



# Personalized medicine: Vinpocetine to reverse effects of *GABRB3* mutation

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## Abstract

**Objective:** To screen a library of potential therapeutic compounds for a woman with Lennox-Gastaut syndrome due to a Y302C *GABRB3* (c.905A>G) mutation.

**Methods:** We compared the electrophysiological properties of cells with wild-type or the pathogenic *GABRB3* mutation.

**Results:** Among 1320 compounds, multiple candidates enhanced *GABRB3* channel conductance in cell models. Vinpocetine, an alkaloid derived from the periwinkle plant with anti-inflammatory properties and the ability to modulate sodium and channel channels, was the lead candidate based on efficacy and safety profile. Vinpocetine was administered as a dietary supplement over 6 months, reaching a dosage of 20 mg three times per day, and resulted in a sustained, dose-dependent reduction in spike-wave discharge frequency on electroencephalograms. Improved language and behavior were reported by family, and improvements in global impression of change surveys were observed by therapists blinded to intervention.

**Significance:** Vinpocetine has potential efficacy in treating patients with this mutation and possibly other *GABRB3* mutations or other forms of epilepsy. Additional studies on pharmacokinetics, potential drug interactions, and safety are needed.

## KEYWORDS

epilepsy, Lennox-Gastaut, precision medicine, refractory, vinpocetine

## 1 | INTRODUCTION

We present a woman with Lennox-Gastaut syndrome (LGS), intellectual disability, and autism due to a Y302C *GABRB3* (c.905A>G) mutation. She was diagnosed with LGS early in life. With medication titration, her seizures achieved control, but she had disabling cognitive and behavioral disorders with abundant epileptiform activity during her waking electroencephalograms (EEGs). Using cellular models, we assessed

various compounds, including anesthetic, anti-inflammatory, antibiotic, and antifungal agents, to identify candidates with pharmacological activity that enhanced *GABRB3* channel conductance in a concentration-dependent manner (Table S1). Vinpocetine, an alkaloid derived from the periwinkle plant, was active in the assay and selected as the lead candidate based on safety and efficacy considerations. This cognition-enhancing prescription drug in Europe and Japan is available as a dietary supplement in the United States.<sup>1</sup> Pharmacological effects of vinpocetine include vasodilation,

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antioxidation, anti-inflammation, synaptic modulation, and antithrombosis.<sup>2</sup>

We supplemented this woman's antiseizure drug regimen with vinpocetine and observed a dose-related reduction in epileptiform activity on routine EEGs. In addition, her parents, as well as her therapists, who were blinded to the intervention, observed improvements in language and behavior.

## 2 | CASE REPORT

This 29-year-old woman was the product of a normal pregnancy and delivery. Her family had no history of neurologic disorders. In early life, global developmental delays affecting motor, cognitive, and social function were observed. She was diagnosed with LGS by age 3 years with multiple seizure types including myoclonic, tonic, tonic-clonic, and atypical absence. Her EEGs showed mild generalized slowing with sleep-potentiating runs of 2- to 4-Hz generalized spike-wave discharges. Addition of felbamate to topiramate led to seizure control at age 18 years, although EEGs continued to show abundant epileptiform activity.

Genetic testing revealed a *GABRB3* Y302C missense mutation with tyrosine (Y) replaced by cysteine (C; see Materials and Methods).

Over the next 6 months, vinpocetine was added to her antiseizure regimen and increased to 20 mg three times per day (TID). On three subsequent follow-up visits, each 3 months apart, the patient's spike-wave index (SWI) on routine awake and drowsy EEGs (reviewed by one epileptologist, S.B.) declined to 5.0%, 4.8%, and finally 2.9%.

Caregivers blinded to therapy were asked to rate her on the Clinical Global Impression (CGI) scale daily to determine severity of function and global improvement due to an intervention, then followed by determination of an efficacy index (comparison of patient's baseline condition with a ratio of current therapeutic benefit). CGI scores range from 1 (very much improved) to 7 (very much worse). This patient started off with a baseline of 4, and after 9 months on vinpocetine, her CGI score was 2.5. Both parents reported that she was "brighter," more accurate, and engaged with basic tasks. She used new words and displayed more complex speech with longer sentence lengths. Her therapists noted that she was more spontaneous in task completion and required less prompting. The patient remained seizure-free after addition of vinpocetine.

