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The authors report no conflicts of interest.

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Life-threatening hypoglycemia attributable to haloperidol in a patient with schizophrenia

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Haloperidol is an antipsychotic drug widely used in emergency departments, general medicine wards, and psychiatry units. Long-term therapy is used in psychotic disorders, including schizophrenia and dementia, and bipolar disorders[1]; for short-term use, it is frequently the drug of choice in acutely confused states. We present a case of a patient with an established diagnosis of schizophrenia who developed prolonged, life-threatening hypoglycemia under haloperidol therapy.

A 67-year-old woman was admitted to our emergency department due to altered level of consciousness. She had been diagnosed with schizophrenia in 1980 and been under psychiatric care ever since. She had a previous history of epilepsy, endometrial adenocarcinoma (treated with hysterectomy), and dyslipidemia. Two weeks prior to admission, her haloperidol dose had been increased from 5 mg oral bid to 5 mg tid and 100 mg intramuscular (haloperidol decanoate) every 4 weeks to 100 mg every 2 weeks. She was also on simvastatin (20 mg oral qd), valproic acid (200 mg oral bid), and mirtazapine (15 mg oral qd).

On admission, the patient had sinus bradycardia (heart rate 38 bpm) and was comatose with a Glasgow Coma Score of 3 (O1V1M1), profoundly hypoglycemic (capillary blood glucose 24 mg/dL), and hypothermic (axillary temperature 30.7 °C). Passive rewarming measures and 40 mL of 30% glucose were administered intravenously with a positive response; the patient regained consciousness and became alert without any neurologic deficit. Continuous intravenous infusion of glucose plus 30% glucose boluses and multiple feedings were administered, but during the following 36 hours, recurrent episodes of hypoglycemia developed, as shown in Figure 1. Extensive diagnostic studies were performed to determine the cause of hypoglycemia; infection, organ failure, thyroid abnormalities, suspicion of insulinoma, and adrenal insufficiency were ruled out. A prolonged fasting period or accidental administration of hypoglycemic agents were also excluded. In line with previous cases of hypoglycemia due to haloperidol, insulin levels were elevated, although within normal limits, and C-peptide levels were normal (these tests were added to the first blood sample collected in the emergency department). After the exclusion of other causes of hypoglycemia and due to high suspicion, haloperidol was discontinued after 12 hours in the emergency department. At 36 hours after discontinuation of haloperidol, hypoglycemia had resolved.

All of the patient's medications had been in long-standing use, only in haloperidol has hypoglycemia been described as an adverse effect, and only the dose of haloperidol had been increased recently before the development of hypoglycemia. According to the Naranjo algorithm, this case presents a score of 9, indicating a definite adverse drug reaction.

Although the presence of high or relatively high levels[2] of insulin during haloperidol-induced hypoglycemia in the cases previously described in the literature suggest that glucose sensitization is implicated, the precise mechanism is still unclear.[3,4] Some studies conducted in rats revealed that haloperidol inhibits glucose-stimulated insulin release[2] through the inhibition of ATP-sensitive potassium channels in the pancreatic beta cells.[5] In our patient, the hypoglycemic episode was prolonged and refractory to intravenous glucose (in 48 hours, 554 g were administered, plus oral feedings). We present this case to raise awareness in the medical community to

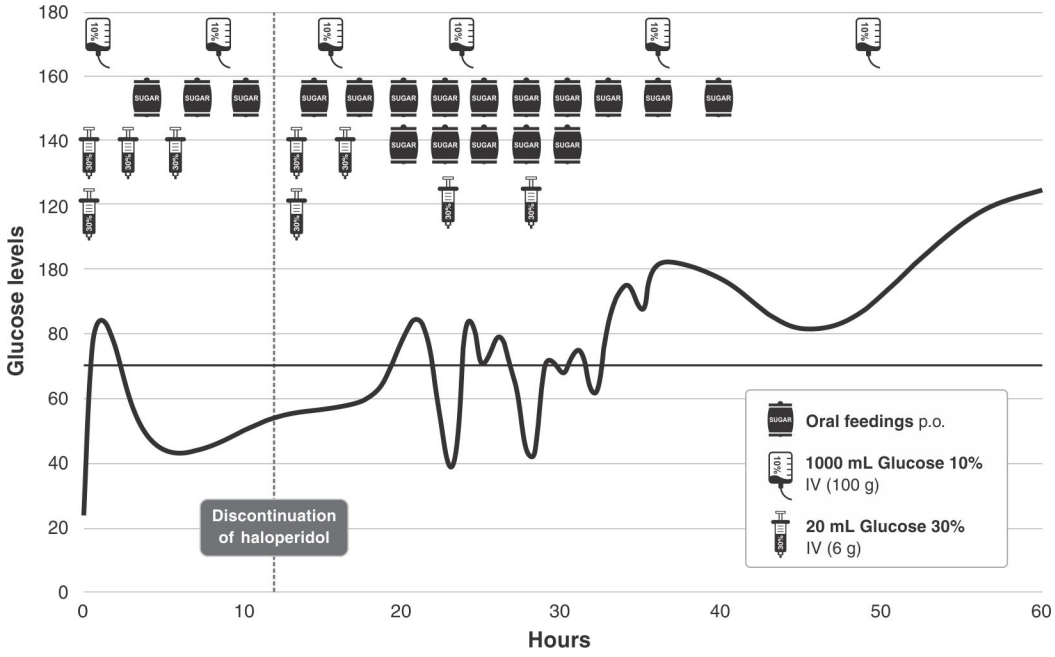

Figure 1 Variation of glucose levels during the 48 hours after admission.

a possible life-threatening side effect of haloperidol, a widely prescribed drug.

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Institutional factors in the medical burnout epidemic

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Physician burnout is being widely discussed in the literature as an epidemic phenomenon. In 2014, 54.4% of U.S. physicians reported at least 1 symptom of burnout, compared with 45.5% in 2011, despite increasing recognition of the problem.[1,2] Medical students are also at great risk for developing burnout, as well as other psychiatric disorders.[3] According to a systematic review and meta-analysis published in this journal, this is also the case in Brazil.[4] The incidence of burnout among U.S. medical students and residents has been estimated at 40-76%.[5] Some risk factors are known, such as female gender, presence of physical illness, medication use, and dissatisfaction with one's academic curriculum or career, among others. Many authors are additionally suggesting that institutional factors also play a role, and should be evaluated and addressed as an essential path for effective solutions.[6] Contemporary physicians are faced with the challenge of delivering high-quality care that is increasingly patient-centered, while also keeping pace with rapid shifts in the economy, technology, and regulatory areas, raising expectations of physician availability. In fact, in the United States, burnout in physicians appears to increase as a direct result of increasing expectations regarding the electronic medical record. Instant messaging tools, e.g., WhatsApp, which is widely used in Brazil, can also raise the demand of being accessible both day and night to