

FDAの医薬品安全性に関するコミュニケーション： FDAは、オピオイドの痛みや咳止め薬をベンゾジアゼ ピンと組み合わせると、深刻なリスクと死亡につい て警告します。最強の警告が必要

FDAは、ベンゾジアゼピンまたは他の中枢神経系抑制剤との薬物療法（MAT）薬の併用に関する新しい情報を発表しました。2017年9月20日に発行された[FDA医薬品安全性コミュニケーショ](https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications)ン([/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications](https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications))を参照してください。

安全に関するお知らせ

[2016年8月31日]米国食品医薬品局（FDA）のレビューによると、オピオイド薬とベンゾジアゼピンまたは中枢神経系（CNS）を低下させる他の薬との併用が増えているため、遅滞などの深刻な副作用が発生しています。または困難な呼吸と死。オピオイドは、痛みや咳の治療に使用されます。ベンゾジアゼピンは、不安神経症、不眠症、発作の治療に使用されます。オピオイドとベンゾジアゼピン、またはオピオイドと他のCNS抑制剤の使用を減らすために、処方オピオイドの痛みと処方オピオイド咳止め薬、およびベンゾジアゼピンの薬物表示に、最も強力な警告であるボックス警告を追加します。

医療専門家は、ベンゾジアゼピンまたは他の中枢神経系抑制剤を含むオピオイド鎮痛薬の処方を、代替治療の選択肢が不十分な患者にのみ制限する必要があります。これらの薬と一緒に処方する場合は、望ましい臨床効果を達成しながら、各薬の投与量と期間を可能な限り最小限に制限してください。呼吸の遅延または困難、および/または鎮静のリスク、および関連する兆候と症状について、患者と介護者に警告します。ベンゾジアゼピンまたはアルコールを含む他の中枢神経抑制剤を服用している患者に処方オピオイド咳止め薬を処方することは避けてください。

ベンゾジアゼピン、他の中枢神経抑制薬、またはアルコールと一緒にオピオイドを服用している患者、およびこれらの患者の介護者は、彼らまたは彼らが世話をしている誰かが異常なめまいまたは立ちくらみ、極度の眠気、呼吸の鈍化または困難の症状を経験した場合、直ちに医師の診察を受ける必要があります。無反応。無反応とは、その人が正常に応答または反応しないか、あなたがそれらを起こすことができないことを意味します。オピオイドまたはベンゾジアゼピンの服用について質問や懸念がある場合は、医療専門家に相談してください（処方オピオイドの痛みと咳止め薬のリスト、およびベンゾジアゼピンとその他のCNS抑制剤のリストを参照）。

オピオイド ([/drugs/information-drug-class/opioid-medications](https://www.fda.gov/drugs/information-drug-class/opioid-medications))は強力な麻薬の一種であり、他の鎮痛薬を服用できない場合や十分な鎮痛効果が得られない場合に、オピオイドの使用を正当化するのに十分な重度の痛みを治療するために使用されます。また、誤

用や乱用、依存症、過剰摂取、死亡などの深刻なリスクもあります。コデインやヒドロコドンなどのオピオイドも、咳を軽減するために他の薬と組み合わせて承認されています。ベンゾジアゼピンは、不安神経症、不眠症、発作などの症状の治療に広く使用されている薬の一種です。

オピオイドとベンゾジアゼピン、中枢神経系を抑制する他の薬物、またはアルコールの併用に深刻なリスクが伴うことを示すいくつかの研究を実施およびレビューしました（データの要約を参照）。¹⁻⁶これらのデータに基づいて、オピオイドとベンゾジアゼピンのラベル、および新規または改訂された患者の投薬ガイド (</drugs/drug-safety-and-availability/medication-guides>)にこれらのリスクを反映するために、いくつかの変更が必要です。これらの変更には、新しいボックス化された警告と、ラベルの警告と注意事項、薬物相互作用、および患者カウンセリング情報のセクションの改訂が含まれます。

