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).[3] 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 reinitiate 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.[4,5]

Among individuals aged 12 to 39 years, Bozkurt et al[6] 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 preexisting 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%.[7] 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.[7] Because most of the cases seem to occur during clozapine titration, a type 1 drug hypersensitivity reaction has been proposed.[7,8] Olanzapine treatment has not been related to the onset of myocarditis.[9]

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.[10–12]

The complete remission shows that early detection of myocarditis in cases of combining clozapine initiation with mRNA vaccination is of the highest importance.[13]

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

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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.[1] Dissociative symptoms often coexist with depressive symptoms in patients with major depressive disorder (MDD),[2] and there is a relationship between depression severity and dissociative symptoms in bulimic patients.[3] 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. [4–7] 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.[8] REL-1017 (esmethadone), the opioid-inactive (*S*)-enantiomer of methadone, is a novel, low potency NMDAR channel blocker, [9] 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.[10–12] We report 2 patients enrolled in a phase 2a trial [11] experiencing a current major depressive episode and with clinically meaningful dissociative symptoms evaluated on the Clinician-Administered Dissociative States Scale (CADSS). [13] 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.[14] 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. [2,15] 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.[2] Given the strong polygenic association of major depressive disorder and PTSD,[16] an overlap in pharmacological 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.

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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.[1] It is characterized 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.[2] 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.[2] 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.[3] A growing number of cases suggest that haloperidol may be the leading candidate for treatment of CHS.[3–8]

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.[3,4,9,10] 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.[9] 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