## 3 | MATERIALS AND METHODS

Consent was obtained from the parents of the patient in this study. The cellular model was generated followed by biophysical characterization and high-throughput screening

### Key Points

- A patient with Lennox-Gastaut syndrome was found to have a Y302C *GABRB3* (c.905A>G) mutation effecting  $\gamma$ -aminobutyric acid conductance
- Precision medicine approach screened 1320 compounds to assess enhancement of electrophysiological function in response to GABA
- Vinpocetine treatment resulted in a dose-related decrease in epileptiform activity and improvement in global clinical function
- Vinpocetine was well tolerated, but its effects on cytochrome p450 3A4 led to a dose-dependent increase in felbamate levels

(HTS) using a fluorescent imaging plate reader (FLIPR) assay at IcaGen. Confirmatory screening in an electrophysiology assay was performed at Charles River Laboratories.

### 3.1 | *GABRB3* wild-type and Y302C HEK293 cell model generation

A clonal cell line with stable coexpression of human *GABRA3* and *GABRG2* genes in HEK293 cells was created. This line was transfected with human *GABRB3* genes to generate the wild-type (WT) and Y302C variant c.905A>G *GABRB3* lines. Site-directed mutagenesis was employed to generate the Y302C *GABRB3* variant c.905A>G construct.

### 3.2 | Biophysical characterization of Y302C *GABRB3*

$\gamma$ -Aminobutyric acid (GABA) concentration-response curves (CRCs) for WT and Y302C *GABRB3* cellular models used Sophion Qpatch automated patch clamp. The voltage protocol held a potential of  $-30$  mV while GABA was added for 3 seconds followed by washout with increasing GABA concentrations between washes. Extracellular solution was  $135$  mmol·L<sup>-1</sup> NaCl,  $5.4$  mmol·L<sup>-1</sup> KCl,  $5$  mmol·L<sup>-1</sup> glucose,  $2$  mmol·L<sup>-1</sup> CaCl<sub>2</sub>,  $1$  mmol·L<sup>-1</sup> MgCl<sub>2</sub>,  $10$  mmol·L<sup>-1</sup> hydroxyethylpiperazine ethane sulfonic acid (HEPES) pH 7.4 with NaOH and  $300$  mOsm measured osmolarity. Intracellular solution was  $90$  mmol·L<sup>-1</sup> KCl,  $10$  mmol·L<sup>-1</sup> NaCl,  $30$  mmol·L<sup>-1</sup> Potassium Chloride,  $10$  mmol·L<sup>-1</sup> ethyleneglycoltetraacetic acid (EGTA),  $10$  mmol·L<sup>-1</sup> HEPES pH 7.4 with KOH and measured osmolarity of  $300$  mOsm. For analysis, peak amplitude was plotted as a function of GABA concentration and fit to a four-parameter Hill equation. Individual concentration-responses were normalized to

