

# When the pain decreased, her troubles began

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Mrs. M, age 74, becomes paranoid, anxious, then delirious after starting a painkiller. Is the drug to blame? And if you stop the analgesic, how do you manage her arthritis pain?



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### **CASE** She's not herself

Mrs. M, age 74, is brought to the ER by her husband after he finds her lying on their bedroom floor, incoherent and extremely drowsy. He reports that his wife, who suffers chronic arthritic back and joint pain, might have overdosed on pain medications.

According to her husband, Mrs. M has been taking combination oxycodone/acetaminophen and transdermal fentanyl at unknown dosages, but he is unsure when she started using these medications or if she is taking others. Serum toxicology screening shows twice the normal values for opioids and benzodiazepines; other laboratory results are normal.

Mrs. M is medically stable but her mental status is altered. She is oblivious to time, place and person, speaks to no one, and seems lost in her own world. The hospital's medical service admits Mrs. M for stabilization and to determine whether the overdose was intentional.

Two days later, we evaluate Mrs. M's mental status at the attending physician's request. She appears confused and cannot answer our questions. Her husband tells us she was "doing fine" until approximately 4 months ago, when she started becoming increasingly forgetful and lethargic. He says

she has been forgetting routine chores such as paying bills and grocery shopping. Recently, she has been getting lost during her evening walk; neighbors often help her find her way home.

Mrs. M has had no past psychiatric or medical problems but her husband says she has become increasingly suspicious and paranoid the past 2 months. After being happily married for 40 years, he says his wife now frequently accuses him of infidelity or stealing her possessions. Last week, she misplaced her medications and accused him of hiding them.

### What is causing Mrs. M's sudden confusion?

- oxycodone/acetaminophen combination
- transdermal fentanyl
- a benzodiazepine
- her age

### The authors' observations

Two opioid medications—oxycodone/acetaminophen combination and transdermal fentanyl—are commonly used to manage moderate or severe pain from any type of chronic arthritis.

- Oxycodone, a semisynthetic opioid analgesic indicated for moderate to moderately severe pain, is used when non-drug measures and non-narcotic medications do not control the pain.

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continued

## Clinical Point

**Mrs. M reports forgetfulness, low energy, and poor concentration; her primary care physician diagnoses depression**

- Transdermal fentanyl, a potent analgesic indicated for persistent moderate to severe chronic pain, typically is prescribed to patients who tolerate oral oxycodone, 30 mg/d; morphine, 60 mg; hydromorphone, 8 mg; or an equianalgesic dosage of another opioid for  $\geq 1$  week.

Mrs. M's confusion and cloudy consciousness at admission strongly suggest delirium. Rapid opioid escalation can cause delirium,<sup>1-3</sup> but no preadmission laboratory work was done to affirm this.

Mrs. M also was taking a benzodiazepine, but which medication—and why she was taking it—were unclear. She had no psychiatric diagnosis, and her husband could not recall her medication history.

We also cannot explain Mrs. M's negative cognitive and behavioral changes. Opioid overuse and onset of dementia-related cognitive decline are possibilities.

### TRANSFER Why is she confused?

Based on information from the pharmacy department, doctors at the medical unit restart oxycodone/acetaminophen, 7.5/325 mg tid, and transdermal fentanyl, 25 mcg/hr every 3 days. After discussing how to treat Mrs. M, the psychiatric and medical services transfer her to the geriatric psychiatric inpatient unit 3 days after admission.

We visit Mrs. M hours after her transfer. She seems lethargic but not confused, although Mini-Mental State Examination (MMSE) score of 15 suggests moderate cognitive impairment. Vitamin B<sub>12</sub> and thyroid levels, erythrocyte sedi-

mentation rate, and syphilis test results are normal, allowing us to rule out organic causes for her dementia. Brain MRI shows no neurologic damage. On a scale of 1 to 5 with 5 being most severe, Mrs. M scores her pain as 2 (mild) and her sedation as 3 (moderate).

Mrs. M acknowledges that on the day she collapsed, she might have forgotten she had taken oxycodone/acetaminophen and took it a second time. She then reveals she also had been taking “nerve pills” and might have taken more than usual that day. She says she has been feeling anxious about her forgetfulness and fears she is developing dementia, but she endorses no other current or past psychiatric symptoms.

With Mrs. M's permission, we call her primary care physician for collateral information. The physician tells us Mrs. M has suffered severe joint pain for 2 years. Nonnarcotic medications and treatments—including counseling, support groups, massage, yoga, exercise, biofeedback, relaxation therapy, and physical therapy—were ineffective.

Approximately 10 months ago, the physician started oxycodone/acetaminophen at 2.5/325 mg bid and titrated it over 6 weeks to 7.5/325 mg tid for Mrs. M's persistent joint pain. Four months ago, with her pain still severe, the physician added transdermal fentanyl, 25 mcg/hr every 3 days, after which the patient reported mild improvement.

