# THE CARLAT REPORT HOSPITAL PSYCHIATRY

*A CME Publication*

UNBIASED INFORMATION COVERING HOSPITAL PSYCHIATRY




Special Double First Issue!


**Victoria Hendrick, MD**
**Editor-in-Chief**



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## IN THIS ISSUE

*Focus of the Month:*
**Psychiatric Emergencies**



### Learning Objectives

*After reading these articles, you should be able to:*

1. Evaluate the role of esketamine for acute suicidality and pharmacologic treatment for schizophrenia in an emergent hospital setting.
2. Describe best practices for treating deliberate foreign body ingestion.
3. Differentiate serotonin syndrome and neuroleptic malignant syndrome for appropriate assessment and treatment.
4. Summarize some of the current research findings on psychiatric treatment.

# Intranasal Esketamine: New Hope for Suicidal Patients?


*Victoria Hendrick, MD. Editor in Chief,* The Carlat Hospital Psychiatry Report. *Chief, Inpatient Psychiatry, Olive View UCLA Medical Center. Daniel Carlat, MD. Publisher,* The Carlat Hospital Psychiatry Report.


Dr. Hendrick and Dr. Carlat have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

It's likely your patients have asked you about esketamine. The buzz is that it's a rapid-acting miracle cure for suicidal depression. Dr. Thomas Insel, former director of NIMH, declared that ketamine "might be the most important breakthrough in antidepressant treatment in decades" (www.nimh.nih.gov/about/directors/thomas-insel/blog/2014/ketamine.shtml). How well does it actually work? And what are its pros and cons?

### Highlights From This Issue

Esketamine is now FDA approved for major depression with suicidality and its fast antidepressant effects can be lifesaving, but it doesn't always work.

Dr. Laura Tormoehlen discusses the management of neuroleptic malignant syndrome and serotonin syndrome and summarizes how to distinguish between these acute conditions.

Polypharmacy for schizophrenia can be effective, argues Dr. T. Scott Stroup, but only with certain medications.

Patients who deliberately swallow foreign objects fall into four diagnostic categories, each requiring different treatment. We share tips for how to help these patients.


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Q&A With the Expert

## Serotonin Syndrome Versus NMS
## Laura Tormoehlen, MD


*Associate Professor of Clinical Neurology and Clinical Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN.*


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

**CHPR: Can you start by telling us about yourself?**
**Dr. Tormoehlen:** Sure. I am a neurologist and have completed a medical toxicology fellowship. I am an attending physician for the neurology service at Indiana University Health Methodist Hospital, as well as for the toxicology service at Methodist, University, Riley, and Eskenazi Hospitals. I also run the neurotoxicology clinic here at Indiana University and serve as the vice chair of clinical practice for the neurology department.
**CHPR: You recently wrote a review of neuroleptic malignant syndrome (NMS) and serotonin syndrome. Can you tell us about these syndromes?**
**Dr. Tormoehlen:** Sure. Let's start by reviewing some of the basics of these two conditions. NMS is a rare but potentially life-threatening reaction to antipsychotic medications, due to blockage of dopamine receptors. Serotonin syndrome results from excessive serotonin activity in the central nervous


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## Expert Interview—Serotonin Syndrome Versus NMS

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system and can range from mild to severe, even potentially fatal. Both disorders often present with muscle rigidity, hyperthermia, and altered mental status.

**CHPR: What's your approach to differentiating the two?**

**Dr. Tormoehlen:** Once you see either an increased tone or an elevated temperature of unknown origin, then the next step is a review of the patient's medications, keeping in mind that many drugs we might not think of as serotonergic can be serotonergic as a secondary mechanism.

**CHPR: Can you give us some examples?**

**Dr. Tormoehlen:** There are several ways drugs can be proserotonergic (ie, lead to increased serotonin activity). For example, they can increase serotonin release, inhibit serotonin metabolism, inhibit serotonin reuptake, or activate serotonin receptors (*Editor's note:* Examples of medications that contribute to serotonin syndrome are available at www.thecarlatreport.com/SerotoninSyndrome). Fentanyl, linezolid, and OTC drugs like dextromethorphan are all examples of proserotonergic medications that tend to be overlooked. You also want to get information on any supplements like St. John's wort.

**CHPR: Do you also take the medication's serotonergic potency into account?**

**Dr. Tormoehlen:** Yes, that matters. A reasonable example would be triptans. Triptans are proserotonergic, and if you prescribe a triptan to a migraine patient who is also on amitriptyline as a prophylaxis, your EMR will send you an alert. However, triptans are fairly weakly proserotonergic, so your patient would likely have to be on a heavy regimen of the triptan on top of high doses of other serotonergic meds to develop serotonin syndrome.

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*EDITORIAL INFORMATION*

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This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

## Introducing *The Carlat Hospital Psychiatry Report (CHPR)*

To all my devoted readers: Welcome to the inaugural issue of *CHPR*—our fourth CME newsletter. Over the past couple of years I have been working full time as the director of inpatient psychiatry at a community hospital just outside of Boston. I spend my days helping people who are afflicted with serious mental illness, and whose lives are a nightmare of delusions, suicidality, substance use—and often agitation and violence. I've had chairs thrown at me. I've had patients who have swallowed pencils and eyeglasses. I've managed delirious patients who are refusing dialysis and are close to dying of uremia. The work is fulfilling, and the challenges are enormous, so I decided we owe it to you to present the latest techniques for helping our most seriously ill patients.

Unlike our other newsletters, which are focused on outpatient practice, the focus of *CHPR* is on hospital psychiatry, including inpatient units, emergency rooms, and consult liaison work. Beyond that, we have kept our usual format—incisive interviews with experts in the field, practical reviews of clinical topics, and summaries of the latest clinical trials pertaining to hospital psychiatry. Luckily, I was able to recruit a long-time Carlat Report subscriber to edit this new journal, Victoria Hendrick, MD.

I hope you enjoy this exciting new venture. Please drop me a line to let me know how you like it and what topics you'd like to see covered.