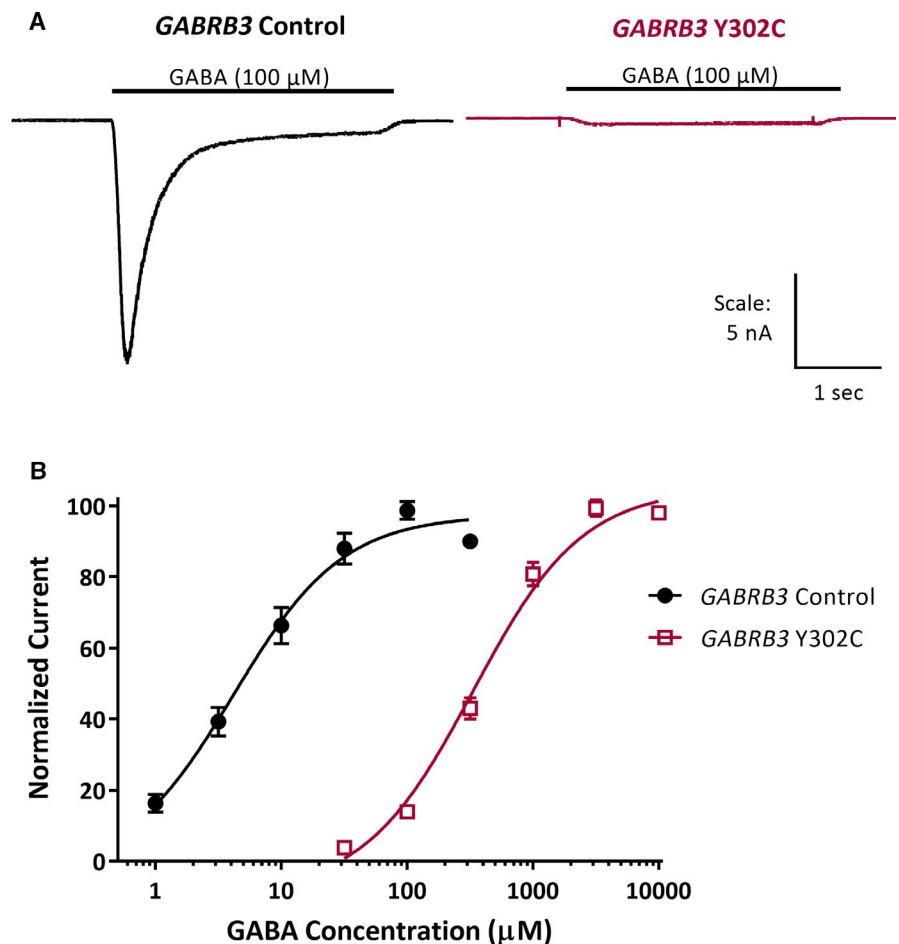
the fitted  $E_{\max}$ , and data points are reported as mean  $\pm$  SEM percentage maximal response.

### 3.3 | HTS and CRCs in the FLIPR assay

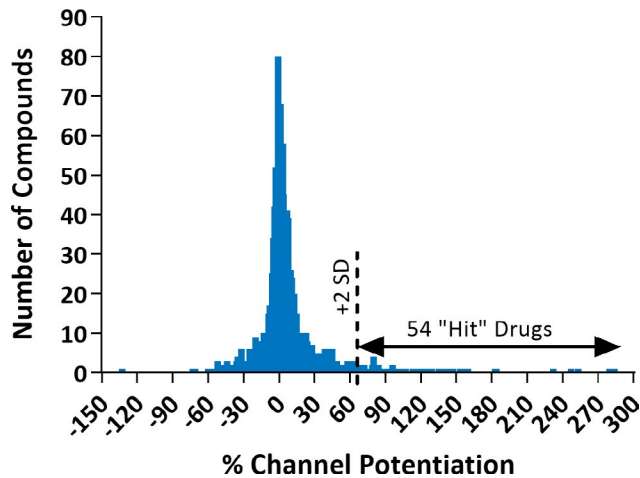
A membrane potential FLIPR assay was developed and validated using a Molecular Devices FLIPR TETRA in 384-well plate format. Single-point screening ( $10 \mu\text{mol}\cdot\text{L}^{-1}$ ) of a repurposing library of 1320 compounds identified activators and potentiators of the WT *GABRA3/GABRB3/GABRG2*  $\text{GABA}_A$  receptor using the clonal HEK293 cell line expressing this receptor. A voltage-sensitive fluorescent dye (R8042, Molecular Devices) was loaded into cultured cells. Cells were washed and then incubated in test compound for 4 minutes followed by addition of GABA to a concentration of  $15 \text{ nmol}\cdot\text{L}^{-1}$  (near the  $\text{EC}_{20}$  for GABA stimulation for this assay). Percentage potentiation was measured and compared to the maximum response ( $15 \text{ nmol}\cdot\text{L}^{-1}$  GABA and  $1 \mu\text{mol}\cdot\text{L}^{-1}$  diazepam). Potency determination with eight-point CRCs in half-log dilution steps starting at  $30 \mu\text{mol}\cdot\text{L}^{-1}$  was performed for selected compounds. The  $\text{EC}_{50}$  of reference compounds diazepam and phenobarbital in this assay was  $28 \text{ nmol}\cdot\text{L}^{-1}$  and  $90 \mu\text{mol}\cdot\text{L}^{-1}$ , respectively.

