

Nothing up his sleeve: Decompensation after bariatric surgery

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Mr. G, age 64, has schizoaffective disorder and has been stable for years. Weeks after undergoing bariatric surgery, he rapidly develops depressive symptoms. What could be the cause?



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CASE Sudden-onset low mood

Mr. G, age 64, is obese (body mass index [BMI] 37 kg/m²) and has a history of schizoaffective disorder. He is recovering from a sleeve gastrectomy, a surgical weight-loss procedure in which a large portion of the stomach is removed. Seven weeks after his surgery, he experiences a sudden onset of “low mood” and fears that he will become suicidal; he has a history of suicide attempts. Mr. G calls his long-term outpatient clinic and is advised to go to the emergency department (ED).

For years, Mr. G had been stable in a group home setting, and had always been adherent to treatment and forthcoming about his medications with both his bariatric surgeon and psychiatrist. Within the last month, he had been seen at the clinic, had no psychiatric symptoms, and was recovering well from the sleeve gastrectomy.

HISTORY A stable regimen

Mr. G's psychiatric symptoms initially developed when he was in his 20s, during a time in which he reported using “a lot of drugs.” He had multiple suicide attempts, and multiple inpatient and outpatient treatments. He was diagnosed with schizoaffective disorder.

Mr. G has been stable on medications for the last 2 years. His outpatient psychotropic regimen is divalproex sodium extended-

release (ER), 2,500 mg every night at bedtime; iloperidone, 8 mg twice a day; escitalopram, 10 mg/d; and mirtazapine, 30 mg every night at bedtime.

In the group home, Mr. G spends his days socializing, studying philosophy, and writing essays. He hopes to find a job in the craftsman industry.

Mr. G's medical history includes obesity (BMI: 37 kg/m²). Since the surgery, he has been receiving omeprazole, 40 mg/d, a proton pump inhibitor (PPI), to decrease the amount of acid in his stomach. Three weeks after surgery, he had an unremarkable postoperative outpatient psychiatry visit. Divalproex sodium ER was maintained at the pre-surgical dose of 2,500 mg/d.

continued

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Clinical Point

The treatment team believed Mr. G's decompensation had to be related to a recent event, such as his surgery and/or medication change



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EVALUATION Depressed and frightened

In the ED, Mr. G's vitals are normal, but his serum valproic acid (VPA) level is 33.68 µg/mL (therapeutic range: 50 to 125 µg/mL), despite being compliant with treatment. Mr. G is discharged from the ED and told to follow up with his outpatient psychiatrist the next day.

At his outpatient psychiatry appointment, Mr. G's vital signs are normal, but he reports increasing depression and worsened mood. On mental status examination, Mr. G's appearance is well groomed, and no agitation nor fidgeting are observed. His behavior is cooperative but somewhat disorganized. He is perseverative on "feeling so low." He has poor eye contact, which is unusual for him. Mr. G's speech is loud compared with his baseline. Affect is congruent to mood, which he describes as "depressed and frightened." He is also noted to be irritable. His thought process is abstract and tangential, which is within his baseline. Mr. G's thought content is fearful and negativistic, despite his usual positivity and optimism. He denies hallucinations and is oriented to time, place, and person. His judgment, attention, and memory are all within normal limits.

Why might Mr. G's serum VPA level be low?

- his claim of being compliant with medication is not true
- the bariatric surgery impaired absorption of the medication
- the bloodwork was done at the wrong time of the day, leading to a false reading of the serum VPA level
- a laboratory error occurred when measuring the VPA concentration
- another medication is preventing the release of divalproex sodium ER

The authors' observations

The psychiatrist rules out malingering/nonadherence due to Mr. G's long history of treatment compliance, as evidenced by

his past symptom control and therapeutic serum VPA levels. Mr. G was compliant with his postoperative appointments and has been healing well. Therefore, the treatment team believed that Mr. G's intense and acute decompensation had to be related to a recent change. The notable changes in Mr. G's case included his sleeve gastrectomy, and the addition of omeprazole to his medication regimen.

