Paradoxically, the patient most likely would have been better off if TDM had not been performed. This situation thus demonstrates a significant shortcoming of TDM that could be amended by using analytical methods that measure unbound drug; however, such methods are more time consuming, technically challenging and costly, and not widely available. Clinicians using TDM services, as well as pharmacologists offering them, should be aware of the complex effects of inflammation on the pharmacokinetics of risperidone and, potentially, several other psychoactive drugs.

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The authors declare no conflicts of interest.

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Severe Cognitive Impairment Associated With a High Free But Therapeutic Total Concentration of Valproic Acid Due to Hypoalbuminemia in an Older Patient With Bipolar Disorder

To the Editors:

Valproic acid (VPA) is highly protein bound in blood (80%–95%), mainly to albumin.[1,2] Binding of VPA to albumin is nonlinear, concentration-dependent, and saturable. The unbound VPA concentration can therefore rise substantially with a dosage increase, or if the number of binding sites for VPA decreases.[1,2] In hypoalbuminemic patients, VPA binding may decrease, in which case a patient can experience toxic effects although the total concentration is within the therapeutic range, because it is the free concentration that is pharmacologically active and correlates best with brain concentrations.[1] It is then clinically relevant to measure the free concentration of VPA.[1,3,4] In clinical practice, total VPA serum concentrations (tVPAcs) are generally measured instead of free concentrations owing to analytical difficulties, a lack of an established reference range, and guidelines not requiring the measurement of free concentration.[1,2,5] We present a 66-year-old woman with bipolar disorder since 2001 who developed severe reversible cognitive impairment associated with a high free concentration of VPA probably owing to hypoalbuminemia. She had no comorbidities, was living independently, had no history of alcohol abuse, and recently stopped smoking. She had been stable on citalopram and lithium therapy for 15 years managed by her general practitioner without cognitive complaints. Because of a lithium encephalopathy (3.1 mmol/L), she was admitted to the internal medicine department, which led to the decision to stop lithium and subsequently citalopram. Secondly, a nephrotic syndrome was diagnosed and a renal biopsy showed antiphospholipase A2 receptor (anti-PLA2R) membranous nephropathy, which may have caused the lithium intoxication and proteinuria (14 g/10 mmol creatinine) with hypoalbuminemia. Prednisone and cyclophosphamide were prescribed to treat the proteinuria. A month after discharge, she became hypomanic. Valproic acid (300 mg/d) was initiated (day 1), as she refused lithium reintroduction and was referred to a psychiatric outpatient clinic. No cognitive impairment was present at referral (day 13), with a Montreal Cognitive Assessment (MoCA) score of 24 of 30 during hypomania.[6] After VPA initiation, blood test results (day 18) (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/JCP/A493) were unremarkable besides a tVPAc of 21 mg/L (40–120), erythrocyte sedimentation rate of 108 mm/h (1–12), glomerular filtration rate of 53 mL/min/1.73 m^2 (>90), and albumin of 23 g/L (35–55). The tVPAc was determined with an immunoassay technique (Siemens, Dimension EXL200). Valproic acid was gradually increased to the maximum of the recommended dose range of 2500 mg/d, still resulting in a low tVPAc of 30 mg/L as shown in Figure 1 (day 49). Liver function tests were all within reference range (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/JCP/A493), and there were no drug interactions that could induce a low tVPAc.

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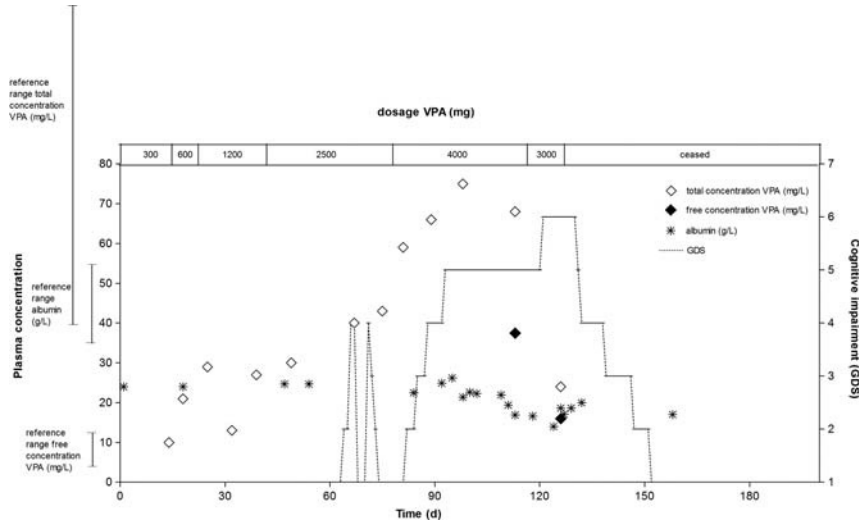