オピオイド依存症および依存症の治療に使用される薬物療法（MAT）薬と、ベンゾジアゼピンまたは他の中枢神経系抑制剤の併用に関する証拠の評価を続けています。また、他の中枢神経抑制剤にラベルの変更が必要かどうかを評価しており、より多くの情報が利用可能になったときに公開を更新します。

患者と医療専門家は、ページ下部の「FDAに連絡」ボックスの情報を使用して、オピオイド、ベンゾジアゼピン、またはその他の医薬品に関連する副作用をFDAMedWatchプログラムに報告することをお勧めします。

処方オピオイドの痛みと咳止め薬のリスト

Generic Name	Found in Brand Name(s)
alfentanil	Alfenta
buprenorphine	Belbuca, Buprenex, Butrans
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Soma Compound w/ codeine, Tylenol w/ codeine, Prometh VC w/ codeine (cough), Triacin-C (cough), Tuzistra-XR (cough)
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER, Flowtuss (cough), Hycufenix (cough), Obredon (cough), Rezira (cough), Tussicaps (cough), Tussionex (cough), Tussionex Pennkinetic (cough), Vituz (cough), Zutripro (cough)

hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

ベンゾジアゼピンおよびその他の中枢神経抑制剤のリスト*

Generic Name	Brand Name(s)
Benzodiazepines	
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed
lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral

temazepam	Restoril
triazolam	Halcion
Other Sleep Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix
dantrolene	Dantrium, Revonto, Ryanodex
metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex
Antipsychotics	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed

haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis
paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

*This is not a comprehensive list.

オピオイドとベンゾジアゼピンについての事実

- Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines cannot be taken or are not able to provide enough pain relief. Opioids such as codeine and hydrocodone are also available in combination with other medicines to treat coughing (see [List of Prescription Opioid Pain and Cough Medicines](#)).
- Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, and slowed or difficult breathing. Opioids also carry serious risks, including [misuse and abuse \(/drugs/resources-you/educational-resources-misuse-prescription-pain-relievers\)](#), addiction, overdose, and death.
- Benzodiazepines are a class of medicines that are widely used to treat conditions including anxiety, insomnia, and seizures (see [List of Benzodiazepines and Other CNS Depressants](#)).

- Common side effects of benzodiazepines include drowsiness, dizziness, weakness, and physical dependence.
- Both opioids and benzodiazepines depress the central nervous system (CNS).
- Both opioids and benzodiazepines are commonly prescribed drugs. In 2014 in the U.S., 81 million patients were dispensed an opioid, and 30 million patients were dispensed a benzodiazepine.¹

患者のための追加情報

- Combining opioid pain or prescription opioid cough medicines with medicines called benzodiazepines, which are used for anxiety, insomnia, and seizures, can result in extreme sleepiness, slowed or difficult breathing, coma, or death. These serious side effects result because both opioids and benzodiazepines impact (depress) the central nervous system (CNS). The CNS controls most of the functions of the brain and body.
- These serious side effects can also occur when opioids are combined with other medicines that depress the CNS or alcohol (see List of Prescription Opioid Pain and Cough Medicines, and List of Benzodiazepines and Other CNS Depressants).
- Do not drink alcohol with any of these medicines. Alcohol also depresses the CNS and can increase the risk for these serious and life-threatening side effects.
- Given the serious side effects that may occur, if you are already taking both opioids and benzodiazepines or other medicines that depress the CNS, talk to your health care professional to see if continued combined use is needed.
- Do not take opioid pain medicines with benzodiazepines or other medicines that depress the CNS without discussing it with your health care professional. Do not take opioid cough medicines with benzodiazepines or other medicines that depress the CNS.
- Always inform all your health care professionals about all the medicines you are taking, including prescription and over-the-counter (OTC) medicines. It is helpful to keep a list of all your current medicines in your wallet or another location where it is easily retrieved. You can fill out and print a copy of [My Medicine Record \(/media/73856/download\)](/media/73856/download).
- If you are taking an opioid pain or cough medicine or a benzodiazepine and don't know if you are also receiving other medicines that may interact, contact your pharmacist or other health care professional.
- If you are taking both an opioid pain medicine and a benzodiazepine or other medicine that depresses the CNS, avoid driving or operating heavy machinery until you know how the medicines affect you.

