THE CARLAT REPORT
ADDICTION TREATMENT

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CURRENT COVERAGE OF TOPICS IN ADDICTION MEDICINE

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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Opioid Epidemic Update

Learning Objectives
After reading these articles, you should be able to:

1. Implement safety planning strategies for patients with substance use disorders at elevated risk of suicide.
2. Guide patients through at-home induction of buprenorphine.
3. Describe the waves of the opioid epidemic.
4. Summarize some of the findings in the literature regarding addiction treatment.

Suicide Safety Planning for the Patient With Addiction

Jessica Casella, LCSW. Private practice social worker, Branford, CT. Adjunct faculty member at Sacred Heart University School of Social Work. Active member of the state of Connecticut's Suicide Advisory Board.

Ms. Casella has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Suicide is an epidemic in itself, with over 45,000 completed suicides in 2019 alone. It is the 10th leading cause of death in the US and the second among people ages 10–34 (Cerel J et al, *Suicide Life Threat Behav* 2019;49(2):529–534). With media attention focused on the growing number of accidental overdose deaths, suicide among people with addiction may not always be at the forefront of clinicians' minds; however, people with addiction are at a much higher risk of suicide than the general population.

Highlights From This Issue

- Home induction of buprenorphine can be just as successful as induction in the clinic.
- The epidemic of fatal drug overdoses continues to evolve, with current increases largely driven by illicitly manufactured fentanyl and methamphetamine.
- Suicide safety planning is a straightforward tool that clinicians can implement to minimize suicide risk in patients with addiction.

Suicide and addiction
Substances are frequently involved in suicide attempts. Alcohol and opioids are each implicated in a fifth of suicides, followed by cannabis (10.2%), cocaine (4.6%), and amphetamines (3.4%) (Esang M and Ahmed S, *Am J Psych Residents* 2018;13(6):6–8). A tobacco use disorder

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Q&A With the Expert

Buprenorphine Treatment
Noah Capurso, MD

Assistant professor of psychiatry at Yale University, CT. Editor-in-chief of The Carlat Addiction Treatment Report.

Dr. Capurso has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Dr. Capurso, given your role as an expert on various things related to addiction and the editor-in-chief of *The Carlat Addiction Treatment Report,* we've had several discussions about buprenorphine treatment. To begin with the basics, why use buprenorphine at all?
Dr. Capurso: Buprenorphine binds to the mu-opioid receptor, the very same receptor bound by commonly misused opioids. As a partial agonist, it can provide enough agonism to prevent craving and withdrawal but does so with a much lower risk of overdose. The effects of partial agonists plateau at high doses, which is what provides a higher safety margin. We call this a "ceiling effect." Another property of buprenorphine that makes it helpful is its long half-life. Drugs that take effect

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diagnosis is associated with double the suicide risk, and a person with tobacco, drug, and alcohol use disorders has more than an 11-fold increased risk of suicide (Lynch FL et al, *Addict Sci Clin Pract* 2020;15(1):14).

Unfortunately, we don't have a reliable way of knowing who might attempt suicide or when they might make the attempt. The best tool available for clinicians is a thorough suicide risk assessment, and the Substance Abuse and Mental Health Services Administration (SAMHSA) recommends conducting one during all initial appointments for patients with addiction (www.tinyurl.com/wte6sn4c).

Many clinicians prefer standardized risk assessment tools. We recommend the Columbia-Suicide Severity Rating Scale (C-SSRS), the Suicide Assessment Five-Step Evaluation and Triage (SAFE-T) Tool, or the Ask Suicide Screening Questions (ASQ) Toolkit.

In addition to the risk assessment, any patient categorized as high risk for suicide should engage in safety planning before walking out of your office.

What is safety planning?

Safety planning is a six-step process in which clinicians and patients work together to write a safety plan—a document that patients can use to prevent a suicidal crisis (Stanley B and Brown G, *Cog Beh Practice* 2012;19(2):256–264). Research has shown that safety planning can decrease suicidal behavior, increase treatment engagement, and minimize days in the hospital (Stanley B et al, *JAMA Psychiatry* 2018;75(9):894–900; Bryan CJ et al, *J Affect Disord* 2017;212:64–72). It's usually done on paper, but can be done electronically as well—see www.tinyurl.com/4pdcts6c for an example of an app, and search online for resources on social media platforms and in other languages. At the end of a safety planning session, the patient should have a straightforward and easy-to-read list of steps that will help keep them safe. Here are the steps (also see the box on page 3).

Step 1: Identifying the crisis

This first step helps patients identify when suicidal thinking might be on the way. Issues like loneliness, relationship difficulties, financial strain, mental illness, and of course addiction are all potential catalysts of suicidal thinking. Helping patients recognize triggers for substance use will in turn help them recognize circumstances that could lead to suicidal thinking or a suicide attempt.

Step 2: Coping

Here patients come up with ways to distract themselves from suicidal thoughts when they occur. Common coping strategies include exercising, listening to music, and watching movies. Many patients with addiction are used to turning to substances to feel better, so be explicit about what constitutes healthy and unhealthy coping strategies. The more specific the strategy, the better it is; for example, a patient should write "Watch *Caddyshack*" instead of "Watch something funny."

One excellent strategy is making a "hope box"—a group of tangible reminders of why it is worth staying alive. Have patients gather photos, quotes, sobriety chips/coins, or anything personally meaningful, and have them store these items together so they can be reviewed when the patient is feeling suicidal (Stanley B et al, *J Am Acad Child Adolesc Psych* 2009;48(10):1005–1013). Virtual Hope Box is an app that patients can use to create a digital hope box (www.tinyurl.com/wuwk9rxf).

Steps 3–5: Listing of supports in three categories

Patients should have a list of people to reach out to in a time of suicidal crisis. The midst of this crisis is not the time to look up phone numbers, so make sure contact information is part of the plan. A safety plan should have three contact lists on it: social contacts, friends/family, and professionals. Many patients with addiction have friends in recovery or sponsors that can serve as supports in a time of crisis. Peer groups like Alcoholics Anonymous (AA) can be great sources of support as well.