### 3.4 | Concentration-response testing using electrophysiology

An independently generated HEK293 cell model expressing human WT *GABRA3/GABRB3/GABRG2* receptors was tested on an IonWorks Barracuda automated patch clamp. Ten-point CRCs were generated for the indicated compounds with half-log dilution steps starting from  $60 \mu\text{mol}\cdot\text{L}^{-1}$ .  $\text{EC}_{50}$  and  $E_{\max}$  values were obtained for each compound. CRCs were normalized to currents produced by  $30 \mu\text{mol}\cdot\text{L}^{-1}$  GABA. Compounds were applied to naive cells for 2 minutes followed by addition of  $30 \mu\text{mol}\cdot\text{L}^{-1}$  GABA (near the  $\text{EC}_{25}$  for GABA stimulation in this assay), to produce current flow through the  $\text{GABA}_A$  receptors as a direct agonist and as a positive allosteric modulator (PAM). Data are presented as a percentage of maximum response to GABA added to control cells treated with  $30 \mu\text{mol}\cdot\text{L}^{-1}$  GABA alone. Intracellular solution was  $50 \text{ mmol}\cdot\text{L}^{-1}$  CsCl,  $90 \text{ CsF}$ ,  $5 \text{ mmol}\cdot\text{L}^{-1}$   $\text{MgCl}_2$ ,  $1 \text{ mmol}\cdot\text{L}^{-1}$  EGTA, and  $10 \text{ mmol}\cdot\text{L}^{-1}$  HEPES pH 7.2 with CsOH. Extracellular solution was  $137 \text{ mmol}\cdot\text{L}^{-1}$  NaCl,  $4 \text{ mmol}\cdot\text{L}^{-1}$  KCl,  $3.8 \text{ mmol}\cdot\text{L}^{-1}$   $\text{CaCl}_2$ ,  $1 \text{ mmol}\cdot\text{L}^{-1}$   $\text{MgCl}_2$ ,  $10 \text{ mmol}\cdot\text{L}^{-1}$  glucose, and  $10 \text{ mmol}\cdot\text{L}^{-1}$  HEPES pH 7.4 with NaOH. Holding potential was 10 mV.



**FIGURE 1** A, Wild-type (WT) *GABRB3* cells (black line) demonstrated a robust response to  $100 \mu\text{mol}\cdot\text{L}^{-1}$   $\gamma$ -aminobutyric acid (GABA). In contrast, *GABRB3* Y302C cells (red line) had a very small response to  $100 \mu\text{mol}\cdot\text{L}^{-1}$  GABA. B, Concentration-response curves for WT *GABRB3* cells (black) and *GABRB3* Y302C cells (red) show the reduced response of *GABRB3* Y302C cells in the rightward shift in the curve for Y302C cells, indicating that much higher concentrations of GABA are required to elicit an equivalent relative current response