FIGURE 1. Valproic acid dosage, total and free VPA plasma concentration, albumin concentration, and cognitive impairment. Valproic acid dosage is increased to 4000 mg, resulting in (sub)therapeutic total VPA concentrations after which cognitive impairment becomes visible. Albumin levels are continuously below the reference range with a drop around day 120. Free concentration of VPA is measured on days 113 and 126; both values are far above the reference range. Whereas the total VPA concentrations were (sub)therapeutic, the free concentrations were toxic. On day 66 and day 70, a decline in cognitive function can be seen owing to the concurrent deliria due to infection and urinary retention. Cognitive impairment was not measured continuously but by interval with the MoCA at that time and determined afterwards on a GDS. Cognitive impairment: 1, no cognitive decline; 2,very mild cognitive decline; 3, mild cognitive decline; 4,moderate cognitive decline; 5, moderate severe cognitive decline; 6, severe cognitive decline; 7, very severe cognitive decline.[8]

The patient shifted from hypomania towards mania. To treat the mania, lithium reintroduction was attempted alongside VPA. Reintroduction failed twice as a result of concurrent deliria due to an infection (day 66) and urinary retention (day 70). As her mania worsened during subtherapeutic tVPAc and while awaiting planned admission to a psychiatric medicine unit for lithium reintroduction, VPA was increased to 4000 mg/d (day 77), exceeding the maximum approved dose of 60 mg/kg per day by 700 mg. The VPA dose increase resulted in a tVPAc of 59 mg/L (day 81). Upon admission, she exhibited cognitive dysfunctions (day 88). She was disorientated, answering questions sometimes inadequately or only tangentially and was not structurable. Besides her mania, considered causes included the recent alleged lithium intoxications or a postdelirium state. Based on clinical symptoms, she had moderate cognitive impairment comparable with Global Deterioration Scale (GDS) 4.[7] Lithium (400 mg/d) was reintroduced (day 90) and increased to 800 mg/d after 1 week. Two days thereafter, she clinically worsened with hypotension, disorientation, and somnolence. Because of the severity of her symptoms, she was transferred to the internal medicine department (day 98). Cyclophosphamide was stopped owing to a pancytopenia. A lithium level of 1.3 mmol/L led to the decision to halt the lithium reintroduction (day 99). Her MoCA had declined to 15 of 30, and Mini-Mental State Examination was 20 of 30 (day 109). Her cognitive function further deteriorated to severe cognitive impairment (GDS 5) after lithium cessation. A computed tomography scan revealed no evidence of cerebral pathology besides mild atrophy. As a precaution, VPA 4000 mg/d (tVPAc 68 mg/L) was reduced to 3000 mg/d (day 118) below the maximum dose of 60 mg/kg per day. The free concentration of the 3000 mg VPA as well as that of the previous 4000 mg blood sample was extracted by ultrafiltration, using centrifugation at 1000 to 2000 *g* at 25°C as the driving force for the ultrafiltration. The free VPA in the ultra filtrate was measured by an immunoassay technique (Abbott ARCHITECT). Albumin had dropped to 14 g/L (day 124). In the meantime, the patient severely deteriorated with conative function deficits and activities of daily living dependency (GDS 6). She became apathetic, could barely be motivated to eat or drink, and was in need of a wheelchair. She lost the motivation to continue living, spending most of her time in the fetal position. Valproic acid was stopped immediately (day 126) after the laboratory result of the VPA 3000 mg/d indicated a free fraction of 66%, with a free concentration of 15.8 mg/L (reference range, 4–12 mg/L)[8] and tVPAc of 24 mg/L. The sample of VPA 4000 mg/d of day 113, which was determined retrospectively, showed a toxic unbound VPA concentration of 37.8 mg/L, with a tVPAc of 68 mg/L (free fraction 56%). After VPA withdrawal, she switched to a hyperactive delirium and suffered a seizure (day 130). Olanzapine (5 mg) was started, and she regained conative, cognitive, affective, and physical functioning within days with independency in activities of daily living. On day 154, she was transferred to the psychiatric medicine unit for further recovery in instrumental activities of daily living. Liver function test results were within reference ranges, except for a γ-glutamyl transferase of 58 U/L and alkaline phosphatase of 127 U/L. Her cognitive and conative functioning recovered to pre-VPA levels (Mini-Mental State Examination, 27/30; MoCA, 27/30; GDS 1). Discharge followed 197 days after introducing VPA. Later that year, lithium was reintroduced without problems.