Step 6: Lethal means safety counseling

Lethal means safety counseling is all

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about creating a safe environment. Amazingly, in a quarter of cases, less than five minutes separate the decision to attempt suicide and the attempt itself (Simon OR et al, *Suicide Life Threat Behav* 2001;32(1 Suppl):49–59). Delaying access to lethal means by just a few minutes can literally be life-saving. Family and friends are especially helpful when creating a safe living environment, so involve them early if possible.

Lethal means safety counseling starts with identifying the means of suicide your patient has access to—guns and medication are the most common—and seeing which of these can be removed from the patient's living environment. For example, store guns outside of the house, sell them, or dispose of them through gun buyback events. Dispose of excess medication safely at a police station or DEA dropoff site (www.tinyurl.com/brbc7smk). Medication destruction kits are available online.

If a patient won't give up their gun, encourage gun locks, safes, and separate ammunition storage. If a necessary medication carries overdose potential, store it in a lockbox or blister pack, or have it prescribed in smaller quantities. Seemingly small steps can have huge effects. For example, suicide deaths by acetaminophen overdose dropped 43% in the UK after the government required pills to be sold in small blister packs (Hawkton K et al, *BMJ* 2013;346:f403). The key is to make sure patients can't easily get their hands on lethal means at an impulsive moment.

For patients with addiction, lethal means safety counseling also involves limiting access to substances. The conversations to have are similar to ones you probably have with patients all the time: Counsel them to get rid of drugs and alcohol in the house, delete dealer contact information, and consider switching numbers so dealers can't get in touch. Medications for opioid use disorders decrease mortality, but be particularly aware if these medications are suddenly stopped as this is a particularly high-risk period (Bohnert ASB and Ilgen MA, *N Engl J Med* 2019;380(1):71–79).

See the adjacent table for a sample of a completed safety plan. For more detailed information about the steps of safety planning, see: www.tinyurl.com/2dd55uwx

The Six Steps of Safety Planning
1. Identify thoughts, feelings, and behaviors that precipitate suicidal thinking.
2. Identify internal coping strategies that can help decrease the intensity of the crisis.
3. Brainstorm social contacts or settings that can distract from the crisis.
4. Identify family members or friends who can help manage the crisis.
5. Identify professional supports or agencies who can help manage the crisis (eg, mental health provider, National Suicide Prevention Lifeline, SAMHSA National Helpline).
6. Help the patient make their environment safe. Limit access to lethal means such as guns, medications, and substances.

Wrapping up

At the end of a safety planning session, patients should walk out of your office (or the emergency room) holding a physical, easy-to-read document. Have them put a copy on the fridge, in the car, on their bedside table, or anywhere it will be visible and easy to find. Remind patients that the plan won't help them if they can't find it when they need it.

Finally, remember to review your patients' safety plans regularly. Many clinicians find it helpful to review plans at set intervals, such as every six months. Transitions in care are particularly vulnerable times, so always make sure to review the safety plan when patients change providers or level of care.

CATR VERDICT: Addiction is a major risk factor for suicide, so perform a suicide risk assessment on all patients with a substance use disorder and engage in the six steps of safety planning with anyone who is high risk. Be sure that patients have a physical copy of their safety plan and that they keep it accessible. Review the plan at set intervals, at least every six months.

Sample Safety Plan	
Step 1: Triggers, Risk Factors, and Warning Signs	
My depression gets worse	*I start using substances again*
I start craving drugs	*I isolate myself and skip AA meetings*
Step 2: Internal Coping Strategies	
Watch comedy movies like Caddyshack *and funny TV shows like* Bob's Burgers	
Go for a run	
Review my hope box	
Step 3: Social Contacts	
Attend AA meeting at All Saints Church	
Visit the coffee shop on Main Street for a cup of coffee with friends	
Call AA sponsor Bill Smith (555-1122)	
Step 4: Family Members or Friends	
Mother (555-2345)	*Brother: Simon (555-0987)*
Sister: Janet (555-0987)	*Friend: Frank Johnson (555-7846)*
Step 5: Professionals and Agencies to Contact for Help	
Psychiatrist: Dr. Jordan (555-7777)	
Therapist: Sonya Chen (555-4534)	
Crisis hotline: National Suicide Prevention Lifeline (1-800-273-8255)	
Nearest hospital: State Memorial Hospital (32 Walnut St, 555-4433)	
Step 6: Making the Environment Safe	
Remove all drugs and alcohol from the house	
Keep naloxone kit on the bedside table	
Don't keep guns in the house	
Stick a copy of this safety plan on the front of the fridge and by the phone	

Expert Interview—Buprenorphine Treatment

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quickly and leave the body quickly, what I like to call "quick on, quick off," tend to be more reinforcing of addiction behavior. Buprenorphine's long half-life prevents cycles of intoxication, withdrawal, craving, and return to use. A single dose can prevent withdrawal and cravings for an entire day, or even several days, so patients usually just take it as a daily medication. It's a "slow on, slow off" medication, though not as "slow off" as methadone.

CATR: And how does it compare to methadone?

Dr. Capurso: Both are highly effective treatments for opioid use disorder. Pharmacologically, the difference is that buprenorphine is a partial agonist while methadone is a full agonist. This means methadone does not have the same "ceiling effect" and is therefore not as safe in terms of overdose. In fact, there are some data to suggest that overdose risk actually goes up for a few weeks after methadone is started, likely because its long half-life requires some time to titrate up to an effective dose (Kelty E et al, *Am J Drug Alcohol Abuse* 2019;45(3):285–291).

CATR: If buprenorphine and methadone are binding the same receptor, aren't we just substituting one addiction for another?