The treatment team observed that Mr. G had a long history of compliance with his medications and his symptoms were consistent with a low serum VPA level, which led to the conclusion that the low serum VPA level measured while he was in the ED was likely accurate. This prompted the team to consider Mr. G's recent surgery. It is well documented that some bariatric surgeries can cause poor absorption of certain vitamins, minerals, and medications. However, Mr. G had a sleeve gastrectomy, which preserves absorption. At this point, the team considered if the patient's recent medication change was the source of his low VPA level.

The psychiatrist concluded that the issue must have been with the addition of omeprazole because Mr. G's sleeve gastrectomy was noneventful, he was healing well and being closely monitored by his bariatric surgeon, and this type of surgery preserves absorption. Fortunately, Mr. G was a good historian and had informed his psychiatrist about the addition of omeprazole after his sleeve gastrectomy. The psychiatrist knew acidity was important for the absorption of some medications. Although she was unsure as to whether the problem was a lack of absorption or lack of delivery, the psychiatrist knew a medication change was necessary to raise Mr. G's serum VPA levels.

TREATMENT A change in divalproex formulation

The psychiatrist switches Mr. G's formulation of divalproex sodium ER, 2,500 mg/d,

to valproic acid immediate-release (IR) liquid capsules. He receives a total daily dose of 2,500 mg, but the dosage is split into 3 times a day. The omeprazole is continued to maintain the postoperative healing process, and he receives his other medications as well (iloperidone, 8 mg twice a day; escitalopram, 10 mg/d; and mirtazapine, 30 mg every night at bedtime).

Why would a change in valproate formulation lead to increased serum VPA levels for Mr. G?

- the IR formulation is always absorbed better than the ER formulation
- the release of the medication in IR formulation is not affected by gastric acid, and therefore is not affected by the surgery nor the prescribed omeprazole
- this is an anomaly and therefore an unusual case report

The authors' observations

The key component to creating a treatment plan for Mr. G centered on understanding drug metabolism and delivery. Acidity plays a role in dissolution of many medications, which led the team to surmise that the PPI, omeprazole, was the culprit. Through research, they understood that the divalproex sodium ER formulation needed a more acidic environment to dissolve, and therefore, an IR formulation was needed.

Different formulations, different characteristics

Medications can be produced in different formulations such as IR, delayed-release (DR), and ER formulations. Different formulations may contain the same medication at identical strengths; however, they may not be bioequivalent and should be titrated based on both the properties of the medication and the release type.¹

Immediate-release formulations are developed to dissolve without delaying or prolonging absorption of the medication. These formulations typically include

“superdisintegrants” containing croscarmellose sodium² so that they disintegrate, de-aggregate, and/or dissolve when they come into contact with water or the gastrointestinal tract.³⁻⁷

Delayed-release formulations rely on the gastrointestinal pH to release the medication after a certain amount of time has elapsed due to the enteric coating surrounding the tablet. This enteric coating prevents gastric mucosa/gastric juices from inactivating an acid-labile medication.⁸

Extended-release formulations, such as the divalproex sodium ER that was originally prescribed to Mr. G, are designed to release the medication in a controlled manner over an extended period of time, and at a predetermined rate and location following administration.⁸⁻⁹ The advantage of this type of formulation is that it can be used to reduce dose frequency and improve adherence.¹⁰ Extended-release formulations are designed to minimize fluctuations in serum drug concentration between doses,¹¹ thereby reducing the risk of adverse effects.^{12,13} A list of common extended-release psychiatric medications is shown in the *Table (page 18)*.

The 5 oral formulations of medications that contain valproic acid include:

- syrup
- capsule
- sprinkle
- enteric-coated delayed-release and extended-release

A parenteral form via IV is available for patients who are unable to swallow.

Absorption vs delivery

Any gastric bypass surgery can have postoperative complications, one of which can include absorption deficiencies of vitamins and minerals. Sleeve gastrectomy has the least amount of absorption-related nutritional deficiencies.¹⁴ Additionally, this procedure preserves the stomach's ability to produce gastric acid. Therefore, regardless of formulation, there should be no

Clinical Point

Divalproex sodium ER needs a more acidic environment to dissolve, so Mr. G was switched to an IR formulation