One month after starting the fentanyl patch, Mrs. M complained of sudden forgetfulness, low energy, poor concentration, and increased sleep. The physician suspected depression with possible comorbid anxiety and prescribed sertraline, 50 mg/d, and alprazolam, 0.5 mg bid. Mrs. M stopped sertraline after 3 days because it was causing diarrhea but kept taking alprazolam.

Mrs. M saw her primary care physician once after starting alprazolam and sertraline but missed her most recent appointment last month. The physician says he inadvertently approved at least 1 premature request for an alprazolam refill.

Six days after admission, Mrs. M's sedation,



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**Box****Reconstructing a patient history: What to ask for, and how to ask**

**R**econstructing treatment history is critical if the patient or family members cannot recall past treatments or if the patient cannot communicate.

Get permission from the patient or family as required under the Health Insurance Portability and Accountability Act. Then contact the primary care or other prescribing physician to obtain:

- a copy of the physician's last progress note and initial evaluation
- notes about adverse reactions to current or past medications
- trials of medications and other treatments relevant to the current complaint.

In emergent cases when the patient is unresponsive or mentally incapacitated and no family members are available, follow the above steps and initiate treatment.

Carefully document that the patient was incoherent, his life was in danger, and you could not reach a family member for permission to treat.

If you cannot communicate with the patient or contact a family member but care is less emergent, consult the hospital's ethics committee to see if a guardian has been appointed. Contact the primary care physician only after the guardian grants permission.

cognitive impairment, and lethargy persist. She reports no mood and anxiety problems, and we have not restarted alprazolam.

**What was decreasing Mrs. M's alertness and energy?**

- depression
- anxiety
- transdermal fentanyl

**The authors' observations**

The fentanyl patch most likely began to diminish Mrs. M's alertness soon after she started using it. The doctor, however, mistook cognitive slowing for new-onset depression or anxiety. Depressive symptoms can imitate dementia, but Mrs. M's severe sedation and denial of depressive symptoms suggest a medication side effect.

The primary care physician's reconstruction of Mrs. M's history explained her positive benzodiazepine reading, and her use of the short-acting benzodiazepine alprazolam could account for her sudden-onset paranoia and cognitive decline (*Box*). Benzodiazepines can cause behavioral side effects such as disinhibition, agitation, or paranoia, and patients age  $\geq 65$  are at increased risk for these side effects.<sup>4</sup> In particular, benzodiazepines with half-lives

$\geq 6$  to 8 hours such as clonazepam and oxazepam can cause short-term memory impairment, confusion, and delirium.<sup>5-7</sup>

Because alprazolam's mean plasma half-life can be as short as 8 hours, 3 to 4 daily doses usually are necessary for day-long therapeutic effect. Multiple dosing of benzodiazepines, however, can cause withdrawal symptoms such as rebound anxiety and insomnia. To quell these symptoms, patients often take higher or additional benzodiazepine doses without a doctor's permission, leading to potential overuse, addiction, or overdose.

When prescribing benzodiazepines (especially in older patients) watch for signs of overuse or abuse, such as early requests for refills, unkempt appearance, excessive sleepiness, or agitation (*Table 1, page 116*).

**How would you manage Mrs. M's pain, given her inability to tolerate transdermal fentanyl?**

- try another opioid
- try a nonnarcotic painkiller
- refer for intensified physical therapy

**The authors' observations**

Persistent chronic pain in the elderly can diminish health and quality of life, resulting

**Clinical Point**

**Short-acting benzodiazepines require multiple daily doses for clinical efficacy, but resultant rebound symptoms can lead to overuse and addiction**

### Clinical Point

Even at low dosages, opioids can diminish function and cognition and increase risk of delirium

Table 1

### Warning signs of opioid, benzodiazepine overuse

<b>Frequent requests</b> for early refills
<b>Patient exceeds</b> prescribed dosage without authorization
<b>Patient reports</b> lost/stolen prescription; if patient has history of substance abuse/dependence or legal problems, even 1 report should raise a red flag
<b>Patient increasingly</b> unkempt or impaired
<b>Negative</b> mood change
<b>Agitation</b>
<b>Patient involved</b> in car or other accidents
<b>Sedation</b>
<b>Purposeful oversedation</b> , particularly when patient has an apparent secondary gain from opioid use (such as qualifying for disability benefits or escaping from work)
<b>New-onset</b> cognitive impairment
<b>Patient abusing</b> alcohol or other illicit CNS depressants

in depression, social isolation, immobility, and sleep disturbance.

Managing an older patient's pain can be challenging (Table 2). Opioids are effective painkillers, but even at relatively low dosages they can diminish function and cognition and increase risk of delirium. Also, patients' ability to tolerate different opioids at different dosages varies widely.

Mrs. M's opioid regimen was intolerable and numerous other treatments did not alleviate her pain. At this point, replacing fentanyl with another opioid was our best option.<sup>8</sup>

We decided to try methadone, which is indicated for moderate to severe pain that does not respond to nonnarcotic treatments. Methadone often is used for chronic pain associated with arthritis or malignancy.