Dr. Capurso: No, but this is a reasonable question and one that patients ask all the time, so it's important to address. Illicit opioid use is associated with the DSM's criteria for substance use disorder: disrupted social relationships, use in hazardous situations, giving up activities, etc. This is what we think of when we think of addiction—substance use being harmful to your body and your ability to live life. But medication for opioid use disorder (MOUD) is all about preventing these detrimental outcomes. Other than tolerance and withdrawal, which is a purely physiologic phenomenon, these medications allow people to live lives in which substances are not getting in the way of relationships, employment, or activities. These are medications prescribed by professionals; they are much safer than anything bought off the street from a drug dealer. I tell patients about a famous study that followed a group of young men with opioid addiction, average age 25. After 33 years, more than half were dead or incarcerated, and more than one in 10 were totally lost to follow-up (Hser YI et al, *Arch Gen Psychiatry* 2001;58(5):503–508). Those are terrible statistics. Outcomes for patients on MOUD are much better than that.

"It's rare that someone walks into an outpatient clinic in the throes of withdrawal. Usually they say, 'I used a few hours ago and I'll likely go into withdrawal in 12 to 24 hours.' Well, maybe the clinic won't be open then, or they have every intention of coming back, but they end up using again in the meantime. The patient is in the clinic now, so you should try to seize the opportunity and engage them in treatment. This is a perfect time for a home induction."

Noah Capurso, MD

CATR: What kind of outcomes are you talking about here?

Dr. Capurso: Well, I think the most important outcome is mortality, and we have very good data to show that MOUD saves lives (Pearce LA et al, *BMJ* 2020;368:m772). MOUD also retains patients in treatment, decreases illicit opioid use, reduces criminal activity, and decreases incidence of HIV and hepatitis C (www.tinyurl.com/9n28w5am).

CATR: OK, so we have this great medication: buprenorphine. Why do we need extra training and a special DEA waiver to be allowed to prescribe it, and why are there federal laws dictating the numbers of patients that can be treated?

Dr. Capurso: The answer has very little to do with pharmacology. At the end of the day, buprenorphine is much safer than many of the other medications that have no special requirements or training for prescribers. The requirements for buprenorphine prescribing are the result of a legislative fight that occurred between the FDA and DEA when buprenorphine was first approved. The FDA tried to regulate buprenorphine as a medication, while the DEA worried it could become the next big street drug. Their compromise was the cumbersome legislation that we have today, though it has been adjusted several times since then. It's certainly true that buprenorphine can be diverted, but most of the buprenorphine that winds up on the street is taken to avoid withdrawal or maintain abstinence rather than to get high (Cicero TJ et al, *Drug Alcohol Depend* 2018;193:117–123). In my opinion, it's an example of legislative stigmatization of addiction. I recommend an episode of the podcast *Planet Money* that dives into this further: www.tinyurl.com/xawawae9.

CATR: Is that why buprenorphine comes packaged with naloxone?

Dr. Capurso: Yes, exactly. The naloxone prevents misuse through injection. Pure buprenorphine (Subutex) should be reserved for pregnant patients or those with adverse reactions to naloxone.

CATR: Many providers find prescribing buprenorphine intimidating. The process of starting it even has a special name, "induction." Why is it tricky to start buprenorphine?

Dr. Capurso: The trickiness comes from two of its pharmacological properties: the high receptor affinity and the partial agonism. Let's say a patient who's recently used heroin comes into your office. Their opioid receptors are occupied by morphine molecules (remember that heroin is a morphine prodrug), which are sending full agonist signals. If your patient immediately takes buprenorphine, it will kick the morphine off the receptor since buprenorphine has a much higher affinity for opioid receptors than morphine.

CATR: So now you have one opioid that is replacing another opioid on the receptor. What's the big deal? Either way, their opioid receptors are being activated, right?

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Dr. Capurso: Not exactly. The buprenorphine is not a full agonist, but rather a *partial* agonist, and therefore those opioid receptors will suddenly be sending much less of a signal. The result is instant opioid withdrawal and all the discomforts that go along with that. That's called precipitated withdrawal. The way around this is for your patient to wait long enough since their last heroin use to have some mild to moderate withdrawal symptoms. Patients will be very familiar with these symptoms—things like runny nose, chills, anxiety, craving. These can be measured with the Clinical Opiate Withdrawal Scale (COWS). I usually administer buprenorphine once the patient reaches a COWS of 8 or more. One sign I like to look for is pupil size; dilated pupils usually mean that the patient is ready for a dose of buprenorphine.

CATR: What you're describing is what happens in a clinic or emergency room. These days, a lot of inductions are happening at home, are they not?

Dr. Capurso: They are. We don't have numbers of how many in-office inductions are done versus at home, but home inductions are becoming more and more common. Personally, I've had many patients with successful home inductions, and studies show they work just as well as in-office inductions (Lee JD et al, *J Gen Intern Med* 2009;24(2):226–232).

CATR: How do you determine if a patient is a candidate for home versus in-office induction?

Dr. Capurso: The first distinction is whether the patient presents in withdrawal or not. If the person shows up to the office already withdrawing, they are a good candidate for an in-office induction; you're able to give the medication, see the response, and monitor. This is a common scenario in an emergency room. But it's pretty rare that someone walks into an outpatient clinic in the throes of withdrawal. Usually they say, "I used a few hours ago and I'll likely go into withdrawal in 12 to 24 hours." Well, maybe the clinic won't be open then, or maybe the patient won't be able to come back, or maybe they have every intention of coming back, but they end up using again in the meantime. The patient is in the clinic now, so you should try to seize the opportunity and engage them in treatment. This is a perfect time for a home induction.

CATR: What are the differences between in-office and home induction?

Dr. Capurso: At the end of the day, there actually aren't many differences. The dosing strategies are the same. I'll run through the nuts and bolts of buprenorphine induction, then point out some considerations for when it's done at home. The induction protocol is laid out nicely in the Substance Abuse and Mental Health Services Administration's *Treatment Improvement Protocol* series, which is a great free resource that I highly recommend (www.ncbi.nlm.nih.gov/books/NBK82999/). As we discussed, the first buprenorphine dose should be taken once the patient is in mild to moderate withdrawal. I recommend a first dose of 2 mg for a patient using small amounts of opioids, or 4 mg for patients using large amounts of opioids, such as a bundle or more of heroin daily (which is the equivalent of 10 bags or approximately half a gram). Doses can be repeated every 1–2 hours for a total of 8 mg in the first 24 hours. On rare occasions, a patient might require 12 mg. The dose can be increased to a total of 16 mg on day 2 (spaced throughout the day) and up to 24 mg on day 3.

