

HCA Health Advisory: Unintentional Overdose Deaths Associated with Methadone and Other Opioids

Washington is among those states with the highest rate of opioid-related deaths in the U.S. This now exceeds both motor-vehicle accidents and firearms as the leading cause of injury-related death. Prescribers need to be aware of the potential for deaths and life threatening side effects in patients taking methadone, morphine, fentanyl, oxycodone and other opioids. Providers need to be knowledgeable about the specific opioid's indication, dosing, pharmacology, pharmacokinetics and toxicities before prescribing these dangerous drugs.

What should providers do?

- Read and follow the best practices outlined in the Agency Medical Directors' Group (AMDG) Opioid Dosing Guideline (<http://www.agencymeddirectors.wa.gov/opioiddosing.asp>).
- Read and follow the FDA labeling before prescribing an opioid.
- Carefully weigh the risks with potential benefits before prescribing an opioid.
- Review the new Pain Management Rules on prescribing opioids for chronic non-cancer pain.
- Access the Prescription Monitoring Program (PMP) to review your patient's controlled substances history available as of January 4, 2012.
- Closely monitor patients who receive opioids, especially during treatment initiation and dose adjustments.
- Use extreme caution in prescribing opioids in combination with sedative hypnotics or benzodiazepines.
- "Stop and take a deep breath" by seeking assistance with patients on doses of 120 mg/day or higher and when pain and function are not improving.
- Complete the 4 hours of free Category I CME available (<http://www.agencymeddirectors.wa.gov/opioiddosing.asp> - Click on the "CME Activities" tab)
- To prevent serious complications from methadone, providers who prescribe methadone should read and carefully follow the methadone (Dolophine) prescribing information.

The FDA has issued a public health advisory to alert patients and their caregivers and health care professionals to the following important safety information on methadone:

- **Prescribing methadone is complex.** Methadone should only be prescribed for patients with moderate to severe pain when their pain is not improved with other non-narcotic pain relievers. Pain relief from a dose of methadone lasts about 4 to 8 hours. However methadone stays in the body much longer—from 8 to 59 hours after it is taken. As a result, patients may feel the need for more pain relief before methadone is gone from the body. Methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements.
- **Patients should take methadone exactly as prescribed.** Taking more methadone than prescribed can cause breathing to slow or stop and can cause death. A patient who does not experience good pain relief with the prescribed dose of methadone, should talk to his or her doctor.
- **Patients taking methadone should not start or stop taking other medicines or dietary supplements without talking to their health care provider.** Taking other medicines or dietary supplements may cause less pain relief. They may also cause a toxic buildup of methadone in the body leading to dangerous changes in breathing or heart beat that may cause death.
- **Health care professionals and patients should be aware of the signs of methadone overdose.** Signs of methadone overdose include trouble breathing or shallow breathing; extreme tiredness or sleepiness; blurred vision; inability to think, talk or walk normally; and feeling faint, dizzy or confused. If these signs occur, patients should get medical attention right away.

Please use caution when prescribing these potentially dangerous drugs and read the important safety information (attached) on long-acting opioids.

Important Safety Information on Long-acting Opioids:

FENTANYL

DURAGESIC contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (**DURAGESIC**) may be a particular target for abuse and diversion.

DURAGESIC is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time,
- and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

DURAGESIC should **ONLY** be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to **DURAGESIC** 25 mcg/h. 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.

Because serious or life-threatening hypoventilation could occur, **DURAGESIC** (fentanyl transdermal system) is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g., use on an as needed basis [prn]) (See **CONTRAINDICATIONS** for further information.)

Since the peak fentanyl concentrations generally occur between 20 and 72 hours of treatment; prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of **DURAGESIC** with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving **DURAGESIC** and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see **CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION** for further information).

The safety of **DURAGESIC** has not been established in children under 2 years of age. **DURAGESIC** should be administered to children only if they are opioid-tolerant and 2 years of age or older (see **PRECAUTIONS** Pediatric Use).

DURAGESIC is **ONLY** for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the **DURAGESIC** dose when converting patients from another opioid medication can result in fatal overdose with the first dose (see **DOSAGE AND ADMINISTRATION – Initial DURAGESIC Dose Selection**). Due to the mean half-life of approximately 20-27 hours, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

DURAGESIC can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing **DURAGESIC** in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

DURAGESIC patches are intended for transdermal use (on intact skin) only. Do not use a **DURAGESIC** patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

Avoid exposing the **DURAGESIC** application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing **DURAGESIC** systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the **DURAGESIC** dose should be adjusted if necessary.

METHADONE

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

MORPHINE LONG-ACTING PRODUCTS

MS CONTIN contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

MS CONTIN Tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

MS CONTIN Tablets are NOT intended for use as a prn analgesic.

MS CONTIN 100 and 200 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

MS CONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MS CONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

KADIAN contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

KADIAN capsules are NOT for use as a prn analgesic.