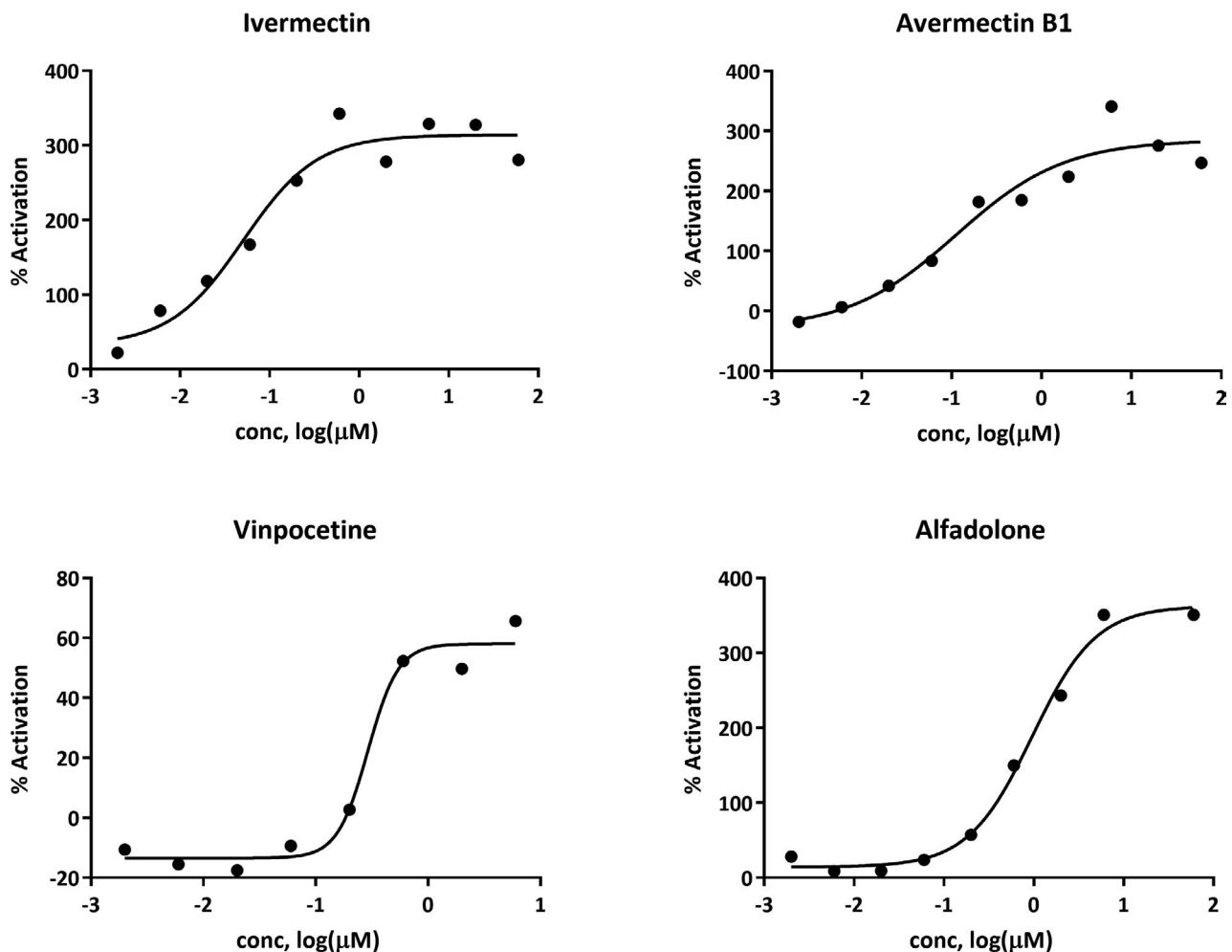
**FIGURE 2** Percentage potentiation of the  $\gamma$ -aminobutyric acid type A receptor activity plotted as a histogram for the 1320 compounds in the library. The cutoff for significant activation was set at  $>2$  SD (71%) from the group mean (7.7%). There were 54 drugs above this cutoff, with activity ranging from 72% to  $>280\%$  in the fluorescent imaging plate reader assay

## 4 | RESULTS

### 4.1 | Y302C mutation in *GABRB3* causes a significant reduction in the response to GABA

WT and Y302C *GABRB3* subunits were characterized in HEK293 cell lines coexpressing *GABRA3* and *GABRG2* as the basis for WT and Y302C mutation cellular models. The *GABRB3* WT cellular model demonstrated a rapid current in response to GABA (Figure 1A, left). In contrast, the *GABRB3* Y302C cellular model showed a much smaller response to GABA (Figure 1A, right), indicating a significant loss of function in the GABA<sub>A</sub> receptor resulting from the Y302C mutation. This corroborates an earlier study finding that the Y302C mutation causes a profound loss of function.<sup>3</sup>