CATR: It's the same dosing whether the patient is in the office or at home, correct?

Dr. Capurso: Yes, that's right. In the clinic, the severity of withdrawal is determined with COWS, and the timing of the first buprenorphine dose is up to the prescriber or nurse. At home, the patient decides when to take the first dose. For home inductions, I review the symptoms of opioid withdrawal with the patient and then provide them with a Subjective Opiate Withdrawal Scale (SOWS) printout, which is available for free online (www.tinyurl.com/7s9d77km). The SOWS is very similar to the COWS and allows patients to give their withdrawal severity a score. I tell them to take a 2–4 mg dose once their symptoms cross into the "moderate" category. They should start feeling relief pretty quickly. I tell them, "You'll start feeling better in 15 minutes or so. After an hour, if you're still feeling uncomfortable and your score on the SOWS is 10 or more, take a second dose."

CATR: Do patients who are withdrawing actually fill out the SOWS? I'd be nervous that someone with free access to buprenorphine would take it too early, throw themselves into withdrawal, and make things a whole lot worse.

Dr. Capurso: That's actually pretty rare. I say, "The longer you wait, the better your relationship with this medication is going to be." Whether patients actually fill out the SOWS is variable. Honestly, most patients have experienced withdrawal, and many have taken buprenorphine, either from the street or prescribed. Many patients know what it feels like when it is safe for them to take buprenorphine, and for these patients I don't worry too much about the exact SOWS score. And for our more tech-savvy patients, the Buprenorphine Home Induction app can be helpful (available through Apple App Store and Google Play).

CATR: OK, you've walked us through the first 24 hours. Now what?

Dr. Capurso: Whatever amount patients took on the first day, I have them take that same amount when they wake up on day two. It's repetitive after that—wait a few hours, take another 2–4 mg if still in withdrawal, and repeat up to a total of 16 mg. Then the whole thing again, for the third 24 hours, with a total up to 24 mg. I should mention that there are other approaches being developed called "microdosing" or "microinduction." These strategies are not standard practice, but preliminary studies are encouraging *(Editor's note: See our research update "Buprenorphine Induction Without Withdrawal" on page 8).*

CATR: And what guides dosing? Do you have a preset target, or are you just going symptomatically?

Dr. Capurso: Dosing is guided by symptoms, but the symptoms you are treating depends on the patient's goals. Do they want ongoing buprenorphine treatment or just a detoxification? I always strongly recommend ongoing buprenorphine treatment. Detoxification is not adequate addiction treatment, and patients need to understand this. Nonetheless, if the patient insists on just a detox, your target is to minimize physiologic symptoms—diarrhea, rhinorrhea, aches, nausea, etc—and 8 mg of buprenorphine is usually enough to treat these symptoms. The dose is then tapered over a few days. For ongoing treatment, the

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Q&A With the Expert

Drug Overdoses in the US: Trends and Prevention Strategies

Joshua Sharfstein, MD

Professor of the Practice of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Dr. Sharfstein has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Welcome, Dr. Sharfstein. Tell us about your background.

Dr. Sharfstein: I am professor of the Practice of Health Policy and Management at the Johns Hopkins Bloomberg School of Public Health. I'm a pediatrician by training and have worked in the public sector. I was a health policy advisor for Congressman Henry Waxman and the health commissioner of Baltimore. I also was the principal deputy commissioner of the FDA and the health secretary for the state of Maryland.

CATR: How would you categorize the waves of the opioid epidemic?

Dr. Sharfstein: Nationally, we've seen three distinct waves. The first began in the late 1990s and was driven by major increases in opioid prescriptions. The second wave was around 2010 when heroin use surged, fueled by cheap heroin and people transitioning to it from prescription opioids. The third wave, which we're in now and which started around 2013, is characterized by the rise of synthetic opioids, particularly fentanyl, which is very cheap to produce and so highly potent that just the tiniest amount can cause a fatal overdose. In addition, we've seen increases in methamphetamine overdoses, which we can consider the potential beginning of a fourth wave in the pandemic of overdose deaths.

CATR: What are some of the demographic trends that characterize this most recent wave?

Dr. Sharfstein: For much of the opioid epidemic, the overdose death rate among white Americans was higher than any other group, but that has been shifting. In the last few years, there has been a surge in overdoses among Black Americans, which I think is reflective of the high level of distress and the harmful impact of drug law enforcement in many of these communities, so you have a double hit. And given the disproportionate impact of the pandemic, it's possible that we will see overdose mortality among Black Americans exceed that of white Americans in 2020. Again, these changes are really being driven by fentanyl.

CATR: What are some shifts that providers should be aware of when it comes to fentanyl?

Dr. Sharfstein: A couple of years ago, fentanyl was more common on the East Coast. But now we're seeing it take over the illicit opioid market throughout the country. So in 2021, everyone needs to be vigilant for fentanyl. It's really a question of whether fentanyl has totally taken over the market for injectable opioids or is in the process of taking over that market. Initially, fentanyl was mixed in with heroin, and overdoses spiked because many people weren't prepared for the higher potency. But over time, fentanyl has driven heroin out of many drug markets. More recently, fentanyl is being mixed into methamphetamine and cocaine, which is contributing to methamphetamine- and cocaine-related overdose deaths. There are even rare reports of fentanyl getting mixed into cannabis. This is a challenge that is a bit different from other drug challenges of the past. Many people using fentanyl aren't even aware of it.

CATR: And this is where drug checking comes in.

Dr. Sharfstein: Exactly. The idea behind drug checking is that people who use drugs can protect themselves better if they know what they are taking. It's consumer protection in the drug market. Surveys show that 90% of people who use drugs say they want to know whether fentanyl is present in what they are consuming (https://americanhealth.jhu.edu/fentanyl). If they know they are consuming fentanyl, they might use less, more slowly, or not at all.

CATR: How is drug checking done?

