high levels of angiotensin II (ANG2) in the corpora cavernosa of the penis extinguish erections, the effect of which can be blocked by losartan, an ANG2 receptor blocker. Whether losartan might have a favorable effect on erectile dysfunction (ED) in diabetic humans has not been definitively confirmed.

Chen et al studied diabetic adults with ED (n = 124) who were randomized to receive either LOS 50 mg/d alone, tadalafil 5 mg/d (TAD) alone, the combination of LOS + TAD, or no treatment for 12 weeks. Persons with poorly controlled hypertension were excluded from the trial.

At the conclusion of the trial, TAD and LOS provided comparable significant improvements in erectile function scores, but the LOS + TAD combination was significantly better than either monotherapy. The control group experienced no significant improvement in erectile function. LOS was very well tolerated, and tolerability was not compromised by combining LOS + TAD. Clinicians might consider the addition of LOS to patients with insufficient ED response to TAD alone. ■

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

FDA Approves Apixaban for Patients with Nonvalvular AF

In this issue: Apixaban approval; new dental clinical practice guideline; apixaban for VTE; aspirin resistance; tamoxifen treatment; and FDA actions.

Apixaban superior to warfarin in trial

The FDA has approved apixaban — the long-awaited third novel oral anticoagulant (NOAC) — for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The drug follows dabigatran (Pradaxa) and rivaroxaban (Xarelto) for this indication, which has been traditionally treated with warfarin. The safety and efficacy of apixaban was demonstrated in the 18,000 patient ARISTOTLE trial, which showed that in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke and systemic embolism, caused less bleeding, and resulted in lower mortality than warfarin. The FDA will likely allow the manufacturers of apixaban to market the drug as "superior to warfarin." Apixaban is dosed twice a day, similar to dabigatran; rivaroxaban is dosed once a day. Apixaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. No head-to-head studies have been done among the three NOACs, which are expected to compete aggressively for this lucrative market that is worth billions of dollars in sales. All three lack a reversal agent, which could potentially increase the risk of serious bleeding. Apixaban is marketed as Eliquis by Bristol-Myers Squibb and Pfizer. ■

New dental prophylaxis guideline

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) have jointly published a clinical practice guideline regarding dental prophylaxis in patients with orthopedic implants. The recommendations, which are based on very limited evidence, state that, "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The guideline further states that they are unable to recommend for or against topical oral antibiotics in patients with implants, but they do recommend that patients with joint implants should "maintain appropriate oral hygiene," even though there is no evidence regarding this recommendation. This guideline does little to settle the debate between orthopedic surgeons, who often recommend lifetime dental prophylaxis, and infectious disease specialists who generally recommend against dental prophylaxis after 1 year. This rather weakly worded guideline is probably not the guidance most primary care physicians were hoping for, since they are generally responsible for prescribing prophylactic antibiotics and are responsible for possible adverse effects. The full guideline is available at www.aaos.org/research/guidelines/PUDP/dental_guideline.asp. ■

Length of treatment for VTE

How long should we treat patients with venous thromboembolism (VTE)? VTE includes deep-vein thrombosis and pulmonary embolism. Current

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

guidelines recommend 3-6 months of anticoagulation for unprovoked VTE — usually low-molecular weight heparin followed by warfarin. A new study suggests that an additional year of the factor Xa inhibitor apixaban (recently approved for stroke prevention in nonvalvular atrial fibrillation, see page 1) may be beneficial for these patients. In an industry-sponsored study, patients with VTE who had completed 6-12 months of anticoagulation therapy were randomized to an additional 12 months of apixaban (2.5 or 5 mg twice a day) or placebo. Nearly 2500 patients were included in the intention-to-treat analysis. Recurrent VTE or death from VTE occurred in 73 of 829 patients randomized to placebo (8.8%) compared to 14 of 840 patients on 2.5 mg of apixaban (1.7%) and 14 of 813 patients on 5 mg of apixaban (1.7%; $P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group and 0.2% and 0.1% in the apixaban 2.5 mg and 5 mg groups, respectively. The rate of death from any cause was 1.7% in the placebo group and 0.8% and 0.5% in the apixaban 2.5 mg and 5 mg groups, respectively. The authors conclude that extended anticoagulation with apixaban at either a treatment dose (5 mg bid) or thromboprophylactic doses (2.5 mg bid) reduced the risk of recurrent VTE without increasing the rate of major bleeding (*N Engl J Med* published online Dec. 8, 2012. doi: 10.1056/NEJMoa1207541). In this study, the majority of patients were younger than age 75 without other comorbities such as low body weight or renal impairment. It is also unknown if the results of this study are applicable to other approved anticoagulants such as rivaroxaban. ■

Aspirin resistance and enteric coating

Could "aspirin resistance" be due to enteric coating? The concept of aspirin resistance is very controversial with some experts suggesting that it does not exist. A new study suggests that enteric coating of aspirin may be partially responsible for "pseudoresistance." Researchers recruited 400 healthy volunteers who were then screened for their response to a single, oral dose of 325 mg immediate-release or enteric-coated aspirin. Variable absorption caused nearly half of those taking enteric-coated aspirin to have apparent resistance (49%), while this was not seen in any of the subjects taking immediate-release aspirin. On re-exposure, all of those with variable absorption responded to aspirin. The authors conclude that the study failed to identify a single case of true aspirin resistance, but pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric-coated but not immediate-release aspirin (*Circulation* published online Dec. 4, 2012. doi: 10.1161/CIRCULATIONAHA.112.117283). This study seems to contradict the concept that up to 40% of the population is "aspirin resistant." There is a suggestion that the concept of aspirin resistance has been touted by the manufacturers of expensive brand-name aspirin substitutes. This study may question the wisdom of the routine use of enteric-coated aspirin, especially given that enteric coating has very little benefit with regard to gastrointestinal protection. ■

Is 10 years of tamoxifen better?

Ten years of tamoxifen may be better than the standard 5 years for women with estrogen receptor (ER)-positive breast cancer, according to a new study from the United Kingdom. Researchers randomized about 6800 ER-positive women with early breast cancer who had completed 5 years of adjuvant tamoxifen to another 5 years of treatment or stopping therapy. There were 617 recurrences in the 3428 women who took tamoxifen for 10 years vs 711 in 3418 women who stopped at 5 years ($P = 0.002$). There was also a lower death rate (331 vs 397, $P = 0.01$) and reduced overall mortality (639 vs 722, $P = 0.01$) in the 10-year group. There were higher rates of endometrial cancer (relative risk [RR] 1.74, 95% confidence interval [CI], 1.30-2.34) and pulmonary embolism (RR 1.87; CI, 1.13-3.07) in the 10-year group, but no higher rate of stroke and a lower risk of ischemic heart disease (RR 0.76; CI, 0.60-0.95). The authors suggest that 10 years of tamoxifen in ER-positive patients can approximately halve breast cancer mortality during the second decade after diagnosis (*Lancet* published online Dec. 5, 2012. doi.org/10.1016S0140-6736(12) 61963-1). ■

FDA actions

The FDA has approved pasireotide diaspartate injection for the treatment of Cushing's disease in patients who are not candidates for surgery or for whom surgery has not worked. The drug is considered an orphan drug. The safety and efficacy were evaluated in a trial of 162 patients with Cushing's disease who were randomized to one of two doses of the drug. About 20% of participants had normal urine cortisol levels within 6 months. Side effects included increased blood sugar levels and liver injury. The drug is administered subcutaneously twice a day. It is marketed by Novartis as Signifor. In February 2012, the FDA approved mifepristone (Korlym) for the treatment of Cushing's syndrome. ■