Sincerely,
Daniel Carlat, MD
dcarlat@thecarlatreport.com

## Welcoming Our New Editor-in-Chief

We're pleased to introduce **Victoria Hendrick, MD,** as *CHPR*'s editor-in-chief. Dr. Hendrick is a clinical professor at the David Geffen School of Medicine at UCLA and the director of inpatient psychiatry at Olive View UCLA Medical Center, where she carries a caseload of patients and teaches and supervises medical students and psychiatry residents. After finishing medical school and psychiatric residency at UCLA, she spent several years as a principal investigator and co-investigator on NIMH-funded research studies. Dr. Hendrick has published over 75 research papers, editorials, and books. She has an enduring interest in the needs of severely mentally ill patients from underserved populations and has worked in community mental health settings for her entire career.

Expert Interview—Serotonin Syndrome Versus NMS

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**CHPR: So we look for the number and potency of serotonergic medications that the patient is taking. Should we also look for drug interactions?**

**Dr. Tormoehlen:** Yes, because some drugs inhibit cytochrome P450 enzymes and can cause serotonin syndrome when they're combined with serotonergic medications. For example, ciprofloxacin, which inhibits CYP3A4, or fluconazole, which inhibits CYP2C19, can cause serotonin syndrome in combination with certain SSRI or SNRI antidepressants. Serotonin syndrome is predictable. If a patient takes enough serotonergic drugs, especially if they have different mechanisms, you will observe serotonin syndrome. It's more common than we realize because mild cases occur that we don't think of as being serotonin syndrome.

**"Serotonin syndrome is much more likely to be acute in onset, while NMS is subacute. If your patient was fine 4 hours ago and is now suddenly hyperthermic and rigid, it's much more likely to be serotonin syndrome."**

Laura Tormoehlen, MD

**CHPR: What are the symptoms of these mild versions?**

**Dr. Tormoehlen:** Anytime you counsel your patients, "You might have diarrhea or tremor from the addition of this medication to your regimen," you're telling them they might have mild serotonin syndrome. It's important to review patients' side effects carefully because they can indicate the beginning of serotonergic excess. These milder forms of serotonin syndrome tend to happen as adverse effects from a therapeutic dose, like from starting a new drug or increasing the dose. The acute-onset, more severe cases are typically from overdoses or excessive amounts of proserotonergic drugs.

**CHPR: What about NMS? Is that predictable?**

**Dr. Tormoehlen:** NMS is much more idiosyncratic and difficult to predict. If you suspect it, you want to check carefully for antidopaminergic medications besides the antipsychotics, although there aren't nearly as many of those as there are serotonergic medications.

**CHPR: But many patients can't give us an accurate medication history, or they might be on antidopaminergic and proserotonergic medications. How else can we diagnose NMS vs serotonin syndrome?**

**Dr. Tormoehlen:** One way to tell the difference is onset (*Editor's note:* See table below for more tips). Serotonin syndrome is much more likely to be acute in onset, on the order of hours, and NMS is likely to be subacute in onset—so days, roughly speaking. If your patient was fine 3 or 4 hours ago and now suddenly they are hyperthermic and rigid, it's much more likely to be serotonin syndrome.

**Differentiating Serotonin Syndrome From Neuroleptic Malignant Syndrome**

| Condition | Med History | Onset | Course | Neuromuscular Findings | Vitals | Labs |
|---|---|---|---|---|---|---|
| Serotonin syndrome | Serotonergic drug | Abrupt (within 24 hours) | Rapidly peaking | Increased tone, legs more so than arms; tremor; hyperreflexia | Hypertension<br>Hyperthermia<br>Tachycardia<br>Tachypnea | Elevated or normal creatinine kinase |
| NMS | Dopamine antagonist | Gradual (days to weeks) | Prolonged | Diffuse "lead pipe" rigidity | Hypertension<br>Hyperthermia<br>Tachycardia<br>Tachypnea | Elevated creatinine kinase |

**CHPR: Are there any distinctive lab findings?**

**Dr. Tormoehlen:** Not really. With both, you can see elevated creatinine kinase (CK) levels (*Editor's note:* CK is also known as creatinine phosphokinase, or CPK), so labs won't help differentiate one from the other. The elevated CK results from the muscle rigidity, as CK is an enzyme that leaks out of damaged muscle tissue.

**CHPR: What about motor features?**

**Dr. Tormoehlen:** Motor features do help differentiate one from the other. Serotonin syndrome classically manifests with clonus.

**CHPR: What does clonus look like?**

**Dr. Tormoehlen:** Clonus refers to involuntary, rhythmic muscle contractions. Interestingly, it tends to happen more in the lower vs upper extremities, so you must check the legs—not only for tone, but also for clonus. Sometimes our bedside exam gets a little too quick, and we check for tone in the arms and maybe skip the legs, but if you do this, you might miss the increased tone and clonus. Conversely, NMS is primarily about rigidity—typically described as "lead pipe"—rather than clonus. You might observe a substantial increase in tone, even to the degree that you can't check for inducible clonus at the ankles because the tone is so high.

**CHPR: How do you induce clonus?**

**Dr. Tormoehlen:** If you briskly flex the patient's foot upward, you'll see a rhythmic beating of the foot and ankle. Make sure you sustain that passive dorsiflexion of the foot. If the rhythmic beating continues beyond a couple of beats, that would be abnormal.

**CHPR: Once you've established the diagnosis, what are the best treatments?**

**Dr. Tormoehlen:** First of all, stop any drug that could be contributing to the symptoms: serotonergics, neuroleptics, adrenergics, anticholinergics, etc. The differential diagnosis includes other syndromes besides NMS and serotonin

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Expert Interview–Serotonin Syndrome Versus NMS

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syndrome, such as sympathomimetic syndrome and anticholinergic syndrome, so you want to stop all potentially offending drugs. And then for treatment, fortunately, we treat NMS and serotonin syndrome the same way at the beginning. First-line treatment is benzodiazepines. We usually use lorazepam or diazepam. Essentially, we're trying to "chill the brain out." A good way to make the brain be quieter regardless of which neurotransmitter system is overreacting is GABA agonist therapy, like with benzos (*Editor's note:* See table below for more information).