Dr. Sharfstein: The easiest way for patients to check drugs themselves is with test strips, usually fentanyl test strips, which were developed for urine. But they're quite accurate when used on drugs dissolved in water.

CATR: How can patients get fentanyl test strips?

Dr. Sharfstein: Many city public health departments will pass them out, as will harm reduction programs. They're also widely available for purchase online. Providers should be aware, however, that test strips are regulated at the state level and are considered drug paraphernalia in some jurisdictions. In some places, those laws are enforced, but not in others. In some states, like here in Maryland, laws protect the ability to have test strips. I would advise clinicians talk to their local health department about what's permitted because drug testing is a powerful harm reduction tool that patients can utilize during this incredible surge in overdoses.

CATR: How does fentanyl use manifest differently compared to prescription opioid analgesics and heroin?

Dr. Sharfstein: First, fentanyl has a very short half-life, so people have to take fentanyl more often to avoid withdrawal: every two to four hours or so. Second, there is a very narrow margin for error. Fentanyl is so highly potent that using just a little bit more than usual can result in a fatal overdose. And the potency can vary widely from batch to batch. Sometimes, it may only be after several overdoses that people realize a particular batch is more potent than others. Also, there seem to

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be differences when it comes to starting medications for opioid use disorder (OUD), particularly buprenorphine *(Editor's note: see our research update "A New Buprenorphine Dosing Strategy for Easier Induction From Fentanyl" on page 9).*

CATR: There was a small decrease in overdose deaths in 2018, but those gains were immediately erased in the COVID-19 pandemic. How did that happen?

Dr. Sharfstein: It's important to note that overdoses started going back up in August 2019, well before the pandemic. But then there was a big acceleration once the pandemic hit for a number of reasons. You can think of three major contributors when it comes to the pandemic and overdose deaths: 1) individual-level factors, 2) environmental factors, and 3) the drugs themselves. COVID-19 caused significant impacts in all three areas. Individuals were experiencing enormous levels of stress, which makes drug use more likely. In terms of the environment, people were isolated and out of work, and many lost loved ones and supporters. In many cases, the pandemic profoundly disrupted treatment access. And in terms of the drugs themselves, COVID-19 actually disrupted the opioid supply for a little while, but this was transient, and when drugs flowed back into the country the market became even more dominated by fentanyl than ever before, as evidenced by overdoses.

CATR: How do we as providers make an impact?

Dr. Sharfstein: It's helpful to divide providers into three groups. First are the addiction providers. Now that we're two years into the pandemic, it's important for people in this group to take a step back in order to learn lessons from the changes that happened within their own treatment system. What worked? What didn't? For example, many systems began to allow buprenorphine prescribing through telemedicine (Samuels E et al, *J Addict Med* 2020;14(4):e8–e9). This flexibility, I believe, was a major countervailing force that helped prevent overdose fatalities from increasing even further. The lesson for addiction providers is to hold onto the changes that worked and build on them to create even more accessible effective treatment programs in the future.

"It's really a question of whether fentanyl has totally taken over the market for injectable opioids or is in the process of taking over that market. Over time, fentanyl has driven heroin out of many drug markets. More recently, fentanyl is being mixed into methamphetamine and cocaine, which is contributing to methamphetamine- and cocaine-related overdose deaths."

Joshua Sharfstein, MD

CATR: What's the second group?

Dr. Sharfstein: These are clinicians, including mental health providers, who come into contact with people who use drugs on a regular basis but who are not primarily focused on addiction treatment. For this group, it is essential to integrate addiction care into the clinical environment as much as possible. Many systems of care have an entrenched, artificial divide between mental health and addiction treatment that causes a lot of missed opportunities. Not only does proper addiction treatment save lives, but it makes mental health treatment easier and better. Psychiatrists should get the training to prescribe buprenorphine and know how to refer their patients to addiction specialists if needed. Administrators should ensure that their programs have close working relationships with opioid treatment programs. It is incredibly important for the mental health community to feel a sense of ownership over addiction treatment.

CATR: And the final group?

Dr. Sharfstein: This group contains what might be called "other medical practitioners": emergency room doctors, hospitalists, and primary care providers. We have evidence that our treatments enormously reduce morbidity and mortality. Yet so many facilities, particularly hospitals, don't offer these highly effective treatments. Patients can't access them. That's a failure of the medical system. Just like general mental health providers, individuals in this "other medical practitioner" group should prescribe buprenorphine for OUD. Unfortunately, far too few doctors, nurse practitioners, and physician assistants are willing or able to do that. In my view, the epidemic of overdose deaths is not entirely dissimilar from COVID-19, where systems have had to adopt whole new sets of policies to provide good care. We are in a crisis of overdose deaths that is taking more than 93,000 lives a year—we all have to think about doing our jobs differently.

CATR: Some providers will say that if they start providing buprenorphine treatment, their practice will become a magnet for people who use drugs. How do you respond to that?

Dr. Sharfstein: My wife is an addiction medicine physician. She and I wrote a book on the opioid epidemic (Olsen Y and Sharfstein JM, *The Opioid Epidemic: What Everyone Needs to Know.* Oxford University Press; 2019) and we heard this concern frequently. It's an unfortunate way of seeing things because, in our experience, many providers who start giving real addiction treatment actually end up feeling very satisfied when they can help patients recover control over their lives. It just takes getting over that initial hump of training and certification. But there are legal arguments for providing treatment too. A recent Bloomberg American Health Initiative–funded report from the Legal Action Center pointed out the potential legal liability of hospitals that don't provide effective addiction treatment in the emergency department (https://americanhealth.jhu.edu/themes/custom/bahi/assets/pdfs/LAC_Report.pdf).

CATR: Can you say a few words about implementing harm reduction techniques?

Dr. Sharfstein: Keeping a harm reduction perspective across treatment settings is crucial. First of all, providers should always meet people where they are. For instance, patients may not be interested in medication for OUD, but they're

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Expert Interview—Drug Overdoses in the US: Trends and Prevention Strategies

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interested in fentanyl checking and naloxone that will keep them alive. And then they might be interested in more treatment at the next encounter. Anything that moves people toward health and gives them a greater sense of agency is a step toward recovery and regaining control of their lives. Removing barriers to care is also very important and can be life-saving.

