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The FDA Advises Clinicians About Fentanyl Caused Deaths

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Prompted by reports of death and serious side effects from overdoses in patients using the fentanyl transdermal skin patches for pain control, the Food and Drug Administration (FDA) issued a public health advisory in July regarding the use of fentanyl patches (Duragesic and generics).¹

Fentanyl is an extremely potent opioid; on the order of 100 times more potent than morphine.² It is a good agent to use for patients who require high doses of opioid for long periods of time and particularly for those unable to take oral medicines. When given in equivalent analgesic doses, fentanyl is similar to morphine in its respiratory effects, but exhibits little hypnotic activity, and histamine release rarely occurs.

Fentanyl is available as fentanyl lozenges (Actiq) and fentanyl patches (Duragesic and generics). **These drugs are not be used in opioid naïve patients.**^{3 4} Use in opioid naïve patients may lead to fatal respiratory depression. Actiq and Duragesic are intended only for use in the opioid tolerant, defined in the labeling as those already receiving

- hydromorphone oral 8 mg per day or
- morphine 60 mg per day or
- oxycodone 30 mg per day, or
- equi-analgesic dose of another opioid for a week or longer.

Actiq and Duragesic both carry FDA black box warnings and recommend use only by those with experience in chronic pain management. Despite widespread misconception, Actiq and Duragesic have a high potential for abuse, including diversion, and are especially dangerous around children.

Fentanyl Patches (Duragesic)

In June 2005 the Duragesic product label was updated to add new safety information in several areas of labeling. A "Dear Healthcare Professional" letter about these changes was issued by the manufacturer.⁵

There is limited data on conversion of transdermal fentanyl to other opioids. The manufacturer's recommendations are based on clinical trials with oral morphine. The conversion ratios have not been extensively tested with other opioids.⁶ The manufacturer also states that the recommended dose conversion results in under-dosing of up to 50% of patients.³ Because steady state serum levels of fentanyl are not attained for about 3-6 days after application of the patch, a low dose of the previously used opioid (at least 25% of the dose used during the previous 24 hours) should be prescribed to avoid withdrawal and short-acting opioids should be used for break-through pain.⁷

Most patients are maintained adequately with fentanyl patches applied at 72-hour intervals; however, some patients may require application of the patches at 48-hour intervals to maintain sufficient analgesia. For patients not responding to a given dose, ample time (24-48 hours) should pass for adequate evaluation. Before shortening the dosing interval, an increase in dose should be tried so that patients can be maintained on a 72-hour regimen.³

Fentanyl patches are not recommended for patients where frequent dose adjustments are needed. The mean elimination half-life of fentanyl patches is 17 hours.³ Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after patch removal. Geriatric, cachectic, or debilitated patients should not receive initial transdermal doses exceeding 25 mcg/hour unless they are currently receiving an opioid dose equivalent to more than 135 mg of oral morphine sulfate daily.³

All patients and their caregivers should be advised to avoid exposing the patch application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the patches. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.

Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches may be a particular target for abuse and diversion. Case reports indicated that fentanyl has been extracted from the patches and administered intravenously or the patches licked or swallowed.^{8 9 10 11 12 13} Used patches can be safely disposed of by folding the sticky side of the patch together (until it sticks to itself) and flushing it down the toilet.

Because of dosing and diversion risks, it is recommended fentanyl patches be reserved for patients with chronic pain, requiring consistent high opioid doses and who are unable to tolerate or who are inappropriate candidates for oral long-acting morphine, long-acting oxycodone or methadone.

Fentanyl Lozenges (Actiq)

Fentanyl transmucosal lozenges are only indicated for the management of breakthrough pain in adult patients who are already being treated with, and are tolerant of, opioids used for chronic cancer pain.

Because life-threatening hypoventilation can occur at any dose in patients not taking chronic opioids, fentanyl lozenges are contraindicated in acute or postoperative pain. FDA recommends prescribing only by oncologists and clinicians knowledgeable of and skilled in the use of fentanyl to treat cancer pain. The lozenges should be consumed over a period of 15 minutes, not chewed, to insure safe administration.