GABA concentration-responses were performed for each cellular model (Figure 1B). The *GABRB3* Y302C model required more GABA to produce an electrical response equivalent to the WT model. The  $EC_{50}$  values for GABA were  $6 \mu\text{mol}\cdot\text{L}^{-1}$  for *GABRB3* WT cells and  $378 \mu\text{mol}\cdot\text{L}^{-1}$  for



**FIGURE 3** Results from the Electrophysiology (EP) assay demonstrating a concentration (conc)-dependent increase in percentage activation of  $\gamma$ -aminobutyric acid type A activity for four of the top performing compounds: ivermectin, avermectin B1, vinpocetine, and alfadolone. Curves were generated by fitting to a four-parameter sigmoidal curve. See Table S2 for additional data on compound activity

*GABRB3* Y302C cells, a 63-fold difference. Mean maximal currents were also lower for *GABRB3* Y302C cells, 5.1 nA compared to 12.2 nA for WT.

## 4.2 | Identifying potentiators of GABA at the GABA<sub>A</sub> receptor

Because mutant GABA<sub>A</sub> receptors containing the *GABRB3* Y302C variant display lower potency for GABA, there was concern about the ability to identify compounds that could compensate for this effect within physiological ranges. For this reason, and because the patient heterozygously expressed the *GABRB3* Y302C variant, we screened compounds using the WT model to identify *GABRA3/GABRB3/GABRG2* receptor potentiators. HTS used the FLIPR assay with the WT GABA<sub>A</sub> receptor cellular model. Screening used a threshold concentration of GABA to identify compounds that enhance, or potentiate, GABA activity on the receptor, because most approved drugs that stimulate GABA<sub>A</sub> receptors are potentiators rather than direct agonists.

A total of 1320 compounds were screened in the WT cellular model. Each compound was tested at a concentration of 10  $\mu\text{mol}\cdot\text{L}^{-1}$  in the presence of 15  $\text{nmol}\cdot\text{L}^{-1}$  GABA. The test compound response was normalized to the 1  $\mu\text{mol}\cdot\text{L}^{-1}$  diazepam response (also in the presence of 15  $\text{nmol}\cdot\text{L}^{-1}$  GABA) to yield percentage channel potentiation. The potentiating activity of each compound is plotted in Figure 2. Most compounds (96%) had little effect. The mean potentiating activity for all compounds was 7.7% ( $\pm 32.5\%$  SD). Compounds with  $>2 \times \text{SD}$  were progressed to follow-up electrophysiological testing. Fifty-four hit compounds significantly potentiated GABA<sub>A</sub> activity above this cutoff (see Table S1 for all hit compounds).

To confirm the hits, we performed concentration-response analysis using an Electrophysiology (EP) assay. CRCs were generated for the 54 hit compounds from the library at 10 concentrations. For this EP analysis, a different cell line expressing WT GABA<sub>A</sub> was used, because the original WT and mutant *GABRB3* cell lines were hypersensitive to GABA stimulation, even showing GABA<sub>A</sub> channel activity without GABA (data not shown).

From the 54 compounds evaluated in the second EP assay, 18 generated saturating CRCs. The  $\text{EC}_{50}$  values ranged from 39  $\text{nmol}\cdot\text{L}^{-1}$  to 22  $\mu\text{mol}\cdot\text{L}^{-1}$  (Table S3). CRCs for four of the top five compounds are shown in Figure 3. (Prenylamine had an  $\text{EC}_{50}$  of 60  $\text{nmol}\cdot\text{L}^{-1}$  but was omitted due to cardiac toxicity.) Ivermectin was the most potent compound tested, with an  $\text{EC}_{50}$  of 39  $\text{nmol}\cdot\text{L}^{-1}$ . The related compound avermectin had an  $\text{EC}_{50}$  of 113  $\text{nmol}\cdot\text{L}^{-1}$ . The vasodilator and anti-inflammatory compound vinpocetine had an  $\text{EC}_{50}$  of 291  $\text{nmol}\cdot\text{L}^{-1}$ . GABA<sub>A</sub> PAM alfadolone had an  $\text{EC}_{50}$  of 336  $\text{nmol}\cdot\text{L}^{-1}$ . Several GABA<sub>A</sub> potentiators in the original HTS library did

not show activation in the original FLIPR assay, possibly because they overstimulated the cell line.