CATR: What sort of barriers to care might providers be able to address in the clinic?

Dr. Sharfstein: For example, it is very common for providers or systems to require that individuals meet a certain standard of behavior before they can get help: requiring group participation as a prerequisite for buprenorphine, for instance. Well, some people might not be able to make weekly group, but they are still worthy of assistance and still have dignity. Other examples include requiring patients to participate in lengthy intake assessments before receiving treatment when they might be in uncomfortable withdrawal, or scheduling intake appointments for dates that are days away. The patient could use drugs while waiting for that appointment and risk overdose. A clinic can tweak these standards relatively easily and have a huge impact. We should be trying to see what's possible, not erecting arbitrary barriers based on historical practice with little evidence.

CATR: We are also seeing a concerning rise in fatal overdoses from stimulants. What should clinicians know?

Dr. Sharfstein: Well, methamphetamine is the biggest culprit, and its use is more common among younger people. It's also more prevalent on the West Coast compared to the East Coast, though that might be changing. Most clinicians are aware if methamphetamine is endemic to their area. But unlike opioids, stimulants have much fewer medication options, so in some ways, it can be harder to treat than opioid addiction. One of the most effective techniques is contingency management, but those programs are pretty limited. So severe stimulant use disorder often requires focused and specialized treatments (see *CATR* May/June 2021 for information on the diagnosis and treatment of stimulant use disorders).

CATR: Thank you for your time, Dr. Sharfstein.

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Research Updates

MICROINDUCTION

Buprenorphine Induction Without Withdrawal

REVIEW OF: Ahmed S et al, *Am J Addict* 2021;30(4):305–315

Buprenorphine is notorious for precipitating withdrawal in patients who have recently taken opioids. Its high receptor affinity and partial agonism at the mu receptor can make inductions tricky. Giving it too soon can cause severe withdrawal, yet giving it too late means patients are in discomfort from withdrawal while awaiting their first buprenorphine dose. A fair number of inductions result in some level of precipitated withdrawal (estimates range from 5% to 16.8%), and it has been speculated that the higher prevalence of fentanyl on the street has increased this rate even further. But there may be an alternative.

This review examined a novel approach, called microinduction, for transitioning patients to buprenorphine from an opioid agonist like methadone or heroin. In this strategy, microdoses of buprenorphine (0.2–0.5 mg) are introduced and gradually increased without waiting for withdrawal to start. Microinduction is based on the theory that multiple small doses of buprenorphine, given its high receptor affinity, will gradually replace the lower-affinity opioid that is occupying the mu receptor sites. This gradual change from full to partial agonist causes a less dramatic physiological shift, and hence fewer withdrawal symptoms. In contrast, a single large dose of buprenorphine will quickly replace the opioid and result in a sudden drop in agonist signaling.

This literature review examined 18 reports (n = 63) of various buprenorphine microinduction strategies. The individual studies were quite heterogeneous, varying in opioid agonists, buprenorphine dosing, and time course. However, they all started with very low doses of buprenorphine (0.2–0.5 mg) and increased this dose slowly over time (3–112 days). Most transitioned over 4–8 days and stabilized patients on daily buprenorphine doses of 8–16 mg. Some utilized symptomatic treatment with clonidine during the induction period.

In most cases, the opioid agonist was continued while buprenorphine was introduced, then tapered over time or discontinued when the buprenorphine dose was judged adequate. Six studies chose instead to utilize a transdermal patch, given its ability to consistently deliver small amounts of medication. These patches (buprenorphine in all cases, save one that used fentanyl) served as a bridge from full agonist to eventual higher doses of sublingual buprenorphine. In most but not all of these cases, the previous opioid was discontinued when the transdermal patch was started.

The review highlights a few situations in which microinduction might be particularly beneficial, namely when transitioning to buprenorphine from methadone and for patients with chronic pain. The long half-life of methadone makes for an extended withdrawal period when utilizing traditional buprenorphine induction. Patients in this study were transitioned from methadone doses as high as 200 mg without requiring prior decrease of dose. Patients hospitalized for medical or surgical conditions could transition from illicit opioids without withdrawal. Individuals with chronic pain were transitioned without having to endure an increase in pain during the opioid withdrawal period.

Before we jump to microinduction for all of our patients, there are caveats

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Illustrative Buprenorphine Microdosing Protocol		
Day	**Buprenorphine Dosage**	**Preexisting Opioid Dosage (methadone, heroin, fentanyl, etc.)**
1	0.5 mg[1] once	Full dosage
2	0.5 mg BID	Full dosage
3	1 mg BID	Full dosage
4	2 mg BID	Full dosage
5	2 mg TID	Full dosage
6	2 mg QID	Full dosage
7	4 mg TID	STOP
Start 0.5 mg buprenorphine; patient can continue opioid agonist use. Gradually increase buprenorphine dose as tolerated by the patient until the patient reaches 8–12 mg of buprenorphine, then stop opioid agonist and titrate buprenorphine until patient is no longer experiencing cravings.		
[1]Small doses can be obtained by cutting 2 mg strips into sections (eg, ¼ of a strip provides 0.5 mg, and ½ of a strip provides 1 mg).		

to consider. All of these papers were case reports or case series, with only one open-label trial. Most did not evaluate withdrawal with validated measures. There is no standard protocol for microinduction and no randomized trials comparing microinduction to the usual method of induction. Nevertheless, this review shows the promise of this technique as an alternative for safe, effective initiation of buprenorphine treatment.

CATR'S TAKE

While not yet standard of care, microinduction could be considered for patients who are difficult to induce. However, there is still work to do in standardizing and validating this approach.