Methadone is less sedating, more tolerable, and carries a lower risk of cognitive side effects than other opioids. Methadone also is fast- and long-acting—its analgesic

effects begin within 30 minutes to 1 hour of oral administration<sup>9</sup> and last approximately 12 hours, thus reducing the risk of breakthrough pain. Methadone also:

- has no active metabolites, which decreases the risk of hepatic side effects
- offers a high volume of distribution, thus allowing clinical effect with minimal dosing.

Oral methadone is a strong analgesic—20 mg is as potent as 100 mg of oral morphine. Start methadone at 5 to 10 mg bid or tid for chronic pain management and titrate according to clinical response and tolerability.<sup>10-12</sup>

Beware the potential for addiction when prescribing opioids to any patient.<sup>13,14</sup> The U.S. Drug Enforcement Agency classifies both methadone and fentanyl as schedule II substances, which applies to highly addictive medications with FDA-approved indications. See patients at least biweekly, especially when switching or titrating pain medications, and watch closely for signs of overuse or addiction. Inform patients to:

- watch for symptoms such as oversedation, memory and concentration problems, and sudden changes in personality
- call you to clarify if these symptoms are methadone side effects.

Increase methadone by 5 mg every 3 to 4 days based on patient tolerance and response. If side effects decrease function or treatment response is lacking, consider a different opioid or another treatment. Decrease visit frequency to once monthly when the pain is under control and the patient experiences no side effects.

Watch for other potential side effects of methadone, such as constipation, sedation, breakthrough pain, sexual dysfunction, decreased immunity, respiratory depression, or prolonged corrected QT intervals.

Patients usually tolerate an immediate switch from transdermal fentanyl to methadone, but a sudden switch from high-dose

Table 2

## Chronic pain management in the elderly: Dos and don'ts

### DO

**Use self rating scales**, as patient can gauge his/her own pain most accurately

**Consider** nonpharmacologic treatments and nonnarcotic analgesics first

**Watch closely** for side effects and drug-drug/ drug-disease interactions in patients receiving analgesics long-term

**Monitor patients** receiving opioids long-term for oversedation, changes in cognition and function

**Consider switching** to methadone or another opioid if patient cannot tolerate current opioid regimen

### DO NOT

**Prescribe** propoxyphene or meperidine—which carry a higher risk of adverse effects than other opioids—to older patient

**Prescribe** opioids if the medical history is unclear

**Increase** opioid dosages without seeing the patient

fentanyl can reduce methadone's effectiveness. Starting methadone at a high dosage to compensate for loss of effectiveness could increase side effect risk. If the fentanyl dosage exceeds 100 mcg/hr, taper by 25 mcg weekly. Simultaneously start methadone at a low dosage and titrate by 5 to 10 mg weekly as needed.

### TREATMENT Medication change

We stop transdermal fentanyl and start oral methadone, 5 mg bid, while continuing oxycodone/acetaminophen at the previous dosage.

Two days later, Mrs. M is much more alert. Since admission 1 week ago, her sedation rating has improved from 3 (mildly sedated) to 4 (almost fully alert). She rates her pain as mild and reports no breakthrough pain or other side

# BROKEN PROMISES



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\*Results from a population survey of 500 ADHD adults and 501 gender- and age-matched non-ADHD adults which investigated characteristics of ADHD and its impact on education, employment, socialization, and personal outlook.

Reference: 1. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67:524-540.



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## Clinical Point

A sudden switch from high-dose transdermal fentanyl to methadone can reduce methadone's effectiveness as an analgesic

effects from methadone. Her MMSE score has improved to 24—suggesting close to normal cognition—and she is much more interactive with staff and family.

Eight days after we start methadone, we stop oxycodone/acetaminophen and increase methadone to 10 mg bid to further improve cognition and alertness and to see if 1 pain medication is sufficient. Two days later, we discharge Mrs. M. She is fully alert, feels little or no joint pain, and is tolerating the methadone increase.

At outpatient follow-up 4 weeks later, Mrs. M remains pain-free and her MMSE score is 29, suggesting normal cognition. Over 8 months, we continue to see her monthly and then bi-monthly, after which we refer her to her primary care physician.

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## Related Resources

- American Association for Geriatric Psychiatry. [www.aagponline.org](http://www.aagponline.org).
- American Pain Society. [www.ampainsoc.org](http://www.ampainsoc.org).

### Drug Brand Names

Alprazolam • Xanax  
 Clonazepam • Klonopin  
 Fentanyl (transdermal) • Duragesic  
 Hydromorphone • Dilaudid  
 Meperidine • Demerol  
 Methadone • Dolophine  
 Oxazepam • Serax  
 Oxycodone • OxyContin, Roxicodone  
 Oxycodone/acetaminophen • Percocet  
 Propoxyphene • Darvon  
 Sertraline • Zoloft

### Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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## Bottom Line

When older patients present with sudden cognitive decline, check for a medical cause or negative drug reaction. Opioids and benzodiazepines can cause short-term memory impairment, confusion, and delirium. Changing opioids can help, but watch for signs of overuse, cognitive changes, or other side effects. See patients at least biweekly when switching or titrating pain medications.