Table

Different psychiatric medication formulations^a

| Medication | Absorption/delivery |
|-----------------------------|--|
| Divalproex sodium ER tablet | Hydrophilic matrix |
| Venlafaxine ER capsule | Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH-dependent |
| Bupropion SR tablet | Hydrophilic matrix |
| Bupropion XL tablet | A moisture-barrier coating surrounding a control-release coating |
| Paroxetine tablet | A moisture-barrier coating surrounding a hydrophilic matrix |
| Methylphenidate ER tablet | An immediate-release drug coating surrounding a tri-layer core. The tri-layer core is composed of 2 drug layers containing the drug, and a push layer containing osmotically active components |
| Methylphenidate ER capsule | Enteric-coated, delayed-release beads (made by applying a coating of a water-insoluble, dissolution rate-controlling polymer to IR beads) |
| Methylphenidate LA capsule | Contains 50/50 IR/ER beads |
| Clonidine ER | Hydrophilic matrix |

^aAll formulations can vary depending on the manufacturer
ER: extended-release; IR: immediate-release; LA: long-acting; XL: extended-release

Clinical Point

Switching Mr. G to an IR formulation bypassed the need for a low pH and the VPA was delivered and absorbed

initial postsurgical need to change psychotropic medication formulations. However, because VPA is related to B-vitamin deficiency, supplementation can be considered.

Omeprazole is a PPI that increases pH in the stomach and is often prescribed to promote healing of gastric surgery. However, in Mr. G's case, omeprazole created a non-acidic environment in his stomach, which prevented the divalproex sodium ER formulation from being dissolved and the medication from being delivered. Mr. G's absorption ability was preserved, which was confirmed by his rapid recovery and increased serum VPA levels once he was switched to the IR formulation. There is no literature supporting a recommended length of time a patient can receive omeprazole therapy for sleeve gastrectomy; this is at the surgeon's discretion. Mr. G's prescription for omeprazole was for 3 months.

Proper valproate dosing

In Mr. G's case, it could be hypothesized that the VPA dosing was incorrect. For mood disorders, oral VPA dosing is 25 mg/kg/d. Mr. G lost 40 pounds, which would translate

to a 450-mg *reduction* in dose. Despite maintaining his original dose, his serum VPA levels decreased by almost 50% and could not be attributed to trough measurement. In this case, Mr. G was prescribed a higher dose than needed given his weight loss.

Divalproex sodium ER is a hydrophilic matrix tablet that requires a low pH to dissolve. Switching to an IR formulation bypassed the need for a low pH and the VPA was delivered and absorbed. Mr. G was always able to absorb the medication, but only when delivered. The **Table** lists other psychiatric medications that clinicians should be aware of that utilize similar hydrophilic matrix technology to slowly release medications through the gastrointestinal tract and also require low pH to release the medication from the tablet.

OUTCOME Stable once again

Two and a half weeks after his medication formulation is changed from divalproex sodium ER to IR, Mr. G shows improvement in his symptoms. His serum VPA level is 52 µg/mL, which is within therapeutic limits. He continues

receiving his previous medications as well. He reports “feeling much better” and denies having any depressive symptoms nor anxiety. Mr. G is able to maintain eye contact, and has positive thought content, improved organization of thinking, and retained abstraction.

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Related Resources

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- ObesityHelp, Inc. <https://www.obesityhelp.com/medications-after-bariatric-surgery-wls/>

Drug Brand Names

| | |
|--|--|
| Bupropion • Wellbutrin, Zyban | Mirtazapine • Remeron |
| Clonidine ER • Kapvay | Omeprazole • Prilosec, Zegerid |
| Divalproex sodium extended-release tablets • Depakote ER | Paroxetine • Paxil |
| Escitalopram • Lexapro | Valproic acid immediate-release capsules and solution • Depakene |
| lloperidone • Fanapt | Valproate sodium IV • Depacon |
| Methylphenidate ER tablet • Concerta | Venlafaxine • Effexor |
| Methylphenidate ER capsule • Metadate, Jornay | |
| Methylphenidate LA capsule • Ritalin LA | |

Clinical Point

Two and a half weeks after his divalproex formulation is switched, Mr. G’s serum VPA level and symptoms improve substantially

Bottom Line

All medication changes should be identified at each visit. Many extended-release psychiatric medications require lower pH to release the medication from the tablet. When evaluating nonresponse to psychotropic medications, anything that affects pH in the stomach should be considered.