**CHPR: And what if the patient is not only stiff but also hyperthermic?**

**Dr. Tormoehlen:** Then we've got to get them cooled. Benzodiazepines will also help with hyperthermia because they decrease muscle tone. The hyperthermia is mostly from overgeneration of heat from muscle activity, so antipyretics won't be effective, but if you can relax the muscles, then you will decrease the temperature. External cooling is important. If your patient is hot, with a temperature greater than 104°F, then prophylactic intubation, mechanical ventilation, and pharmacologic paralytics may be necessary, although that isn't commonly required.

**CHPR: So these measures help serotonin syndrome as well as NMS. Are there any treatments that are specific for NMS or serotonin syndrome?**

**Dr. Tormoehlen:** If you are sure of what you're treating, then there are antidotes that can be aimed directly at the neurotransmitters causing the problem. For serotonin syndrome, it is the serotonin antagonist cyproheptadine, which you can only give by mouth (adult dosing: 12 mg followed by 2 mg q2 hours until improvement, then 8 mg q6 hours maintenance dosing). It's an antihistamine and it's also anticholinergic, so if there's a chance your patient has anticholinergic syndrome, then you don't want to use this.

**CHPR: And for NMS?**

**Dr. Tormoehlen:** For the management of NMS, bromocriptine—a dopamine agonist—is the potential antidote (2.5–5 mg orally or by NGT every 8 hours). The second agent we might add, but only if the rigidity is severe, would be dantrolene (3–5 mg/kg IV divided TID, or orally at 100–400 mg/day QID). Dantrolene is a muscle relaxant, so it only treats the rigidity; it does not help with any of the CNS symptoms. Most of the time we get away with using benzodiazepines plus or minus bromocriptine, without the dantrolene. If dantrolene is needed, you will need to monitor hepatic function as dantrolene can cause liver toxicity. In addition, bromocriptine has some proserotonergic activity, so it should be avoided if serotonin syndrome remains possible.

**CHPR: Once you've begun these interventions, how long does it take for patients to recover?**

**Dr. Tormoehlen:** With either syndrome, patients can be very ill at initial presentation, but with good care they generally recover fully. They will usually improve quickly with aggressive management in either syndrome, but NMS takes longer to completely recover, so patients need a management plan on the order of weeks. If serotonin syndrome is severe, then it may take several days to recover in the ICU, but once patients are medically stable and ready for discharge, they typically do not require any outpatient management; once it's done it's done.

**CHPR: And when can you reinstate the medications that they were taking?**

**Dr. Tormoehlen:** It's much easier in serotonin syndrome because those patients typically either overdosed or had a drug interaction. Acute serotonin syndromes are found in the overdose patients; those with drug interaction tend to be much less severe. Typically, you'd wait 24–48 hours after complete resolution of their syndrome, and then they can go back to previously prescribed medicines as long as you limit the number of proserotonergics and restart only the most important medications. If possible, start with one agent at low dose.

**CHPR: What about restarting antipsychotics in patients who recovered from NMS?**

**Dr. Tormoehlen:** Because NMS is an idiosyncratic reaction, it is much harder to predict who's going to get it. And once a patient has had it, we tend to have trepidation about resuming antipsychotics. But if the indication to resume is strong, you can restart an antipsychotic as long as you start at a low dose and titrate up slowly. You want to wait until the symptoms are completely resolved, at least 2 weeks, and then pick a second-generation antipsychotic because they appear less likely to cause NMS. Also, you want to choose a different drug than the one that caused the NMS, and don't use depot injections.

**CHPR: Thank you for your time, Dr. Tormoehlen.**

**Management of Serotonin Syndrome and NMS**

| Symptoms | Management |
|---|---|
| Mild: Mild hypertension, tachycardia, diaphoresis, mydriasis, tremor, myoclonus, hyperreflexia | • Discontinue all offending medications<br>• Support via stabilizing vital signs, external cooling measures<br>• Benzodiazepines |
| Moderate: Above plus temperature of > 40°C, moderate hypertension, spontaneous clonus or moderate rigidity, agitation | • All of the above<br>• Higher and more frequent dosing of benzodiazepines or continuous infusion<br>• For serotonin syndrome: Cyproheptadine 12 mg followed by 2 mg q2 hours until improvement, then 8 mg q6 hours maintenance<br>• For NMS: Bromocriptine 10 mg oral or NGT, every 6 hours; dantrolene for patients with severe muscle rigidity, 3–5 mg/kg IV divided TID, or orally at 100–400 mg/day QID (avoid if underlying liver disease); bromocriptine or dantrolene should be continued for 10 days beyond symptom resolution |
| Severe: Above plus delirium, severe muscle rigidity, severe hypertension/tachycardia; failure to respond to interventions | • All of the above<br>• Admission to the intensive care unit<br>• Pharmacologic paralytics; intubation/ventilation |

*Source: Tormoeblen LM and Rusyniak DE,* Handb Clin Neurol *2018;157:663–675; Volpi-Abadie J et al,* Ochsner J *2013;13(4):533–540*

# Deliberate Foreign Body Ingestion

*Adrienne Grzenda, MD, PhD. Clinical Assistant Professor of Psychiatry & Biobehavioral Sciences, UCLA David Geffen School of Medicine and UCLA-Olive View Medical Center.*

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

*During morning rounds at your inpatient unit, you are informed by staff that your patient M, a 32-year-old woman with bipolar disorder and borderline personality disorder, has swallowed a small pencil. This is her fourth swallowing episode since her admission to the unit 2 weeks ago. Even though you had restricted her access to sharp objects, she has managed to take them from other patients or pick them up off the floor. You are not sure whether to call a GI consult because you are wary of encouraging her behavior with the secondary gain of medical attention. You do a literature search on deliberate foreign body ingestion to help come up with a plan for M.*

Patients with repeated deliberate foreign body ingestion (DFBI) are among the most challenging we see. DFBI is costly and resource intensive, in part because of these patients' extremely high rate of repeated swallowing attempts: Over 80% of DFBI presentations occur in patients with prior ingestions (Palta R et al, *Gastrointest Endosc* 2009;69(3 Pt 1):426–433). A retrospective analysis of 305 cases of DFBI found they involved only 33 patients and generated over $2 million in costs in a single year (Huang BL et al, *Clin Gastroenterol and Hepatol* 2010;8(11):941–946).

**What do these patients swallow?**

Pens, toothbrushes, and batteries are among the most commonly ingested items. Some patients experience no symptoms, while others present with dysphagia, drooling, emesis, gastrointestinal bleeding, pharyngeal or abdominal pain, and respiratory distress. Fortunately, 80%–90% of swallowed foreign bodies pass spontaneously through the gastrointestinal tract. Another 10%–20% will require intervention via endoscopy, and less than 1% require surgery (Dray X and Cattan P, *Best Pract Res Clin Gastroenterol* 2013;27(5):679–689). Complications, including perforation, impaction, and bleeding, depend on the type, size, and location of the ingested object. Foreign bodies with corrosive properties, such as button batteries, can be particularly harmful as they can result in necrosis and fistulas.

**Why do patients swallow foreign objects?**

In most cases, DFBI patients are not suicidal: They have no greater risk of lifetime suicidal thoughts or actions compared to patients with other types of non-suicidal self-injurious behaviors (Hom MA et al, *J Nerv Ment Dis* 2018;206(8):582–588). What, then, explains this vexing swallowing behavior? Individuals with DFBI fall into four diagnostic categories: malingering, borderline personality disorder (BPD), psychosis, and pica.

1. **Malingering.** DFBI in institutionalized settings, like jails, is often for secondary gain. Incarcerated individuals who swallow foreign objects are more likely to select highly injurious items, like sharp metallic objects, which require transfers to hospitals and prolonged treatment (Zong Y et al, *BMC Gastroenterol* 2020;20(1):90).

2. **BPD.** In DFBI patients with BPD, the swallowing behaviors resemble other forms of self-injury (eg, cutting, burning) in their triggers and intent, such as escape from distress. However, DFBI differs in one important way: It enables patients to exert enormous control over providers. Compared to cutting, for example, where the severity of the injury is immediately evident, suspicion of DFBI often triggers prolonged assessments and treatment.

3. **Psychosis.** About a quarter of DFBI patients have a history of psychosis, and delusions/command hallucinations can prompt swallowing behavior (Velitchkov NG et al, *World J Surg* 1996;20(8):1001–1005). Patients with psychosis-related DFBI are most likely to ingest large numbers of small objects, sometimes numbering in the hundreds.

4. **Pica.** The repeated consumption of non-nutritive substances (eg, dirt, paint), or pica, is most often diagnosed in children, pregnant women, and those with iron deficiency. In adulthood, pica primarily occurs in cases of severe intellectual disability, autism spectrum disorder, and schizophrenia. Pica is classified as voluntary when patients eat what is readily available, and as involuntary when it is driven by compulsions or egodystonic intrusive thoughts—demonstrating strong overlap with OCD (Hergüner S et al, *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(8):2010–2011). Attempting to resist the compulsion results in significant anxiety and distress.

**Management of DFBI**

Surgical management of DFBI depends on the characteristics of the swallowed

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**Current Guidelines for Management of Swallowed Objects**

| Objects Swallowed | Management |
|---|---|
| • Sharp objects (knives, razor blades)<br>• Batteries<br>• Packages of narcotics<br>• Objects that may obstruct or perforate the esophagus | Emergent removal (< 6 hours) |
| Sharp objects that have reached stomach or duodenum<br>• Objects > 6 cm in length<br>• Objects > 2.5 cm in diameter | Remove by endoscopy within 24 hours |
| Blunt objects with rounded edges (coins, buttons)<br>• Objects < 6 cm in length<br>• Objects < 2.5 cm in diameter | Remove non-emergently (outpatient) |
| Small, blunt, non-toxic objects observed in the small intestine | Monitor to ensure uncomplicated, spontaneous passage |

*Source: Ghimire S et al,* Eur J Case Rep Intern Med *2020;7(10):001824*

Intranasal Esketamine: New Hope for Suicidal Patients?
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You'll recall that we first started hearing about ketamine in its intravenous form, which has long been used as a preoperative anesthetic. When infused at significantly lower doses than used in the operating room, studies have found that the treatment quickly reduces suicidality, even after a single dose. The reduction of suicidal ideation occurs within hours and lasts typically for a few hours or days (Kaur U et al, *Eur Arch Psychiatry Clin Neurosci* 2019; Epub ahead of print).

Esketamine (Spravato), the S-enantiomer of ketamine, is delivered as a nasal spray and was developed as a more convenient alternative to IV ketamine. Esketamine recently received FDA approval as an adjunctive treatment for major depressive disorder with suicidality. Some have said the FDA's approval process was too hasty, arguing that the drug's effects are only modest and that we don't know much about its long-term safety. In fact, Great Britain's version of the FDA—the National Institute for Health and Care Excellence (NICE)—rejected intranasal esketamine due to uncertainties about its clinical and cost effectiveness.

**Esketamine clinical trials**

Let's take a deep dive into the evidence. Most of the data have come from three identically designed studies, all from the same research group (Canuso CM et al, *Am J Psychiatry* 2018;175(7):620–630; Fu DJ et al, *J Clin Psych* 2020;81(3):19m13191; Ionescu DF et al, *Intl J Neuropsychopharm* 2021;24(1):22–31).

In these studies, eligible patients had treatment-resistant depression (failure of at least 2 antidepressants). Patients with bipolar disorder or psychosis were excluded. All patients were started on a standard antidepressant (either an SSRI or SNRI, open label) and then were randomly assigned to adjunctive treatment with either esketamine or placebo saline nasal spray twice weekly. The primary outcome was change in the MADRS suicidal thoughts score after 4 weeks. Across all trials, patients assigned to esketamine improved significantly more than those on placebo on the MADRS suicidal thoughts score at 4 hours. By 24 hours and at 25 days, however, there were no significant differences in these scores.

Only one study found esketamine to be significantly more effective than placebo: the Transform-2 trial (Popova V et al, *Am J Psychiatry* 2019;176(6):428–438; published correction appears in *Am J Psychiatry* 2019;176(8):669). In this study, 197 patients completed the treatments, and patients assigned to esketamine had a 21-point reduction in their MADRS score vs a 17-point reduction among placebo-treated patients. Since the MADRS is a 60-point scale, a 4-point difference between drug and placebo may not seem like much, but this is similar to the effect size seen in most successful antidepressant drug trials. Meanwhile, a recent meta-analysis of all studies of esketamine conducted so far (including the studies submitted to the FDA) pooled together data from 774 patients and concluded that esketamine augmentation of an existing antidepressant is indeed more effective than placebo (Papakostas GI et al, *J Clin Psychiatry* 2020;81(4):19r12889).

That's a lot of information to absorb—and lost in the summary above is a critical and unique property of esketamine, which is that it reduces suicidality very quickly and dramatically. For example, in one study of 66 depressed and suicidal patients, only a quarter of esketamine patients reported suicidality at 4 hours post-dose, vs over half of placebo patients. However, this separation diminished over time—by 24 hours it was no longer statistically significant (Canuso, 2018).

For patients who do benefit, how can the therapeutic response be maintained beyond the first few hours? A recent randomized controlled trial of treatment-resistant depressed patients tested longer-term treatment. In this 2-month study, esketamine was dosed at 28–84 mg initially twice weekly, then weekly, and ultimately every 2 weeks. Adjunctive esketamine beat placebo in maintaining treatment response over the 2-month study period and for an additional 2 months after the drug was stopped (Daly EJ et al, *JAMA Psychiatry* 2018;75(2):139–148). Higher doses also led to longer duration of efficacy. This study didn't evaluate suicidality per se, but we know that treatment-resistant depression places patients at risk for suicide, so these results are reason for optimism.

**Nuts and bolts of prescribing esketamine**

Esketamine is a Schedule III controlled substance and has a high potential for abuse—as well as potentially dangerous blood pressure elevations. Because of these issues, the FDA requires that it be administered under direct supervision by a health care professional at a certified facility. To obtain certification, facilities must undergo a stringent approval process through a Risk Evaluation and Mitigation Strategy (REMS). Once a hospital is certified, inpatient units do not need to enroll their patients in the REMS program, but outpatients cannot access the medication until they are enrolled. Outpatient enrollment consists of signing consent forms provided by the outpatient clinic, but even this small step may be a challenge for an acutely suicidal patient.

The REMS program requires facilities to monitor patients for 2 hours after treatment for sedation, dissociation, and blood pressure changes, and patients aren't allowed to drive themselves home after their treatment. These regulations make esketamine less accessible than some of us would like, but the effort is worthwhile if patients are able to overcome their suicidal thoughts. The protocol for patients with MDD with suicidal ideation consists of

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**Intranasal Esketamine Pros & Cons**

| Pros | Cons |
|---|---|
| Rapid reversal of SI, within hours | Only works for some patients |
| Generally well tolerated at doses used for depression | Has a black box warning: risk for sedation and dissociation after administration, and potential for abuse/misuse |
| Intranasal administration is convenient and quick | Can only be administered through stringent REMS program, and patients cannot drive for the rest of the day following treatment |
| May have a role as a bridging therapy until conventional antidepressants kick in | Very expensive if not covered by insurance |

Q&A With the Expert

# Combination Treatment for Schizophrenia

**T. Scott Stroup, MD, MPH**

*Professor of Psychiatry, Columbia University, NY.*

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

**CHPR: You recently published a study on the use of adjunctive medications in patients with schizophrenia (Stroup TS et al, *JAMA Psychiatry* 2019;76(5):508–515). Your findings were provocative as you found that adjunctive medications often help improve patients' outcomes, yet many clinicians avoid polypharmacy because of concern that patients will experience more side effects without a clear benefit.**

**Dr. Stroup:** That was my starting point too. I have always encouraged parsimonious use of psychotropic medications beyond antipsychotics in people diagnosed with schizophrenia. There has been little high-quality research into this question. Many of the studies have been small, and results have generally been mixed or inconclusive. Direct information about the comparative effectiveness of different adjunctive treatments is really lacking.

**CHPR: Is this why you decided to do your study?**

**Dr. Stroup:** Yes. We know that adjunctive medications are widely used for patients with schizophrenia. More than half of patients with schizophrenia receive an antidepressant over the course of a year. Many also take mood stabilizers, benzodiazepines, or additional antipsychotics. We wanted to see if there were any benefits from adjunctive medications and how they compared.

**CHPR: What was your study's methodology?**

**Dr. Stroup:** We took 10 years of national Medicaid data and identified 323,500 patients with a diagnosis of schizophrenia or schizoaffective disorder. We focused specifically on patients who were already taking a single antipsychotic, and then we explored how they responded when a second medication was added. These adjunctive medications were from the following categories: another antipsychotic, an antidepressant, a mood stabilizer, or a benzodiazepine. Out of the initial 323,500 patients, there were 81,921 patients who met these criteria of having been prescribed a second medication.

**CHPR: Which group benefited the most?**

**Dr. Stroup:** We found that people who started antidepressants did better in terms of lower rates of psychiatric hospitalizations and psychiatric emergency department visits. Benzodiazepines, on the other hand, were associated with higher rates of psychiatric hospitalizations and emergency department visits (*Editor's note:* See "In Summary" table on page 9 for risks and benefits of combining medications).

**"The superstar combination was clozapine and aripiprazole, which was associated with a 14% reduced risk of hospitalization compared with clozapine alone. The top 10 combination antipsychotic treatments all included either clozapine or a long-acting injectable medication."**

T. Scott Stroup, MD, MPH

**CHPR: How did you know that the results weren't confounded by indication? A patient on an antidepressant might have had negative symptoms that would have been less likely to lead to a psychiatric admission, while another patient might have received a benzodiazepine for agitation and this was the reason for the psychiatric admission.**

**Dr. Stroup:** Great question. In an observational data set, people are not randomized, so it's hard to make causal inferences. With the advice of my excellent and experienced colleagues, Mark Olfson, Tobias Gerhard, and others, we used propensity score weighting to make sure people in the different medication groups were as similar as possible.