DISCUSSION

The cognitive impairment that started just days before admission to the psychiatric medicine unit was thought to be partially related to age, manic state, neurodegeneration, and lithium intoxications and due to a recent delirium. Change of health care professional contributed to the misinterpretation of cognitive adverse effects, as her baseline MoCA score was not transferred from the outpatient clinic. Lithium was thought to be associated to the cognitive decline, owing to cognitive complaints during the first and second reintroduction, although there were concurrent deliria and a dosage increase of VPA to 4000 mg.

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Reintroduction of lithium (up to 1.2 mmol/L) after dechallenge of VPA did not result in cognitive impairment. The cognitive impairment could be categorized as a definite adverse event of VPA (Naranjo score, 9).[9] Valproic acid was at first neglected as a causal factor, because the tVPAc was below or within the therapeutic range. However, the eventually detected free concentrations of VPA were far above the reference range and are likely to have caused the severe reversible cognitive impairment. The patient's hypoalbuminemia explains the remarkably high free fraction of VPA and was most likely caused by the PLA2R membranous nephropathy. There was a time correlation with the tVPAc, free concentration, and the severity of cognitive impairment (Fig. 1). The cognitive impairment started after a dosage increase of VPA to 4000 mg. Her albumin levels dropped starting day 96 from a low but stable 23 to 26 g/L to 14 g/L on day 124, which could explain why the clinical condition deteriorated dramatically. We presume that the free concentration could have net increased more owing to decreased albumin despite the lowering of the dosage. Dechallenge of VPA gradually resulted in a continuous revitalization.

Previous cases have reported VPA-related dementia and cognitive impairment, even after long-term use.[10] Cognitive and conative adverse effects are known to arise in VPA treatment, although very rarely as severely as seen in our patient. A difficulty is that these features, along with other known adverse effects such as decreased appetite, apathy, aggression, and hyperactivity, can be symptoms of the diseases VPA is given for, particularly bipolar depression and mania. These adverse effects may be misinterpreted, especially when they are less pronounced, progress over time, and with advancing age. It becomes all the more difficult to recognize VPA as the cause of these symptoms when total blood VPA serum levels are within the reference range. Particularly in the elderly, there is a risk of underestimation of the free fraction.[11,12] There is evidence that the VPA affinity for serum proteins decreases with age and age is positively correlated with the free fraction.[13] The need for monitoring of the free concentration of VPA is suggested by multiple other case reports.[3,4] Other cases have been published on VPA-induced encephalopathy due to hyperammonemia.[14] In our case, ammonia was not measured; it is therefore unclear if ammonia could have contributed to the symptoms. Development of hyperammonaemic encephalopathy is unrelated to VPA dose, serum level, or severity of hyperammonaemia.[11] As pointed out, because of the pharmacokinetics of VPA, patients with therapeutic total blood levels can have a high free concentration of VPA,[15] which can therefore be an undetected cause of adverse effects or even toxicity. This is more likely in hypoalbuminemic patients. We recommend measuring albumin during VPA use if free concentration VPA monitoring is not standard, particularly in patients at risk of hypoalbuminemia,[15] including those with nephrotic syndrome,[15] liver disease,[2,15] or older adults.[11,12,15] This case report suggests that it is necessary to monitor the free concentration of VPA in hypoalbuminemic patients to prevent misinterpretation of adverse effects or toxicity.

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Long-Term Near-Infrared Photobiomodulation for Anxious Depression Complicated by Takotsubo Cardiomyopathy

To the Editors:

Photobiomodulation (PBM) with near-infrared radiation (NIR) is a novel treatment approach for major depressive disorder (MDD), delivered transcranially (t-PBM) or intranasally (i-PBM).[1,2] Near-infrared radiation, delivered noninvasively by low-level lasers or by light-emitting diodes, penetrates into the brain,[3] is absorbed by mitochondrial chromophores, boosts brain metabolism,[4] and modulates the cerebral cortex.[5] Both a direct (transcranial) effect of NIR on the brain and an indirect (systemic) effect have been postulated. The latter implies mediation by peripheral tissues, such as blood cells.[6,7] Regardless, the prometabolic action of NIR, its absorption by the mitochondrial enzyme cytochrome-c oxidase, leading to increased production of adenosine triphosphate,[4] is the most likely mechanism of action for its antidepressant effect.[1] Of note, depression is associated with deficits in brain bioenergetics metabolism and with mitochondrial dysfunction.[8] Clinical studies have evaluated the acute efficacy and tolerability of t-PBM for MDD,[9–11] but little is known about its long-term outcomes.