Additional tables with information on specific compounds tests are provided in the supplementary section (Tables S1-S4).

## 5 | DISCUSSION

Using the *GABRB3* Y302C variant detected in a woman with LGS, our precision medicine approach screened 1320 compounds. Vinpocetine was identified as the lead candidate based on safety and efficacy considerations as well as its efficacy in potentiating GABA-evoked currents. Prior to vinpocetine therapy, her SWIs on two 25-minute, routine awake and drowsy EEGs done 6 months apart were 20.1% and 20.2%. She was taking felbamate 1500/1200/1200mg (trough level = 107  $\mu\text{g}/\text{mL}$ ) and topiramate 100 mg twice daily (trough level = 8.2  $\text{mg}/\text{mL}$ ). This regimen was supplemented with vinpocetine titrated to 20 mg three times daily over 9 months. This was associated with a sustained, dose-related decrease in epileptiform activity, with improvement in global clinical function as rated by blinded therapists.

Vinpocetine (14-ethoxycarbonyl-[3a,16a-ethyl]-14,15-eburnamine) is a synthetic derivative of vincamine, an alkaloid extracted from the leaf of *Vinca minor* (periwinkle plant).<sup>2</sup> It has various mechanisms of action and has been used as a treatment for several clinical indications. Vinpocetine was developed and marketed in Hungary in 1978 and later used in Europe and Asia to prevent and treat stroke, dementia, and memory disturbances based on its vasodilatory and anti-inflammatory properties.<sup>3</sup> Vinpocetine passes through the blood-brain barrier and inhibits calcium/calmodulin-dependent cyclic guanosine monophosphate-phosphodiesterase 1, voltage-gated calcium channels, glutamate receptors, and voltage-dependent Na-channels.<sup>4</sup> It exerts anti-inflammatory effects via multiple mechanisms (eg, reduces nuclear factor- $\kappa\text{B}$  and tumor necrosis factor  $\alpha$  expression, decreases the inflammatory response after cerebral ischemia, reduces lipopolysaccharide-induced inflammation) in vitro and in vivo.<sup>5-8</sup> Antiepileptiform effects of vinpocetine could derive from the above, plus its inhibition of sodium channels and potentiation of GABA activity. Many antiseizure drugs modulate voltage-gated sodium channels (eg, carbamazepine, phenytoin, lamotrigine), which are critical in generating action potentials and for synaptic conduction.<sup>9,10</sup> Similar to these antiseizure drugs, vinpocetine has dose-dependent effects on sodium channels. Furthermore, vinpocetine potentiates GABA<sub>A</sub> activity.<sup>11</sup> Sodium channel and GABA<sub>A</sub> modulation by vinpocetine likely contributes to its properties, although no human clinical trials have studied this. Vinpocetine is also thought to have a positive effect on memory via long term potentiation in animals.<sup>1</sup> This could



also be attributed to some of the positive behavior changes seen in this patient.

Few randomized, open-label, controlled, multicenter clinical trials have assessed the efficacy and safety of vinpocetine for stroke or cognition. Most studies suggest that vinpocetine is well tolerated compared to placebo at doses up to 60 mg/d. Infrequent adverse effects include mild gastrointestinal symptoms (dyspepsia, diarrhea, dry mouth) and headaches.<sup>12,13</sup>