- Opioids are powerful medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief. However, even when used properly, opioids also carry serious risks, and they can be [misused and abused \(/drugs/resources-you/educational-resources-misuse-prescription-pain-relievers\)](/drugs/resources-you/educational-resources-misuse-prescription-pain-relievers), causing addiction, overdose, and death. Benzodiazepines also carry the risk of dependence.
- It is important to lock up opioids and benzodiazepines and to [dispose \(/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know\)](/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know) of them properly to keep them from being taken accidentally by children or falling into the wrong hands.
- Talk to your health care professional if you have any questions or concerns about opioids, benzodiazepines, or other medicines you are taking.
- Read the patient [Medication Guide \(/drugs/drug-safety-and-availability/medication-guides\)](/drugs/drug-safety-and-availability/medication-guides) or patient information leaflet that comes with your filled prescription(s).
- Report side effects from opioids, benzodiazepines, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

医療専門家向けの追加情報

- Concomitant use of opioid pain or cough medicines and benzodiazepines, other central nervous system (CNS) depressants, or alcohol may result in profound sedation, respiratory depression, coma, and/or death.
- Reserve concomitant prescribing of opioid analgesics with benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Avoid use of prescription opioid cough medications in patients on benzodiazepines or other CNS depressants.
- If the decision is made to concomitantly prescribe a benzodiazepine or other CNS depressant for an indication other than epilepsy with an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response.
- If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
- Monitor patients closely for respiratory depression and sedation.
- Advise both patients and caregivers about the risks of respiratory depression and sedation if opioids are used with benzodiazepines, alcohol, or other CNS

depressants (including illicit or recreational drugs).

- Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid and benzodiazepine or other CNS depressant have been determined.
- Screen patients for risk of substance-use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants, including alcohol and illicit or recreational drugs.
- Encourage patients to read the [Medication Guides \(/drugs/drug-safety-and-availability/medication-guides\)](/drugs/drug-safety-and-availability/medication-guides) or patient information leaflets that come with their filled prescription(s).
- Report adverse events involving opioids, benzodiazepines, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

データの概要

Concomitant use of opioids and benzodiazepines

FDA conducted two studies that showed an increasing trend in concomitant dispensing of opioid analgesics and benzodiazepines, and an increasing frequency of combined benzodiazepine and prescription opioid misuse, abuse, and overdose, as measured by national emergency department (ED) visit and overdose death rates (from prescribed or greater than prescribed doses).^{1, 2}

The first study examined concomitant use patterns of opioid analgesics and benzodiazepines. Between 2002 and 2014, the annual number of patients dispensed an opioid analgesic increased 8 percent, from 75 million to 81 million, and the annual number of patients dispensed a benzodiazepine increased 31 percent, from 23 million to 30 million. During this period, the proportion of opioid analgesic recipients receiving an overlapping benzodiazepine prescription increased by 41 percent, which translates to an increase of more than 2.5 million opioid analgesic users receiving concomitant benzodiazepines in 2014, compared to 2002. The subgroups with the highest probability of receiving concomitant prescriptions were women, patients older than 65, and chronic users of opioid analgesics. However, in absolute numbers, concomitancy occurred most commonly in nonchronic opioid analgesic users, because they greatly outnumber chronic users.¹

The second study² used the Drug Abuse Warning Network (DAWN) to analyze ED visits due to nonmedical use of both prescription opioid analgesics and benzodiazepines, and the National Vital Statistics System Multiple Cause-of-Death file to analyze drug overdose deaths involving both prescription opioid analgesics and benzodiazepines.

