events, as glucocorticoids can also cause NP disturbances and especially psychosis in SLE patients.[1] Hydroxychloroquine is also known as a rare cause of psychosis.[6]

Given our patient's negative family and personal psychiatric history before the diagnosis of SLE, the absence of other concomitant disease processes, the occurrence of psychosis before the administration of glucocorticoids and hydroxychloroquine, and the concomitant presence of active lupus biological biomarkers, it is more likely that our patient's NP manifestations were primary NPSLE-related to the disease itself.

As mentioned previously, our patient developed, 3 times in succession, an NRC after antipsychotic administration. Early identification and treatment of NRC is of crucial importance because it can progress into neuroleptic malignant syndrome.[7] It has been the subject of a few studies to specify its features. Lee[8] described for the first time the clinical manifestations and treatment response of a group of patients with an NRC. The authors noticed the cooccurrence of catatonic and extrapyramidal symptoms in most reported cases of NRC. