

vaccination with Comirnaty (BioNTech/Pfizer). On this day, clozapine and olanzapine were administered in a reduced dose (clozapine 87.5 mg/d, olanzapine 15 mg/d).

Three days later, the patient reported increasing tachycardia with heart rates up to 136 bpm and now chest pain. On this day, the dose of clozapine had just reached 200 mg/d and the serum level was 250 ng/mL, the dose of olanzapine was 20 mg/d, but was not administered anymore. Immediate blood test showed elevated hs-cTn (94 pg/mL) and elevated C-reactive protein (CRP, 12 mg/dL).<sup>3</sup> The ECG still showed only sinus tachycardia. Because of suspected acute myocarditis under clozapine initiation and after SARS-CoV-2 vaccination, clozapine and olanzapine were discontinued and the patient was transferred to the department of cardiology of our university medical center.

The hs-cTn, B-type natriuretic peptides, and CRP levels were also increased in the control investigations (Table 1). A coronary macroangiopathy was excluded via cardiac catheter examination. Cardiac monitoring still showed sinus tachycardia. Instead of propranolol, bisoprolol was administered. Diagnostically, myocarditis was suspected. The more specific cause could not be identified. Because the patient was clinically stable, the patient was transferred back to our hospital after 5 days. Follow-up checks of hs-cTn and ECG showed no abnormalities. Three weeks later, magnetic resonance imaging of the heart showed no abnormalities, in particular no signs of active myocarditis. Psychopathologically, the patient still showed full remission of the psychotic symptoms. To prevent relapse, we began treatment with cariprazine 3 mg/d but did not reinstate clozapine.

Finally, we were able to discharge the patient in a psychosis-free state for further outpatient treatment. The patient was also symptom free regarding myocarditis.

This case shows a coincidence of myocarditis after the treatment with clozapine and mRNA vaccination. Myocarditis is diagnosed in approximately 10 to 20 individuals per 100,000 per year in the general population and occurs more commonly and at younger ages in males compared with females.<sup>4,5</sup>

Among individuals aged 12 to 39 years, Bozkurt et al<sup>6</sup> reported myocarditis/pericarditis rates of approximately 12.6 cases per million doses of second-dose SARS-CoV-2 mRNA vaccine. Although they state that the mechanisms for development of myocarditis after SARS-CoV-2 vaccination remain elusive, they describe some possible mechanisms like molecular mimicry between the spike protein of the virus and self-antigens, trigger of pre-existing dysregulated immune pathways in certain individuals, immune response to mRNA, activation of immunologic pathways, and dysregulated cytokine expression.

The incidence for clozapine-induced myocarditis reported in the literature ranges from 0.015% to 8.5%.<sup>7</sup> Although it is a widely accepted fact that clozapine can cause myocarditis especially during the initial titration phase, and although the first case report of clozapine-induced myocarditis appeared in the literature over 40 years ago, the underlying mechanisms are unknown.<sup>7</sup> Because most of the cases seem to occur during clozapine titration, a type I drug hypersensitivity reaction has been proposed.<sup>7,8</sup> Olanzapine treatment has not been related to the onset of myocarditis.<sup>9</sup>

As both newly established treatments in this case can cause myocarditis, and the course over time is also typical for both possible causes, the detailed mode of action remains elusive.<sup>10–12</sup>

The complete remission shows that early detection of myocarditis in cases of combining clozapine initiation with mRNA vaccination is of the highest importance.<sup>13</sup>

Written consent to publish a report of the case has been obtained from the patient.

## AUTHOR DISCLOSURE INFORMATION

A.H. has received speakership fees from Lundbeck, Otsuka, Janssen, and Recordati and was member of advisory boards of these companies and as well for Rovi. The other authors declare no conflicts of interest.

## ARTICLE INFORMATION

Received March 2, 2022; accepted after revision April 27, 2022.

DOI: 10.1097/JCP.0000000000001577

### Maximilian Hansbauer, MD

Department of Psychiatry  
Psychotherapy and Psychosomatics  
Medical Faculty  
University of Augsburg  
Augsburg, Germany  
maximilian.hansbauer@bkh-augsburg.de

### Enikő Fastantz

### Justina Lutz

Alkomiet Hasan, MD  
Department of Psychiatry  
Psychotherapy and Psychosomatics  
Medical Faculty  
University of Augsburg  
Augsburg, Germany

## REFERENCES

1. Annamraju S, Sheitman B, Saik S, et al. Early recognition of clozapine-induced myocarditis. *J Clin Psychopharmacol*. 2007;27:479–483.
2. Griffin JM, Woznica E, Gilotra NA, et al. Clozapine-associated myocarditis: a protocol for monitoring upon clozapine initiation and recommendations for how to conduct a

clozapine rechallenge. *J Clin Psychopharmacol*. 2021;41:180–185.

3. Watson CM, Alexander A, John AP. The role of C-reactive protein in early detection of myocarditis associated with clozapine. *J Clin Psychopharmacol*. 2018;38:540–542.
4. Fairweather D, Cooper LT Jr, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol*. 2013;38:7–46.
5. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18:169–193.
6. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation*. 2021;144:471–484.
7. Bellissima BL, Tingle MD, Cicović A, et al. A systematic review of clozapine-induced myocarditis. *Int J Cardiol*. 2018;259:122–129.
8. Siskind D, Sidhu A, Cross J, et al. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Aust N Z J Psychiatry*. 2020;54:467–481.
9. De Las Cuevas C, Sanz EJ, Rohde C, et al. Association between myocarditis and antipsychotics other than clozapine: a systematic literature review and a pharmacovigilance study using VigiBase. *Expert Rev Clin Pharmacol*. 2022;15:65–78.
10. Lee ASY, Balakrishnan IDD, Khoo CY, et al. Myocarditis following COVID-19 vaccination: a systematic review (October 2020–October 2021). *Heart Lung Circ*. 2022;31:757–765.
11. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med*. 2021;385:2140–2149.
12. Hägg S, Spigset O, Bate A, et al. Myocarditis related to clozapine treatment. *J Clin Psychopharmacol*. 2001;21:382–388.
13. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326:1390–1399.

## OPEN

## REL-1017 (Esmethadone) May Rapidly Reduce Dissociative Symptoms in Adults With Major Depressive Disorder Unresponsive to Standard Antidepressants A Report of 2 Cases

### To the Editors:

Dissociative disorders (DDs) and dissociative states coexisting with other psychiatric disorders are highly prevalent in the psychiatric population and may be

**TABLE 1.** Clinician-Administered Dissociative States Scale Total Score and Item Scores for the 2 Patients at 4 Evaluation Time Points: Day 1 Predose, Day 1 Postdose, Day 7 Post–Last Dose, and Day 9

	Patient 1 (Assigned to REL-1017 25 mg, 75-mg Loading Dose on Day 1)	Patient 2 (Assigned to REL-1017 50 mg, 100-mg Loading Dose on Day 1)
CADSS (total score) at each time point	22, 2, 6, 0	35, 14, 9, 0
Single item		
Definition and score for the 2 patients		
1) Do things seem to be moving in slow motion?	2/0/0/0	3/1/1/0
2) Do things seem to be unreal, as if you are in a dream?	0/0/0/0	3/1/1/0
3) Do you have some experiences that separates you from what is happening; for instance, do you feel as you are in a movie or a play, or as if you are a robot?	0/0/0/0	3/1/0/0
4) Do you feel as if you are looking at things from outside of your body?	0/0/0/0	3/1/0/0
5) Do you feel as if you are watching the situation as an observer or spectator?	2/0/0/0	3/1/1/0
6) Do you feel disconnected from own body?	1/0/0/0	3/1/0/0
7) Does sense of your own body feel changed: for instance, does your own body feel changed unusually large or unusually small?	2/0/0/0	1/1/0/0
8) Do people seem motionless/dead or mechanical?	0/0/0/0	3/1/0/0
9) Do objects look different than you would expect?	0/0/0/0	1/0/0/0
10) Do colors seem to be diminished in intensity?	0/0/0/0	0/0/0/0
11) Do you see things as if you are in a tunnel, or looking through a wide-angle photographic lens?	0/0/0/0	2/0/0/0
12) Does this experience seem to take much longer than you would expected?	0/0/0/0	1/1/1/0
13) Do things seem to be happening very quickly, as if there is a lifetime in a moment?	0/0/1/0	0/0/0/0
14) Do things happen that you later cannot account for?	2/0/0/0	1/1/0/0
15) Do you space out, or in some other way lose track of what is going on?	0/0/0/0	1/1/1/0
16) Do sounds almost disappear or become much stronger than you would have expected?	0/0/0/0	0/0/1/0
17) Do things seem to be very real, as if there is a special sense of clarity?	3/0/2/0	0/0/1/0
18) Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?	2/0/0/0	1/1/0/0
19) Do colors seem much brighter than you would have expected?	0/0/0/0	0/0/0/0
20) Do you feel confused about who you really are?	2/0/0/0	2/0/1/0
21) Do feel there are different parts of yourself, which do not fit together?	2/0/0/0	1/1/0/0
22) Do you have gaps in your memory?	3/2/3/0	2/1/1/0
23) Do you feel like you have more than one identity?	1/0/0/0	1/0/0/0

underdiagnosed. In an outpatient psychiatric population, the prevalence of DDs was 29%, and only 5% had previously received a DD diagnosis.<sup>1</sup> Dissociative symptoms often coexist with depressive symptoms in patients with major depressive disorder (MDD),<sup>2</sup> and there is a relationship between depression severity and dissociative symptoms in bulimic patients.<sup>3</sup> Dissociative symptoms may precede the onset of mood disorders, could be a risk factor for their development, and may be added to those more traditionally considered as prodromal in depression.<sup>4–7</sup> Uncompetitive *N*-methyl-D-aspartate receptor (NMDAR) channel blockers have been proposed as a treatment for posttraumatic stress disorder (PTSD). Ketamine, an NMDAR antagonist with antidepressant efficacy, has shown efficacy in PTSD.<sup>8</sup> REL-1017 (esmethadone), the opioid-inactive (*S*)-enantiomer of methadone, is a novel, low potency NMDAR

channel blocker,<sup>9</sup> which currently is in phase 3 clinical trials for MDD. In phase 1 and phase 2 trials, REL-1017 showed very favorable safety, tolerability, and pharmacokinetic profiles and rapid, robust, and sustained antidepressant efficacy without clinically meaningful opioid-like effects or dissociative effects.<sup>10–12</sup> We report 2 patients enrolled in a phase 2a trial<sup>11</sup> experiencing a current major depressive episode and with clinically meaningful dissociative symptoms evaluated on the Clinician-Administered Dissociative States Scale (CADSS).<sup>13</sup> Both patients had been diagnosed with MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria and had inadequate responses to 1 to 3 courses of antidepressant treatment as defined by the Antidepressant Treatment Response Questionnaire.<sup>14</sup> They were admitted to a clinical research unit for approximately 10 days, where they received

REL-1017 or placebo daily, for 7 consecutive days as adjunctive treatment for MDD. Both patients gave written informed consent to publish their cases.

### Case 1

A 31-year-old White male patient who had been diagnosed with MDD at age 18 years and who had a history of recurrent depressive episodes during his lifetime and no other psychiatric history was randomized to the REL-1017 25-mg subgroup in June 2019. In October 2018, he was first started on trazodone 300 mg, which was suspended after 3 months for lack of efficacy. At study entry, the patient had been taking bupropion 300 mg once daily for 11 months. On day 1 before and after the first dose of REL-1017, the total CADSS scores were 22 and 2, respectively, showing a clinically meaningful improvement in dissociative symptoms. This improvement was sustained on day 7 (2 hours

after dose) with a CADSS total score of 6 and after treatment discontinuation, on day 9, with a complete resolution of symptoms (a CADSS total score of 0; Table 1). The baseline depressive symptoms total score, the Montgomery-Åsberg Depression Rating Scale (MADRS) was 18. On day 2 (before dose) and on day 4, the MADRS scores were 15 and 19, respectively. The measurement on day 7 was 17, and the value was not available at day 14 because the patient was lost to follow-up after discharge. The patient reported no adverse events except for mild constipation resolving spontaneously without any treatment.

### Case 2

A 39-year-old African American male patient first diagnosed with MDD at age 21 years was randomized to the REL-1017 50-mg subgroup. The patient had a history of recurrent depressive episodes during his lifetime and no other psychiatric history. In April 2018, he was started on sertraline 100 mg once a day orally, which was suspended in January 2019 because of lack of efficacy. At study entry, the patient had been taking bupropion 300 mg once daily for 6 months. On day 1 before the study drug administration and on day 1 after the first dose, the total CADSS scores reported by the patient were 35 and 14 showing a clinically meaningful improvement in dissociative symptoms. This improvement was sustained on day 7 (2 hours after dose) with a CADSS total score of 9, and after treatment discontinuation on day 9, with a complete resolution of symptoms (a CADSS total score of 0; Table 2). The baseline depressive symptoms total score evaluated on MADRS scale was 31. On day 2 (before dose) and on day 4, the total MADRS scores were 24 and 22, respectively. The measurements on day 7 and on day 14 were 24 and 23, respectively. The patient reported no adverse events except for a mild constipation spontaneously resolved without any treatment.

These case reports suggest a potential therapeutic role for NMDAR uncompetitive antagonists in patients with overlapping symptomatology of depression and dissociation with poor response to standard antidepressant treatments. Different hypotheses have been proposed concerning the nature and role of dissociation in the context of MDD.<sup>2,15</sup> Dissociative symptoms have been related to childhood trauma or traumatic adult life events and are considered risk factors for developing psychiatric disorders and an indicator of severity for MDD, as proposed by the depersonalization item in the Hamilton Rating Scale for Depression.<sup>2</sup> Given the strong polygenic association of major depressive disorder and PTSD,<sup>16</sup> an overlap in pharmaco-

logical treatments for these 2 conditions is conceivable. These preliminary data signal that REL-1017 may potentially determine rapid improvement in dissociative symptoms in patients with MDD experiencing dissociative symptoms with a temporal association to acute changes in mood, which needs further investigations. These preliminary results need to be replicated in larger and longer trials. Ongoing phase 3 clinical trials with REL-1017 could generate additional data supporting the initiation of future clinical studies on REL-1017 for the treatment of PTSD.

### ACKNOWLEDGMENT

*This report has been presented in part at the Neuroscience Education Institute 2021 Congress, November 4–7, 2021, Colorado Springs, Colorado.*

### AUTHOR DISCLOSURE INFORMATION

*C.G., L.P., M.P., S.D., A.M., P.L.M., F.F., and M.F. or their subsidiaries received consultant fees from Relmada during their work on this study. P.L.M. is an inventor on esmethadone patents and other patents licensed to Relmada. G.S., F.B., G.M., and M.T. declare no conflicts of interest.*

*This work was supported by Relmada Therapeutics, Inc, Coral Gables, Florida (Relmada). Relmada was involved in the study design, collection, analysis, interpretation of data, the writing of this article, and the decision to submit it for publication.*

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### ARTICLE INFORMATION

Received February 14, 2022; accepted after revision April 30, 2022.

DOI: 10.1097/JCP.0000000000001583

**Clotilde Guidetti, MD**

**Giulia Serra, MD**

Child and Adolescent Neuropsychiatry Unit  
Department of Neurological and  
Psychiatric Science  
Bambino Gesù Children's Hospital  
Rome, Italy

**Luca Pani, MD**

Department of Psychiatry and  
Behavioral Sciences  
University of Miami School of Medicine  
Miami, FL  
Department of Biomedical  
Metabolic and Neural Sciences

University of Modena and Reggio  
Emilia, Italy

**Marco Pappagallo, MD**

Relmada Therapeutics  
Coral Gables FL  
Department of Anesthesiology  
Albert Einstein College of Medicine  
Bronx, NY

**Gino Maglio, MD**

**Monia Trasolini, MD**

Child and Adolescent Neuropsychiatry Unit  
Department of Neurological and  
Psychiatric Science  
Bambino Gesù Children's Hospital  
Rome, Italy

**Sara De Martin, PhD**

**Andrea Mattarei, PhD**

Department of Pharmaceutical and  
Pharmacological Sciences  
University of Padova  
Padova, Italy

**Francesco Bifari, MD, PhD**

Department of Medical Biotechnology and  
Translational Medicine  
University of Milan  
Milan, Italy

**Franco Folli, MD, PhD**

Department of Health Science  
University of Milano  
Milan, Italy

**Paolo L. Manfredi, MD**

Relmada Therapeutics  
Coral Gables, FL  
pmanfredi@relmada.com

**Maurizio Fava, MD**

Department of Psychiatry  
Massachusetts General Hospital  
Boston, MA

### REFERENCES

1. Foote B, Smolin Y, Kaplan M, et al. Prevalence of dissociative disorders in psychiatric outpatients. *Am J Psychiatry*. 2006;163:623–629.
2. Molina-Serrano A, Linotte S, Amat M, et al. Dissociation in major depressive disorder: a pilot study. *J Trauma Dissociation*. 2008;9:411–421.
3. Greenes D, Fava M, Cioffi J, et al. The relationship of depression to dissociation in patients with bulimia nervosa. *J Psychiatr Res*. 1993;27:133–137.
4. Chatterjee SS, Pal A, Mallik N, et al. Dissociative experience in unipolar and bipolar depression: exploring the great divide. *Clin Psychopharmacol Neurosci*. 2018;16:262–266.
5. Benasi G, Fava GA, Guidi J. Prodromal symptoms in depression: a systematic review. *Psychother Psychosom*. 2021;90:365–372.
6. Mula M, Pini S, Preve M, et al. Clinical correlates of depersonalization symptoms in patients with bipolar disorder. *J Affect Disord*. 2009;115:252–256.

7. Dualibe AL, Osório FL. Bipolar disorder and early emotional trauma: a critical literature review on indicators of prevalence rates and clinical outcomes. *Harv Rev Psychiatry*. 2017;25:198–208.
8. Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry*. 2021;178:193–202.
9. Gorman AL, Elliott KJ, Inturrisi CE. The D- and L-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett*. 1997;223:5–8.
10. Bernstein G, Davis K, Mills C, et al. Characterization of the safety and pharmacokinetic profile of d-methadone, a novel N-methyl-D-aspartate receptor antagonist in healthy, opioid-naïve subjects: results of two phase 1 studies. *J Clin Psychopharmacol*. 2019;39:226–237.
11. Fava M, Stahl S, Pani L, et al. REL-1017 (esmethadone) as adjunctive treatment in patients with major depressive disorder: a phase 2a randomized double-blind trial. *Am J Psychiatry*. 2022;179:122–131.
12. Henningfield J, Aspeloff G, Gorodetzky C, et al. No meaningful opioid abuse liability of REL-1017 (esmethadone; d-methadone), a rapid-acting antidepressant in clinical development: a human abuse potential study. NEI Annual Conference Oct 2021.
13. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998;11:125–136.
14. Desseilles M, Witte J, Chang TE, et al. Massachusetts General Hospital SAFER criteria for clinical trials and research. *Harv Rev Psychiatry*. 2013;21:269–274.
15. Hariri AG, Gulec MY, Oregul FF, et al. Dissociation in bipolar disorder: relationships between clinical variables and childhood trauma. *J Affect Disord*. 2015;184:104–110.
16. Stein MB, Levey DF, Cheng Z, et al. Department of Veterans Affairs Cooperative Studies Program (no. 575B); VA Million Veteran Program. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. *Nat Genet*. 2021;53:174–184.

## Treatment of Cannabis Hyperemesis Syndrome Using Haloperidol in a Pregnant Patient Case Report

### To the Editors:

First described in 2004, cannabis hyperemesis syndrome (CHS) is a diagnostic variant of cyclical vomiting syndrome.<sup>1</sup> It is char-

acterized by episodic nausea, vomiting, and abdominal pain that occurs with chronic cannabis use. One important distinction is the temporary relief of symptoms by compulsive hot showering.<sup>2</sup> Like CHS, hyperemesis gravidarum presents with similar cyclical symptoms but specifically occurs during the first trimester of pregnancy. Their common presentations often pose a diagnostic challenge to clinicians, placing a higher burden on patients and the healthcare system.<sup>2</sup> Treatment modalities for acute episodes of CHS are not yet fully elucidated. In practice, clinicians may rely on standard antiemetic agents; however, in most cases, they are often ineffective.<sup>3</sup> A growing number of cases suggest that haloperidol may be the leading candidate for treatment of CHS.<sup>3–8</sup>

We report a case of CHS in a first-trimester pregnant woman who was effectively treated with haloperidol along with other antiemetic agents and showed no adverse events throughout her pregnancy or to the infant.

### CASE REPORT

A 40-year-old woman at 8-week gestation presented to our emergency department (ED) with a 2-day history of nausea, vomiting, and abdominal pain. This was her second pregnancy. A previous pregnancy had ended in abortion. Her medical history included Roux-en-Y gastric bypass surgery, cholecystectomy complicated by biliary leak and biliary stent removal, a chronic ulcer at the gastrojejunal junction, and up to 1 g of cannabis use daily since the age of 13 years. She had no psychiatric history.

The patient had been seen several times in our ED with similar symptoms over the previous 2 years. She had undergone multiple noncontrast computed tomography scans of her abdomen and pelvis that were unremarkable, 2 upper endoscopies that revealed a well-healed chronic marginal ulcer, an unremarkable colonoscopy, and a transvaginal ultrasound, during which her Skyla intrauterine contraceptive device was removed.

On her current admission, she presented with diffuse, nonlocalized abdominal pain rated as 10/10 in intensity. She appeared to be in severe abdominal distress. She complained of nausea associated with bouts of intractable, nonbilious, nonbloody vomiting occurring several times a day. She reported anxiety described as “skin crawling.” Her mental status examination was significant for a depressed and anxious mood with a tearful affect. Her admission vitals and laboratory data showed a blood pressure of 101/63 mm Hg, sodium of 134 mEq/L (135–145 mEq/L), potassium of 3.2 mmol/L (3.5–5.1 mmol/L), creatinine of 0.38 mg/dL (0.6–1.1 mg/dL), mild leukocytosis K/uL (12.65 K/uL), ketonuria, and a positive serum

human chorionic gonadotropin level. A urine toxicology screen was positive for cannabis, although the patient reported stopping cannabis use 14 days earlier. Her abdominal examination was diffusely tender on palpation. Her mucus membranes were dry. She was then admitted to the antepartum inpatient unit.

The patient was hospitalized for a total of 6 days. A timeline of treatment is described in Table 1 that included trials of ondansetron, prochlorperazine, promethazine, and metoclopramide. At the time, the nurses noted that the patient was taking frequent hot showers that provided momentary relief. The consult-liaison psychiatry team was asked to assess the patient, and a new diagnosis of CHS was made. Per psychiatric recommendations, prochlorperazine was discontinued, and intravenous (IV) haloperidol 1 mg every 4 hours was started for treatment of symptoms. She received 3 mg of IV haloperidol within 12 hours, and her symptoms began to significantly improve. Her abdominal pain and anxiety subsided, and her oral intake improved. After receiving a total of 19 mg of IV haloperidol over the next 3 days, she was discharged free of symptoms. At 1-year follow-up, the patient reported no return of hyperemesis for the remainder of her pregnancy. Her baby was born full-term with no complications. At the time of this writing, the infant is 5 months old and has met all developmental milestones.

The patient has provided written digital as well as verbal consent to publish this report.

### DISCUSSION

In the United States, cannabis is one of the most used substances during pregnancy, and its use is rising. As a growing number of states pass legislation legalizing cannabis use in recreational form, the number of reported cases of CHS has increased.<sup>3,4,9,10</sup> It is becoming increasingly important for clinicians to be able to recognize and treat this condition.

The Rome IV committee for gastrointestinal disorders characterizes CHS as cyclical, severe nausea with persistent vomiting lasting 3 months, with symptom onset at least 6 months before diagnosis and occurring before the age of 50 years. At minimum, cannabis use must occur weekly. It is suggested that symptoms should resolve after cannabis cessation; however, in some cases, CHS has persisted for weeks after cessation.<sup>9</sup> Similarly, our patient continued to experience symptoms 14 days after reported cessation, which may be the longest period after cessation that the diagnosis has been made. More studies are warranted to establish an adequate timeframe for cessation for CHS to resolve.

Like CHS, hyperemesis gravidarum presents with nausea and vomiting but is associated with ketonuria, weight loss, and