—David Moltz, MD. Dr. Moltz has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

A New Buprenorphine Dosing Strategy for Easier Induction From Fentanyl

REVIEW OF: Antoine D et al, *Am J Addict* 2021;30(1):83–87

The escalating rate of opioid overdose deaths has been linked to the rise of illicit fentanyl. Increasing evidence shows that fentanyl and its analogues, such as carfentanil and acetylfentanyl, are fast replacing heroin as the most commonly used illicit opioid for many people with opioid use disorder (OUD). Furthermore, fentanyl has become a common adulterant of many street drugs, meaning it is often used inadvertently with potentially lethal results.

The widespread availability of fentanyl has changed the landscape of opioid treatment, because its pharmacologic properties differ from other opioid agonists. In particular, fentanyl's lipophilicity, rapid crossing of the blood-brain barrier, and sky-high receptor potency can make for tricky buprenorphine induction.

The usual method of buprenorphine induction consists of waiting for the patient to develop moderate withdrawal symptoms, then giving a 2–4 mg dose of sublingual buprenorphine and possibly repeating the dose after a few hours. This works well for most opioids; however, evidence indicates that patients are more likely to suffer precipitated withdrawal from this protocol if they have fentanyl in their system. In addition, "fentanyl" from the street can actually consist of a mixture of fentanyl, various fentanyl analogs, and other opioid agonists, further complicating the picture.

Realizing that precipitated withdrawal could deter people from seeking treatment, the authors set out to investigate whether frequent small doses of buprenorphine initiated at higher Clinical Opiate Withdrawal Scale (COWS) scores resulted in fewer precipitated withdrawal symptoms than the usual induction procedure.

Researchers recruited four participants who had recently used fentanyl but had been abstinent for 24 hours. Two patients underwent induction using the standard procedure: 4 mg of buprenorphine once COWS reached 9, followed by another dose three hours later. The other two patients underwent the novel induction strategy: 2 mg of buprenorphine at COWS of 13, followed by additional 2 mg doses at 1.5, 3.5, and six hours.

The researchers found that the patients who underwent the standard buprenorphine induction had severe precipitated withdrawal (defined as COWS > 12). One patient even had COWS above 30 shortly after receiving the first dose of buprenorphine. The patients who received the modified induction never scored above 10 once buprenorphine was initiated.

This study adds to growing evidence that lower initial doses of buprenorphine can ease the induction process. In a prior issue of *CATR* (November/December 2020), and in the research update on the previous page, we discussed microinduction, in which very low doses of buprenorphine are used to allow patients to start buprenorphine without having to go into withdrawal first. The dosing strategy being studied here is different, in that patients experience withdrawal prior to induction and the dose being utilized (2 mg) lies somewhere between microdosing (0.5 mg) and the standard induction protocol (4–8 mg).

CATR'S TAKE

This was only a small case series, but the strategy may be worth trying for your patients using fentanyl, especially if they have a history of precipitated withdrawal when initiating buprenorphine.

—Oluwole Jegede, MD. Dr. Jegede has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

OUD

Suboxone vs Vivitrol for Opioid Use Disorder: How Do You Choose?

REVIEW OF: Nunes EV Jr et al, *Am J Psychiatry* 2021;178(7):660–671

For decades, methadone and buprenorphine (Bup) have been upheld as the gold standard of opioid use disorder (OUD) treatments, with naltrexone largely considered second line. However, a pair of landmark studies challenged that wisdom by showing the non-inferiority of long-acting injectable naltrexone (XR-NTX) as compared

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Research Updates

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to sublingual Bup (Lee JD et al, *Lancet* 2018;391(10118):309–318; Tanum L et al, *JAMA Psychiatry* 2017;74(12):1197–1205). These papers showed that the treatments are equally effective for patients who manage to start treatment. However, patients are much more likely to tolerate starting treatment with Bup because they need to be abstinent from opioids for only about 12 hours before Bup induction. Conversely, patients must be opioid-free for at least seven *days* before they can start XR-NTX—a tall order for many people with OUD.

The authors of this recent study hoped to drill deeper into these data to better understand which patients might do better with Bup vs XR-NTX. They did this by reexamining data from one of those original papers: the X:BOT trial (Lee et al, 2018). In this trial, 287 patients with OUD were randomized to Bup (8–24 mg sublingual daily) and 283 patients to XR-NTX (380 mg IM every 28 days). Participants were assessed weekly with urine drug screens and self-reported substance use. Authors examined the data for demographic characteristics predictive of successful medication initiation and rate of returning to use.

Overall, it was easier for participants to successfully start Bup (5.9% failure rate) compared to XR-NTX (27.9% failure rate). The following characteristics were most predictive of successful initiation with Bup versus XR-NTX:

1. Presence of chronic pain. Participants with moderate to severe chronic pain had a much higher failure rate with XR-NTX compared to Bup (32.4% vs 2%, OR = 23.68). This makes sense because having chronic pain would make it difficult to stop opioid use for several days.
2. Recent use of opioids. Individuals randomized to XR-NTX soon after their last use (less than three days) had a higher rate of treatment failure compared to Bup (41.3% vs 1.5%, OR = 47.79). This is no surprise, since use of naltrexone soon after opioid use may trigger withdrawal symptoms.
3. Stated preference for Bup. Participants who stated a preference for Bup had a much lower failure rate if they received Bup than if they received XR-NTX (0.88% vs 33.0%, OR = 55.28). Those who did not state a preference for Bup had similar failure rates with both medications.

The following characteristics tended to predict success with XR-NTX:

1. Being on probation/parole. XR-NTX fared better in participants on probation/parole as compared to the study participants overall. In this group, XR-NTX had a similar failure rate to Bup (17.39% vs 14.39%, OR = 1.25, CI = 0.42–3.61).
2. Being homeless. XR-NTX had an edge among homeless individuals where the rate of returning to opioid use was lower in those receiving XR-NTX as compared to Bup (51.6% vs 70.4%, OR = 0.45). This is the only patient characteristic that was predictive of return to use, as opposed to failure to start the medication.

It is worth noting that only opioid-related outcomes were measured, and that other potentially relevant outcomes unrelated to opioid use were not reported. For example, a patient with comorbid alcohol use disorder (AUD) might fare better with XR-NTX since it is an effective medication for both AUD and OUD. XR-NTX might also be preferred for patients with comorbid benzodiazepine use disorder, since Bup and benzos can produce fatal respiratory suppression when combined.

CATR'S TAKE

This study largely confirms previous findings that Bup and XR-NTX are both effective treatments for OUD once started, but that Bup is easier to initiate than XR-NTX. Factors predicting better success with initiating Bup include chronic pain, recent opioid use, and preference for Bup. Initiation of Bup and XR-NTX fared similarly for patients on probation. Homeless patients had lower rates of return to use with XR-NTX. These data provide useful guidance, but other patient factors should still be considered when making a final medication choice.

—Gregory Lande, MD. Dr. Lande has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Expert Interview—Buprenorphine Treatment

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target is to minimize opioid cravings, which requires higher doses of buprenorphine—usually 16 mg or above (Mattick RP et al, *Cochrane Database Syst Rev* 2014;2:CD002207). So if a patient is interested in long-term treatment, I recommend at least 16 mg daily initially. Cravings are a moving target, especially at first. I want to aggressively treat cravings because the early period has the highest risk of returning to use. So I tell patients, "If you are feeling cravings, it's OK to take an extra 4 mg; just keep track of how much you take."

CATR: Are there any other differences to keep in mind between home and in-office induction?

Dr. Capurso: Only one. There are two general approaches to detoxification: 1) using an opioid like buprenorphine or methadone, and 2) symptomatic treatment with clonidine, dicyclomine, loperamide, etc. In an office setting, I advocate for not mixing the two. If you're using buprenorphine, for example, you should give that for withdrawal symptoms—giving clonidine is just going to muddy the waters. But with home inductions, I'm a little less dogmatic. I recommend taking buprenorphine at the doses we discussed, but if patients are still feeling breakthrough symptoms, there is no harm in providing a little ondansetron, loperamide, or clonidine.

CATR: What about follow-up? How often to do you see home induction patients?

Dr. Capurso: For the first few days, you'd ideally see the patient daily, or at least have a phone call with them. Sometimes that's not possible, so you can go two or even three days, though I don't like doing that. For patients starting

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CE/CME Post-Test

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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

1. Which of the following about substance use and suicide is true (LO #1)?
   [ ] a. Cocaine is implicated in a third of suicide attempts
   [ ] b. A person with an alcohol use disorder has more than an 11-fold increased risk of suicide
   [ ] c. Alcohol and cannabis are both implicated in a fourth of suicide attempts
   [ ] d. A person with tobacco, drug, and alcohol use disorders has more than an 11-fold increased risk of suicide

2. According to Dr. Capurso, at what dose can opioid cravings be minimized with ongoing buprenorphine treatment for most patients (LO #2)?
   [ ] a. 2–8 mg [ ] b. 4 mg or greater [ ] c. 8–12 mg [ ] d. 16 mg or greater

3. According to Dr. Sharfstein, the authorization for addiction providers to prescribe buprenorphine through telemedicine was a major countervailing force that prevented further increases in fatal opioid overdoses during the COVID-19 pandemic (LO #3).
   [ ] a. True [ ] b. False

4. In recent studies of patients with opioid use disorder (OUD), which characteristic was predictive of a lower rate of returning to opioid use with long-acting injectable naltrexone, compared to sublingual buprenorphine (LO #4)?
   [ ] a. Probation [ ] b. Chronic pain [ ] c. Homelessness [ ] d. Recent use of opioids

5. Which of the following best describes the six-step safety plan for patients at a high risk for suicide (LO #1)?
   [ ] a. The less specific the safety plan the better
   [ ] b. Safety planning can decrease suicidal behavior increase, treatment engagement, and minimize days in the hospital
   [ ] c. Patients should give their only safety plan document to a friend
   [ ] d. The safety plan should include only one reliable contact, preferably a family member

6. Which of the following describes differences in pharmacology and safety profile between buprenorphine and methadone for OUD (LO #2)?
   [ ] a. Buprenorphine is a partial mu-opioid receptor agonist and has a lower overdose risk than methadone
   [ ] b. Buprenorphine is a full mu-opioid receptor agonist and has a higher overdose risk than methadone
   [ ] c. Methadone is a full mu-opioid receptor agonist and has a lower overdose risk than buprenorphine
   [ ] d. Methadone is a partial mu-opioid receptor agonist and has a higher overdose risk than buprenorphine

7. According to Dr. Sharfstein, which stimulant is the biggest culprit associated with the recent rise in stimulant-related fatal overdoses (LO #3)?
   [ ] a. MDMA [ ] b. Methylphenidate [ ] c. Methamphetamine [ ] d. Cocaine

8. For patients who have recently used opioid agonists, multiple small doses of buprenorphine are less likely to cause withdrawal symptoms than a single large dose (LO #4).
   [ ] a. True [ ] b. False

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Expert Interview—Buprenorphine Treatment

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ongoing treatment, once the dose is stable, I see them weekly for a few weeks. As long as they are doing OK, meaning showing up to appointments, having negative urine drug screens, and taking the medication as prescribed, I'll space them out to every two weeks, and then monthly. That's pretty standard.

CATR: We've covered how to prescribe buprenorphine—what else should providers be thinking about?

Dr. Capurso: Buprenorphine is just one piece of the puzzle. Granted, it's the most important piece—treatment plans that don't incorporate MOUD don't have good outcomes. But these encounters are also an opportunity for psychoeducation and motivational interviewing. I always try to work in some basic behavioral strategies like deleting drug dealers' numbers, getting rid of any drugs in the house, avoiding the "people, places, and things" that can lead to drug use. And I recommend using harm reduction strategies (see *CATR* January/February 2020): prescribe naloxone, offer testing for HIV and hepatitis, refer to primary care if they don't have a PCP, or refer to case management services if that's an option. Some of these patients might benefit from a referral to therapy for comorbid mental health issues; others might benefit from apps such as reSET-O (see *CATR* November/December 2020). For many of these patients, especially ones just receiving withdrawal management, your visit might be one of their very few encounters with the health care system. Make it count.

CATR: Thank you for your time, Dr. Capurso.

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