KADIAN 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

AVINZA capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.

AVINZA CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL WHILE ON AVINZA THERAPY. CONSUMPTION OF ALCOHOL WHILE TAKING AVINZA MAY RESULT IN THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Oramorph SR (morphine sulfate) Sustained Release Tablets are indicated for the relief of pain in adult patients who require opioid analgesics for more than a few days.

Oramorph SR is a sustained release dosage form. Patients must be instructed to swallow the tablet whole; the tablet should not be broken in half, nor should it be crushed or chewed.

The sustained release of morphine from Oramorph SR should be taken into consideration in the event of adverse reactions or overdose. Serious adverse reactions caused by morphine, which can be fatal, include **respiratory depression, circulatory depression, apnea, shock, and cardiac arrest.**

Oramorph SR should be used with extreme caution in any patient who may have decreased respiratory reserve. Respiratory depression is the chief hazard of all morphine preparations. Oramorph SR is contraindicated in patients with respiratory depression in the absence of resuscitative equipment, in patients with acute or severe bronchial asthma and in patients with known hypersensitivity to morphine.

Oramorph SR is also contraindicated in any patient who has or is suspected of having a paralytic ileus.

Morphine sulfate is a Schedule II controlled substance. Morphine is the most commonly cited prototype for narcotic substances that possess an addiction-forming or addiction-sustaining liability. A patient may be at risk for developing dependence to morphine if used improperly or for overly long periods of time. Oramorph SR should be used with caution in individuals with a prior history of substance abuse or dependence.

Oramorph SR should be used with extreme caution in patients with increased intracranial pressure or those with a head injury.

The clearance of morphine or its metabolites may be reduced in patients with hepatic or renal dysfunction. Pharmacodynamic changes in these patients should be considered when adjusting the dose and dosing intervals.

The depressant effects of morphine are potentiated by the presence of other CNS depressants such as alcohol, sedatives, antihistamines, or psychotropic drugs. Opioid receptor agonist/antagonist analgesics should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic.

There has been no systematic evaluation of Oramorph SR as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a sustained-release morphine, it is ordinarily advisable to begin treatment using an immediate release formulation.

OXYCODONE

IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

See full prescribing information for complete boxed warning.

OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

OxyContin is NOT intended for use on an as-needed basis.

OxyContin 60 mg and 80 mg Tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients to avoid fatal respiratory depression.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.

OxyContin tablets must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved which can lead to rapid release and absorption of a potentially fatal dose of oxycodone.

The concomitant use with cytochrome P450 3A4 inhibitors such as macrolide antibiotics and protease inhibitors may result in an increase in oxycodone plasma concentrations and may cause potentially fatal respiratory depression.

OTHER LONG-ACTING OPIOID PRODUCTS

POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

See full prescribing information for complete boxed warning.

OPANA ER contains oxymorphone which is an opioid agonist and a schedule II controlled substance with an abuse liability similar to other opioid analgesics.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA ER is NOT intended for use as an as needed analgesic.

OPANA ER tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed as this leads to rapid release absorption of a potentially fatal dose of oxymorphone.

Patients must not consume alcoholic beverages, prescription or nonprescription medications containing alcohol. Co-ingestion of alcohol with OPANA ER may result in a potentially fatal overdose of oxymorphone.

POTENTIAL FOR ABUSE and IMPORTANCE OF PROPER PATIENT SELECTION

See full prescribing information for complete boxed warning.

BUTRANS is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

BUTRANS contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance.

Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing opioids.

Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation.

Avoid exposing the BUTRANS application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death.

MORE INFORMATION IS ON THE INTERNET:

[HCA Pharmacy Website](http://hrsa.dshs.wa.gov/pharmacy/) -- <http://hrsa.dshs.wa.gov/pharmacy/>

[AMDG Opioid Dosing Guidelines](http://www.agencymeddirectors.wa.gov/opioiddosing.asp) -- <http://www.agencymeddirectors.wa.gov/opioiddosing.asp>

[FDA Website: Methadone](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm) --

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm>

[FDA Website: Oxycontin](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm207196.htm) --

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm207196.htm>

[FDA Website: Fentanyl](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084307.htm) --

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084307.htm>

[FDA Website: Kadian \(Morphine\)](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails) --

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>

[FDA Website: MS Contin \(Morphine\)](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails) --

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>

[Physician Clinical Support System for Methadone](http://www.pcssprimarycare.org/) -- <http://www.pcssprimarycare.org/>

[Washington's Prescription Monitoring Program](http://www.wapmp.org/) -- <http://www.wapmp.org/>

[Patient education materials](http://here.doh.wa.gov/materials/safe-use-of-prescription-pain-medication) -- <http://here.doh.wa.gov/materials/safe-use-of-prescription-pain-medication>