The lollipop design makes the lozenges attractive to children. Patients and their caregivers should be instructed that fentanyl lozenges contain medicine in an amount that can be fatal to a child. A kit provided with Actiq includes a child-resistant lock for storage. Partially used units, including any residue on lollipop handles, should promptly be discarded securely, usually dissolving in hot water. The kit includes a child-resistant container for temporary holding of partial units and handles until proper disposal can be done. The Drug Enforcement Agency can be contacted for help with disposal.²

Fentanyl lozenges averaged over \$1000 per claim for the OHP fee-for-service program in the first quarter of 2005. Due to the high cost and increased risks of fentanyl lozenges, a trial of morphine immediate release or hydromorphone immediate release is recommended first. The lozenges should be reserved for patients who are tolerant to opioids and who cannot tolerate other oral opioids.

Conclusion

Duragesic and Actiq should be reserved for patients unable to tolerate oral morphine or other oral opioids. Fentanyl is a potent opioid that has been reported to be associated with death, serious side effects from overdoses, and diversion.

REFERENCES

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Clarification of OHP Coverage Policy for Anti-fungal and Stimulant Drugs

Stimulant Drugs

On November 15, 2005 stimulant drug coverage policy will be changed to allow open access to amphetamines and methylphenidate at evidence-supported doses (Table 1). This policy change was implemented in response to an observed increase in the number of patients receiving more than the FDA recommended dose of methylphenidate (60mg).

During the second quarter of 2005, 1563 unique patients received methylphenidate, 234 (15%) were on doses exceeding 60mg/day and 46 (3%) were on doses exceeding 90mg/day. Most of these patients (91%) were children 6-19 years old. Six of these children exceeded doses of 135mg/day, more than two times the FDA recommended maximum.

Table 1. Maximum recommended doses for stimulants

Generic	Brands	Dose Requiring PA
Methylphenidate Products— (dl-threo-enantiomer)	Ritalin, Ritalin SR, Methylin ER, Methadate ER, Ritalin LA, Methadate CD, Concerta	>90mg.
Dexmethylphenidate (d-threo-enantiomer)	Focalin	>20mg.
Amphetamine (methamphetamine)	Desoxyn	>60mg.
Mixed Amphetamine Salts (d-amphetamine: l-amphetamine 3:1)	Adderall, Adderall XR	>60mg.
Dextroamphetamine SO4	Dextroamphetamine, Dexedrine, DextroStat, Dexadrine Spansule, Dextroamphetamine CR	>40mg

In order to provide safe, effective pharmacotherapy with stimulant medications, prescribers are encouraged to determine the dose that will allow maximal therapeutic benefit while minimizing adverse effects. While optimal treatment regimens will vary from patient to patient (e.g. adolescents may require lower mg/kg dosing than school-age patients), doses should generally not exceed the FDA maximum recommended doses.¹

Doses above the recommendations will require a prior authorization when not prescribed by a psychiatrist. Prior authorization requests from non-psychiatric prescribers will be approved for children up to 2mg/kg/day for methylphenidate and 0.5mg/kg/day for amphetamines.² Doses above these recommendations will be evaluated on a case-by-case basis. Call 1-800-344-9180 for Oregon Medicaid fee-for-service PA requests.

- Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002;41 (Supplement 2): 26S-49S.
- Pediatric Dosage Handbook, 12th edition

Antifungal Drugs

On November 1, 2005 current OHP coverage policy will be modified to provide open access (no prior authorization [PA]) to two low-cost generic topical products (miconazole and nystatin) for covered conditions. All other topical antifungals, oral itraconazole (Lamisil), and oral terbinafine (Sporanox) will continue to require a PA.

The Oregon Health Plan (OHP)¹ does not cover treatment for dermatophytoses of the nail, foot or groin (Line 583), candidiasis of the mouth, skin or nails (Line 649), diaper/napkin rash (Line 690) and other minor fungal infections (Lines 552, 583, 637, 638). Prior authorization requests for topical antifungals, itraconazole or terbinafine to treat opportunistic infections of the immunocompromised (Line 171) or deep-seated fungal infections and dermatophytosis of the beard or scalp (Line 363) are approvable. Call 1-800-344-9180 for Oregon Medicaid fee-for-service PA requests.

- Oregon Health Plan List of Prioritized Health Services (April 1, 2005). http://egov.oregon.gov/DAS/OHPPR/HSC/current_prior.shtml