Vinpocetine is absorbed after oral administration but undergoes extensive first pass metabolism. It is highly protein bound (~90%), and its bioavailability doubles when taken with food versus fasting.<sup>4</sup> Peak levels are attained within an hour, as its half-life is ~90 minutes.<sup>14,15</sup> Multiple studies have found vinpocetine metabolism is via hepatic cytochrome P (CYP) enzymes, with reversible inhibition of both cytochrome p450 3A4 (CYP3A4) and CYP2D6.<sup>14,15</sup> In our patient, whereas topiramate dosing and levels remained steady throughout vinpocetine titration, felbamate dosing had to be subsequently reduced from 1500/1200/1200 mg to 1080mg TID (level of 137 µg/mL) to 960 mg TID (level of 101 µg/mL). We suspect this ~30% elevation of the felbamate level was due to vinpocetine-mediated inhibition of felbamate metabolism via an effect on CYP3A4. Due to this inhibition, when they are used in conjunction with other compounds that are metabolized by CYP enzymes (eg felbamate, carbamazepine, phenytoin, and phenobarbital), the levels of those individual antiseizure drugs might be affected.<sup>16</sup> The benefit of vinpocetine might be independent or synergistic when combined with other seizure medications. Definite interactions between vinpocetine and other seizure medications, however, have yet to be examined. In this single case report, this patient's felbamate level increased despite a reduction in the medication dosage, in parallel with an increase in vinpocetine dosing.<sup>17</sup> Future, clinical studies in humans are needed to assess the safety and efficacy of vinpocetine in patients with LGS and other epilepsies and to assess interactions with other hepatically metabolized drugs.

There are some limitations identified in this case study. First, CGI was used to gauge improvement in behavior and cognition. It was not disclosed to the caregivers that there was an ongoing intervention. Although presumably this test was administered roughly at the same time of the day (during which the patient was scheduled for therapy) and by the same caregivers, there was room for variability. It is possible that certain caregivers were more lenient on their scoring and the patient was more cognitively alert at different times of the day. However, a more objective test, such as neuropsychological testing, would not be possible in this patient and similar patient populations due to severe cognitive delay. Next, SWI was calculated by one epileptologist, blinded to treatment status, using routine 25-minute EEGs during the awake and drowsy periods. There is variation in spike-wave discharges throughout the day, which might have influenced the final calculated SWI to some degree. However, these routine EEGs

recorded random samples of awake and drowsy periods during the late morning or early afternoon. Lastly, there are currently no available laboratory tests to check for therapeutic vinpocetine ranges, nor are there established guidelines on dosing for antiseizure purposes. This becomes especially important when taking into account its interaction with felbamate in this specific case. One could argue that the changes seen in this patient were secondary to an increase in felbamate levels and not the addition of vinpocetine, but it is important add that this patient had previously had felbamate levels > 100 µg/mL without similar improvements in her EEG spike activity.

Our precision medicine approach led to the identification of vinpocetine as a potent GABA modulator, which proved helpful in reducing epileptiform activity and improving cognitive and behavioral function in a patient with LGS. Vinpocetine may be effective in patients with epilepsy by reducing epileptiform activity as seen on EEG. In our patient, enhancement of GABAergic activity was likely the main mechanism of action, although effects on ion channels and inflammation are other potential mechanisms. Future studies are necessary to further determine vinpocetine's efficacy, pharmacokinetics, interactions, and adverse effects in the treatment of epilepsy.

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## CONFLICT OF INTEREST

S.B., J.M.A., B.C.G., G.R.S., N.B.F., and A.C.G. have no conflict of interest to disclose. O.D. had equity interest in Pairnomix until its recent merger with Q-State Biosciences; he maintains equity interest in this new merged entity. He serves on the scientific and/or medical advisory boards, and has equity interest and/or receives compensation from Receptor Life Sciences, Privateer Holdings/Tilray, Egg Rock Holdings/Papa & Barkley, Tevard, Rettco, Engage Pharmaceuticals, Pairnomix, and Empatica. He has been an investigator and consultant for GW Pharmaceuticals. He has consulted for Zogenix. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## AUTHOR CONTRIBUTIONS

All coauthors have been substantially involved in the study and/or the preparation of the manuscript. No undisclosed

groups or persons have had a primary role in the study and/or in manuscript preparation. All coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

## DATA AVAILABILITY STATEMENT

All data not published within the article are available in a public repository and include digital object identifiers or accession numbers to the datasets. Anonymized data will be shared by request from any qualified investigator.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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