This report describes the case of a 76-year-old white woman, diagnosed with MDD with anxious distress, hypertrophic obstructive cardiomyopathy, and Takotsubo cardiomopathy, who had responded to cautious antidepressant pharmacotherapy, but failed to achieve remission, and who subsequently received a 31-month augmentation with NIR PBM.

Takotsubo cardiomyopathy is an acute coronary syndrome associated with myocardial stunning and apical ballooning of the left ventricle, under emotional stressors. Its clinical presentation is similar to acute myocardial infarction, in the absence of occlusive disease. It has been associated with the use of serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants, and thus, noradrenergic antidepressants are relatively contraindicated.

For 12 months before the PBM, the patient had been treated with the following antidepressant regimen, which was maintained during PBM: duloxetine (30 mg/d), amitriptyline (5 mg/d), perphenazine (1 mg/d), and zolpidem (5 mg/d). This medication regimen had remained stable despite the lack of remission, given the treatment response after a severe depressive episode with suicidal ideation (≥50% decrease in MDD symptom severity) and given the Takotsubo cardiomyopathy, which limited the dose increase. Furthermore, the patient declined psychotherapy. Given the significant residual depression, augmentation with NIR PBM was suggested. The patient was informed of potential benefits and adverse effects and consented to the off-label use of over-the-counter PBM devices. Of note, later, the patient also gave permission to the article.

Because of the very limited evidence supporting the use of PBM for MDD and the uncertainty over the effective dose and best localization for light delivery, it was recommended to the patient to track her symptoms using self-report instruments. The depressive and anxious symptoms were self-rated weekly with the 16-Item Quick Inventory of Depressive Symptomatology Self-Report version (QIDS-SR16; total score ranges, 0–27) and with the Anxiety Symptoms Questionnaire (ASQ; total score ranges, 0–340). The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire was rated monthly. In addition, efficacy and tolerability of PBM were monitored regularly by her treating psychiatrist.

In December 2014, i-PBM was started with the Vielight 810 light-emitting diode source placed in both nostrils. The intranasal modality presumably leverages the systemic effects of NIR. The frequency was progressively increased to maximize clinical benefits and, as tolerated, from twice a week sessions to daily and then twice daily. The i-PBM parameters were as follows: wavelength, 810 nm; power, 14.2 mW; peak irradiance, 14.2 mW/cm^2; pulsing, 10 Hz; duty cycle, 50%; average fluence, 10.65 J/cm^2; treatment window and time, 1 cm^2; and 25 minutes per nostril, respectively. Over time, the total intranasal energy delivered increased from 0.021 to 0.043 kJ/d and from 0.043 to 0.149 and to 0.298 kJ/wk.

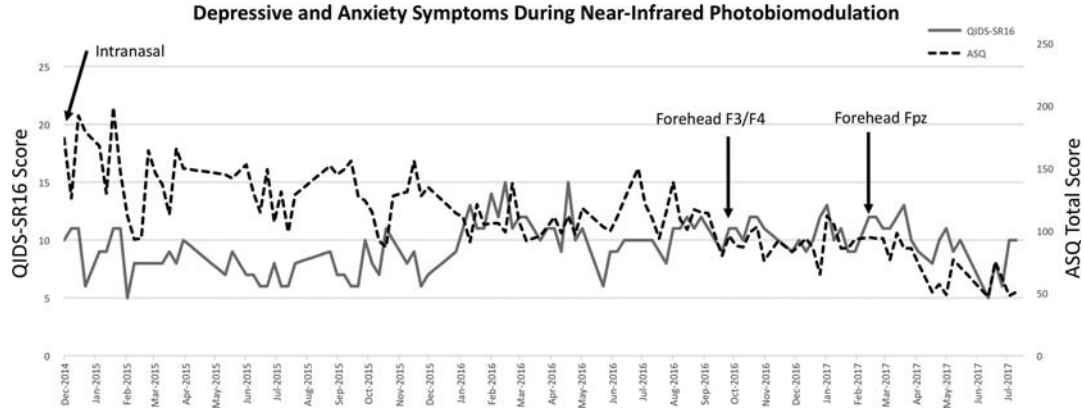

FIGURE 1. Plot of depressive and anxiety symptoms during near-infrared PBM. The scores for the QIDS-SR16 (depressive symptoms) are reported on the left side of the graph; the scores for the ASQ (anxiety symptoms) are on the right, instead. The arrows indicate: 1, the start of i-PBM; 2, the association of t-PBM at the F3 and F4 EEG sites; and 3, the change of the t-PBM to the Fpz EEG site.

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