**CHPR: What is propensity score weighting?**

**Dr. Stroup:** It is a statistical technique that controls for biases in observational studies. It adjusts for differences in pretreatment demographic and clinical variables. In a claims database like Medicaid, of course, clinical information is somewhat limited, so there's still the possibility of unmeasured confounding.

**CHPR: Have any other studies shown benefits to adjunctive antidepressants?**

**Dr. Stroup:** There have been a few. A study using a large patient registry in Sweden found that antidepressant use was associated with reduced mortality when compared to patients on antipsychotic monotherapy (Tiihonen J et al, *Am J Psychiatry* 2016;173(6):600–606).

**CHPR: Were any specific antidepressants more helpful than others?**

**Dr. Stroup:** We did not look at differences among antidepressants in our study. However,

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three years ago a systematic overview of 14 meta-analyses examined 42 pharmacologic co-treatments. They found that SNRI and SSRI antidepressants were both more effective than antipsychotic monotherapy for negative symptoms. SNRIs were also beneficial for total symptom reduction. None of the antidepressants seemed to help positive symptoms (Correll CU et al, *JAMA Psychiatry* 2017;74(7):675–684).

**CHPR: What does the literature tell us about which types of patients with schizophrenia benefit from antidepressants?**

**Dr. Stroup:** The most consistent evidence is that antidepressants are helpful for negative symptoms. Some studies have also reported that antidepressants are helpful for other symptoms besides negative symptoms. It would be reasonable to speculate that they are helpful for depressed mood or anxiety, but our study couldn't address this.

**CHPR: Based on your findings with benzodiazepines, would you caution against using them as adjunctive agents?**

**Dr. Stroup:** I'm skeptical of benzodiazepines in this population. In addition to higher rates of psychiatric hospitalizations and ED visits, benzodiazepines have been associated with higher mortality rates (Tiihonen J et al, *Arch Gen Psychiatry* 2012;69(5):476–483). There is also concern about accidents and the potential for dependence. I recommend minimizing benzodiazepine use in people with schizophrenia.

**CHPR: Are there any studies on combinations of two antipsychotic medications?**

**Dr. Stroup:** A recent registry-based study from Finland worked with a database of 62,250 patients over 20 years and found about a 10% lower risk of psychiatric rehospitalization among patients treated with antipsychotic polypharmacy as opposed to monotherapy with a single antipsychotic (Tiihonen J et al, *JAMA Psychiatry* 2019;76(5):499–507).

**CHPR: So combining two antipsychotics was more effective? That contradicts received wisdom.**

**Dr. Stroup:** Indeed it does. It may be time to modify the current treatment guidelines that discourage combination therapy.

**CHPR: In that Finnish study, were there any antipsychotic combinations that were especially effective?**

**Dr. Stroup:** Yes, the superstar combination was clozapine and aripiprazole, which was associated with a 14% reduced risk of hospitalization compared with clozapine alone, which was the most effective of all the monotherapies studied. The top 10 treatments all included either clozapine or a long-acting injectable medication, so my interpretation is that those are the key ingredients for effective antipsychotic combinations (*Editor's note:* See table at right). On the other hand, quetiapine was the poorest monotherapy performer in this study, and adding any antipsychotic to quetiapine was better than quetiapine alone.

**CHPR: What about mood stabilizers?**

**Dr. Stroup:** The Correll study I mentioned earlier found benefits when lithium or lamotrigine were added as adjunctive agents. Lithium was helpful for total symptom reduction, while lamotrigine was helpful for positive symptoms, negative symptoms, and total psychopathology. While open studies have reported that adjunctive valproate helps with specific symptoms such as aggression, randomized controlled trials have not found convincing evidence that valproate augmentation is beneficial.

| Top 10 Medication Combinations That Reduced Rehospitalization |
|---|
| 1. Clozapine + aripiprazole |
| 2. Any LAI + olanzapine |
| 3. Clozapine + olanzapine |
| 4. Clozapine monotherapy |
| 5. Clozapine + any LAI |
| 6. Clozapine + risperidone |
| 7. Clozapine + quetiapine |
| 8. Clozapine + other oral |
| 9. Any LAI + quetiapine |
| 10. Any LAI + other oral |

*Source: Tiihonen J et al,* JAMA Psychiatry *2019;76(5):499–507*

**CHPR: What's known about other agents?**

**Dr. Stroup:** The Correll study also saw some benefits for other adjunctive agents, including minocycline, topiramate, and non-steroidal anti-inflammatory agents (NSAIDs). It's important to keep in mind that some of this information came from small studies or a single study.

**CHPR: Are there any subgroups of patients with schizophrenia that respond less well when adjunctive agents are added to the antipsychotic medication?**

**Dr. Stroup:** When we did the CATIE schizophrenia trial, we found that among people who use illicit substances, none of the antipsychotic medications worked particularly well (Swartz MS et al, *Schizophr Res* 2008;100(1–3):39–52). In the current study, patients without substance use disorders (SUDs) benefited from the addition of antidepressants more than those with SUDs. We also found that the subgroup of people with SUDs had a much higher rate of psychiatric hospitalizations compared to people without SUDs. This was more evidence that this is a challenging clinical problem.

**CHPR: Did your research lead you to any recommendations about long-term, maintenance treatment?**

**Dr. Stroup:** Our follow-up was for 1 year. Although that may not seem long term for people diagnosed with schizophrenia, the findings have made me less skeptical about using additional medications, whether for acute or for maintenance treatment. I no longer say, "Avoid using additional medications" like I might have at one time.

**CHPR: A statement you made in one of your papers struck me. You said, "Because breakthroughs do not appear imminent, we must find ways to use current treatments better."**

**Dr. Stroup:** And that's what I've focused on: conducting comparative effectiveness studies in

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## Expert Interview—Combination Treatment for Schizophrenia

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clinical trials and more recently using secondary data. The research community can learn from practice, ie, "practice-based evidence." Lately I have been using Medicaid data to look at geographic variations in the way medications are prescribed. We are finding that for patients with schizophrenia, adjunctive antidepressants are used consistently across the country. This finding that antidepressant use is consistent across the US makes me think even more that there must be something to learn from this practice.

**CHPR: Thank you for your time, Dr. Stroup.**

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**In Summary: Evidence on Combining Medications With Antipsychotics in Schizophrenia**

| Adjunctive Medication | Risk/Benefit | Notes |
|---|---|---|
| Antidepressants | • Lower rates of psychiatric hospitalizations and ED visits<br>• Improvement in negative symptoms | Little research on the comparative efficacy of different adjunctive antidepressants |
| Antipsychotics | • Benefit appears limited primarily to combinations where one of the antipsychotics is either clozapine or a long-acting injectable<br>• Clozapine + aripiprazole has the lowest rate of psychiatric rehospitalizations compared to other agents either alone or in combination | Combinations of other antipsychotics are of questionable benefit |
| Benzodiazepines | • Poorer outcomes, including more psychiatric admissions and ED visits | Best to minimize |
| Mood stabilizers | • Lithium: total symptom reduction[1]<br>• Lamotrigine: total symptom reduction, positive & negative symptoms<br>• Valproate: RCTs show no evidence of benefit | |
| Other agents (minocycline, NSAIDs, topiramate) | • Total symptom reduction, positive & negative symptoms | Not enough evidence yet to recommend as adjunctive treatments |

[1] *Based on the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS)*

## Deliberate Foreign Body Ingestion

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object, time since ingestion, current location in the GI tract, and presence of complications. Non-contrast CT is better than x-ray in evaluating for ingested objects; if the ingested object is radiolucent, x-rays are of no use.

Current guidelines recommend emergent removal (< 6 hours) of sharp objects (eg, knives, razor blades), batteries, packages of narcotics, or any objects that may result in the obstruction or perforation of the esophagus.

For sharp objects that have already progressed to the stomach or duodenum or objects greater than 6 cm in length and/or greater than 2.5 cm in diameter, removal by endoscopy is recommended within 24 hours. Blunt objects with rounded edges (eg, coins, buttons), smaller than 2.5 cm in diameter, and/or smaller than 6 cm in length can be removed non-emergently in an outpatient clinic. Small, blunt, nontoxic objects observed in the small intestine can be monitored to ensure uncomplicated, spontaneous passage. Once objects reach the stomach, most will pass within 4–6 days. Seek surgical consultation if the object fails to progress after 72 hours or the patient develops symptoms of perforation, obstruction, or peritonitis. (*Editor's note:* See table on page 5.)

DFBI patients require a multidisciplinary approach involving surgery, medicine, and psychiatry. Frustration with the patient may lead to animosity between services due to the perception that psychiatry is not "doing enough" to prevent repeated behaviors. Consultant-liaison providers can help the treatment team or caregivers to: 1. recognize countertransference forces at play, 2. provide education on the limited efficacy of pharmacologic and behavioral treatments, 3. set limits to lessen reinforcement of maladaptive behaviors, and 4. foster realistic expectations regarding recurrence. At present, we know little about the long-term prognosis for patients with recurrent DFBI.

General management of DFBI for inpatient and institutionalized settings focuses on reducing the frequency and potential lethality of ingestions. We can minimize swallowing incidents by monitoring patients closely and minimizing their access to swallowable items (eg, utensils, pens, combs, toothbrushes).

Specific management principles vary depending on the subtype. For DFBI due to malingering, minimize the secondary gain: Transfers for hospital treatment should be kept as brief as possible. When personality disorders are the underlying cause, target the impulsivity with the use of mood stabilizers, naltrexone, or clonidine (Gitlin DF et al, *Psychosomatics* 2007;48(2):162–166). Dialectal behavior therapy and cognitive behavior therapy can also help.

Like for other self-injurious behaviors in patients with BPD, inpatient admissions after a swallowing incident can be counterproductive, fostering an exacerbation of symptoms (Poynter BA et al, *Gen Hosp Psychiatry* 2011;33(5):518–524). Unless there are additional indications (eg, psychotic symptoms, suicidal ideation), swallowing incidents alone do not justify psychiatric admission.

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# Research Update IN PSYCHIATRY

## ANTIPSYCHOTICS

### *Antipsychotic Dosing: How High?*

**REVIEW OF: Leucht S et al, *Am J Psychiatry* 2020;177(4):342–353 (published correction appears in *Am J Psychiatry* 2020;177(3):272)**

How high should we go when dosing antipsychotics in schizophrenia? Surprisingly little is known about optimal doses. During drug development, dosing is estimated from animal studies, but more detailed studies in humans are rare. A recent meta-analysis of 68 studies examined dose-response relationships in randomized controlled trials of antipsychotic medications for schizophrenia and schizoaffective disorder. The outcome of interest was the dose producing a 95% reduction in symptoms (ED95).

For many medications, the ED95 dose differed greatly from the FDA-recommended maximum. For example, aripiprazole's ED95 was 11.5 mg/day, in contrast to the 30 mg/day maximum licensed dose. For numerous medications, including olanzapine (for positive symptoms), clozapine, and lurasidone, the dose response curves did not plateau, implying that dose escalation beyond the ED95 may still be efficacious. Other medications, such as quetiapine, cariprazine, and brexpiprazole, showed a clear plateau in dose response—implying no extra benefit of further escalation. Several medications showed a bell-shaped dose response curve, including haloperidol, risperidone, olanzapine (for negative symptoms), and aripiprazole, implying a negative response with a higher dose.

#### CHPR'S TAKE

For most antipsychotics, the ED95 is slightly lower than the FDA maximum dose. For some commonly used agents, such as aripiprazole and quetiapine, we may be dosing patients more aggressively than needed. Others may need to be tailored to the individual.