Between 2004 and 2011, the rate of nonmedical use-related ED visits involving both opioid analgesics and benzodiazepines increased from 11 to 34.2 per 100,000 population (p-trend 0.0001).>0.0001).>

Two additional studies published in the medical literature show more direct evidence of increased risk of adverse events occurring in patients dispensed both opioid analgesics and benzodiazepines. A prospective observational cohort study conducted in North Carolina found the rates of overdose death among patients co-dispensed opioid analgesics and benzodiazepines were 10 times higher (7.0 per 10,000 person-years; 95% confidence interval (CI): 6.3-7.8) than among patients dispensed opioid analgesics alone (0.7 per 10,000 person-years; 95% CI: 0.6-0.9).³ A case-cohort study examined the Veterans Health Administration data from 2004-2009 and found the risk of death from drug overdose increased among those with concomitant opioid analgesic and benzodiazepine prescriptions. Compared to patients taking opioid analgesics with no history of a benzodiazepine prescription, patients taking opioid analgesics with a history of a benzodiazepine prescription had an increased risk of fatal overdose (hazard ratio (HR)=2.33 (95% CI: 2.05-2.64)), and those with a current benzodiazepine prescription had a similarly increased risk (HR=3.86 (95% CI: 3.49-4.26)) for fatal overdose. In addition, the risk of drug overdose death increased as the daily benzodiazepine dose increased.⁴

Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in these four studies, we are requiring a new *Boxed Warning* to be added to the labeling of opioid analgesic and opioid cough medications and benzodiazepines. Related revisions will also be made to the *Warnings and Precautions*, *Drug Interactions*, and *Patient Counseling Information* sections of the labeling.

Concomitant use of opioids and other central nervous system (CNS) depressants

Recent studies in the literature show that concomitant use of opioid analgesics and CNS depressants other than benzodiazepines, including alcohol, is also associated with serious adverse events. One study reported that opioid analgesics contributed to 77 percent of deaths where benzodiazepines were determined to be a cause of death, and benzodiazepines contributed to 30 percent of deaths where opioid analgesics were determined to be a cause of death. This study also analyzed the involvement of other CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) in these deaths and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.⁵ A second study analyzed 2010 DAWN data and found that alcohol was involved in 18.5 percent of opioid analgesic abuse-related ED visits and 22.1 percent of opioid analgesic-related deaths.⁶

All of the studies were based on opioid analgesics; however, because of similar pharmacologic properties, it is reasonable to expect similar risks with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol. Based on these studies, the *Boxed Warning* for opioid analgesics and opioid cough medications will also highlight the risk of concomitant use with other CNS depressants.

Due to the unique medical needs and benefit/risk considerations for patients taking medication-assisted therapy (MAT) to treat opioid addiction and dependence, we are continuing to examine available evidence regarding the concomitant use of benzodiazepines and MAT drugs.

参考文献

1. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. *Am J Prev Med* 2016;51:151-60.
2. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med* 2015;49:493-501.
3. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-dose Opioid Analgesics on Overdose Mortality. *Pain Med* 2016;17:85-98.
4. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350:h2698.
5. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA* 2013;309:657-9.
6. Jones CM, Paulozzi LJ, Mack KA; Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths - United States, 2010. *MMWR Morb Mortal Wkly Rep* 2014;63:881-5.

[enEspañol \(/drugs/drug-safety-and-availability/la-fda-advierte-acerca-de-los-graves-riesgos-y-muerte-cuando-se-combinan-medicamentos-opioides-para\)](#)

[医薬品安全性コミュニケーション \(/media/99761/download\)](#) (PDF-74KB)

関連情報

- [オピオイド薬 \(/drugs/information-drug-class/opioid-medications\)](#)

- FDAの医薬品審査プロセス：医薬品が安全で効果的であることを確認する
(</drugs/information-consumers-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective>)
- 考え抜く：医薬品の利点とリスクの管理 (</drugs/information-consumers-drugs/think-it-through-managing-benefits-and-risks-medicines>).