MEDWATCH The FDA Safety Information and Adverse Event Reporting Program

Opioid Pain Medicines: Drug Safety Communication - New Safety Warnings Added to Prescription Opioid Medications

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FDA 針對所有鴉片類止痛藥發布安全警訊，這些安全風險可能是有害的藥物交互作用結果，像是腎上腺問題，和降低性荷爾蒙，我們需要改變所有鴉片類止痛藥的仿單內容，警告可能會有這些風險。

- **鴉片類止痛藥與抗憂鬱藥物和偏頭痛藥物的交互作用**，可能造成嚴重的中樞神經系統反應，serotonin syndrome，高濃度的化學物質 serotonin 在腦內積聚而導致毒性產生。在 FDA 不良反應通報系統的資料中發現造成 serotonin syndrome 的不良反應案件，通報的藥物大部分是使用建議劑量下的 fentanyl 和 methadone，所以 FDA 要求增加新的警語在這些藥物的仿單上，一些鴉片類藥物像是 tramadol，tapentadol，和 meperidine 已經在仿單上警告可能會導致 serotonin syndrome 的副作用，另外也有其他的鴉片類藥物被通報，所以所有的鴉片類止痛藥物將會更新 serotonin syndrome 這方面的資訊在藥物仿單上的交互作用和藥物不良反應處。
  病患如果同時服用鴉片類止痛藥物和血清素類藥物而產生 serotonin syndrome 應該立即尋求醫療協助，serotonin syndrome 包括情緒激動、幻覺、心跳加速、發燒、發汗過多、發抖、肌肉抽搐或僵硬、協調障礙，和/或噁心、嘔吐、腹瀉等症狀，鴉片類止痛藥物因為藥物交互作用導致 serotonin 在腦部的作用增強，進而產生的 serotonin syndrome，其症狀開始可能幾個小時到幾天的時間，但也有可能發生的時間更晚，尤其是在增加劑量之後。

- **使用鴉片類止痛藥物可能會造成罕見但嚴重的腎上腺功能障礙，無法產生正常量的可體松賀爾蒙**，可體松可以幫助身體反應壓力，FDA 正要求所有的鴉片類止痛藥物在仿單上的警語處加註可能造成腎上腺皮質功能不全。
  病患如果有腎上腺皮質功能不全的症狀，包括噁心、嘔吐、食慾不振、虛弱、無力或低血壓時，應立即尋求醫療協助。

- **長期使用鴉片類止痛藥可能會導致性荷爾蒙降低**，症狀包括減少性慾、性無能或是不孕。
  FDA 審視了文獻，評估性荷爾蒙在長期慢性使用鴉片類止痛藥的影響，但因為資料有限，無法判別症狀是因為鴉片類止痛藥還是其他原因所造成的。
  病患如果有性慾低下、性無能、勃起功能障礙、月經缺乏，以及不育等症狀時，應該告知醫療人員。

建議：

- **serotonin syndrome**：
  如果懷疑是鴉片類止痛藥造成 serotonin syndrome，醫療人員應該停止使用鴉片類止痛藥和/或改用其他的藥物
- **腎上腺皮質功能不全**：
  如果懷疑是鴉片類止痛藥造成腎上腺皮質功能不全，醫療人員應該執行診斷測試，如果診斷結果確實為腎上腺皮質功能不全，應該給予可體松治療，並評估是否停用鴉片類止痛藥，如已經停用

鴉片類止痛藥，後續也應追蹤腎上腺功能，評估可體松是否可以停用。

- **降低性荷爾蒙：**
  如果病患有出現性荷爾蒙降低的相關症狀，醫療人員應執行實驗室評估。

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Opioid Pain Medicines: Drug Safety Communication - New Safety Warnings Added to Prescription Opioid Medications

AUDIENCE: Family Practice, Psychiatry, Pain Management, Nursing, Endocrinology

ISSUE: FDA is warning about several safety issues with the entire class of opioid pain medicines. See the FDA Drug Safety Communication for a complete listing. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. We are requiring changes to the labels of all opioid drugs to warn about these risks.

• **Opioids can interact with antidepressants and migraine medicines** to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see List of Serotonergic Medicines in the FDA Drug Safety Communication).

Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Therefore, FDA is requiring a new statement in the Warnings and Precautions section to be added to these drug labels. Some opioids, including tramadol, tapentadol, and meperidine, already have warnings about serotonin syndrome. Cases were also reported with other opioids, so the labels of all these drugs will be updated to include information about serotonin syndrome in the Drug Interactions and Adverse Reactions sections.

Patients taking an opioid along with a serotonergic medicine (see List of Serotonergic Medicines) should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase.

• **Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol.** Cortisol helps the body respond to stress. FDA is requiring a new statement about adrenal insufficiency to be added to the Warnings and Precautions section of all opioid labels.

Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

• **Long-term use of opioids may be associated with decreased sex hormone levels** and symptoms such as

reduced interest in sex, impotence, or infertility.

FDA reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically; however, all had limitations that make it difficult to determine whether the symptoms were caused by the opioids or other factors. The labels of some opioids already describe this possible risk, and FDA is now adding consistent information to the Adverse Reactions section of all opioid labels.

Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.
BACKGROUND: Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief (see List of Opioid Medicines in the FDA Drug Safety Communication). However, opioids also carry serious risks, including of misuse and abuse, addiction, overdose, and death.

Prescription opioids are divided into two main categories – immediate-release (IR) products, usually intended for use every 4 to 6 hours; and extended release/long acting (ER/LA) products, intended to be taken once or twice a day, depending on the individual product and patient.

See the FDA Drug Safety Communication for additional information, including a listing of opioids, serotonergic medicines, and a data summary.

RECOMMENDATIONS:

Serotonin syndrome:
Health care professionals should discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.

Adrenal insufficiency:
Health care professionals should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.

Decreased sex hormone levels:

Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.