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

**Dose-Response Relationships for Antipsychotic Drugs**

| Drug | ED95 (mg/day) | FDA Max Licensed Dose (mg) | Did Not Plateau (ie, dose escalation beyond the ED95 may help) | Plateaued (ie, no extra benefit from dose escalation beyond the ED95) | Bell-Shaped (ie, dose escalation beyond the ED95 worsened response) |
|---|---|---|---|---|---|
| Aripiprazole | 11.5 | 30 | | | X |
| Aripiprazole LAI (Lauroxil) | 463 (q4wks) | 882 (q4wks) | | X | |
| Asenapine | 15 | 20 | | X | |
| Brexpiprazole | 3 | 4 | | X | |
| Cariprazine | 8 | 6 | | X | |
| Clozapine | 567 | n/a | X | | |
| Haloperidol | 6 | 100 | | | X |
| Iloperidone | 20 | 24 | X | | |
| Lurasidone | 147 | 160 | X | | |
| Olanzapine, predominant negative symptoms | 6 | n/a | | | X |
| Olanzapine, predominant positive symptoms | 15 | 20 | X | | |
| Olanzapine LAI | 277 (q2wks) | 300 (q2wks) | X | | |
| Paliperidone | 13 | 12 | X | | |
| Paliperidone LAI | 120 | 234 | X | | |
| Quetiapine | 482 | IR: 750; XR: 800 | | X | |
| Risperidone | 6 | 16 | | | X |
| Risperidone LAI | 37 (q2wks) | 50 | | | X |
| Sertindole | 23 | 24 | X | | |
| Ziprasidone | 186 | 160 | X | | |

1. In a 2019 study of schizophrenia, which adjunctive medication class to antipsychotic therapy was associated with the lowest rates of psychiatric hospitalizations and ED visits (LO #1)?
   [ ] a. Antipsychotics [ ] b. Mood stabilizers [ ] c. Benzodiazepines [ ] d. Antidepressants
2. What is the specific management principle for a patient with deliberate foreign body ingestion (DFBI) due to malingering (LO #2)?
   [ ] a. Treat the underlying psychosis
   [ ] b. Minimize the secondary gain by keeping hospital transfers as brief as possible
   [ ] c. Target the impulsivity with the use of mood stabilizers
   [ ] d. Admit the patient for inpatient treatment
3. According to Dr. Tormoehlen, a patient who has recovered from neuroleptic malignant syndrome (NMS) can be restarted on a second-generation antipsychotic as long as their symptoms are completely resolved after at least ____ (LO #3).
   [ ] a. 24–48 hours [ ] b. 1 week [ ] c. 3 days [ ] d. 2 weeks
4. Which antipsychotic has a dose response curve that does not plateau (LO #4)?
   [ ] a. Quetiapine [ ] b. Lurasidone [ ] c. Risperidone [ ] d. Brexpiprazole
5. Recent data show that esketamine significantly improved MADRS suicidal thoughts scores at 24 hours and 25 days, compared to placebo (LO #1).
   [ ] a. True [ ] b. False
6. Your DFBI patient is driven to swallow non-nutritive substances by compulsions. If they resist their compulsions, significant anxiety and distress results. Which is the best first-line pharmacotherapy option for your patient (LO #2)?
   [ ] a. Fluoxetine [ ] b. Naltrexone [ ] c. Mood stabilizers [ ] d. Clonidine
7. Which of the following about serotonin syndrome versus NMS is true (LO #3)?
   [ ] a. Bromocriptine is an antidote for serotonin syndrome
   [ ] b. Benzodiazepines are the first-line treatment for serotonin syndrome and NMS
   [ ] c. "Lead pipe" muscle rigidity, rather than clonus, is common in serotonin syndrome
   [ ] d. Cyproheptadine is an antidote for NMS
8. According to a 2019 study of schizophrenia, what combination of antipsychotics yielded the greatest reduction in risk of rehospitalization, compared to clozapine monotherapy (LO #4)?
   [ ] a. Clozapine and risperidone [ ] c. Clozapine and aripiprazole
   [ ] b. Clozapine and any long-acting injectable [ ] d. Any long-acting injectable and quetiapine

## Intranasal Esketamine: New Hope for Suicidal Patients?

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intranasal esketamine 84 mg twice weekly for 4 weeks. Each intranasal device contains 28 mg, so this dose requires 3 devices. The dose can be reduced to 56 mg twice weekly for tolerability. When insurance does not cover the cost, esketamine averages $600–$980 per dose.

At the doses used to treat depression, esketamine is generally well tolerated. The most common adverse events are nausea, dizziness, somnolence, dissociation, blood pressure elevations, and headache. The dissociative symptoms usually resolve within 2 hours after esketamine administration and seem to diminish with repeated doses. Nevertheless, esketamine's potential for misuse is a concern, and we still know little about its long-term safety.

**CHPR VERDICT:** Esketamine appears to be an effective adjunctive agent for patients with treatment-resistant depression. But the drug's real superpower is its rapid reversal of suicidality, which is most robust within 24 hours and disappears over the next few days. Esketamine's antisuicide effects make it potentially useful in the following settings: 1. Psychiatric emergency rooms, to diminish acute suicidality in patients who can't otherwise be discharged; 2. Inpatient units, for acutely suicidal patients who require one-to-one observation. In both cases, consider esketamine a bridging therapy until conventional treatments take effect. Unfortunately, the drug's high cost will make it a difficult sell for hospital formularies.

THE CARLAT REPORT
HOSPITAL PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950



## Deliberate Foreign Body Ingestions

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For DFBI rooted in delusional beliefs or driven by command hallucinations, treat the underlying psychosis. SSRIs—fluoxetine in particular—appear effective for DFBI due to pica/OCD (Upadhyaya SK and Sharma A, *Indian J Psychol Med* 2012;34(3):276–278).

*You ascertain that the pencil M swallowed was less than 6 cm and was not sharpened; your GI consultant (also frustrated with the patient after several endoscopies) recommends a wait-and-see approach with serial x-rays to assess whether the object progresses through the GI tract. You ask M why she swallowed the pencil, and she says she was frustrated by all the restrictions placed on her access to unit objects. You work with her to create a clear behavior plan allowing for gradual reintroduction of objects with every 24 hours of non-swallowing behavior. After 1 week, M has complied with the plan and has regained her privileges.*

**CHPR VERDICT:** Patients with recurrent DFBI are among the most difficult to treat. Identify the subtype to choose the most effective treatment, minimize psychiatric admissions as these can be counterproductive, and collaborate closely with a gastroenterologist.

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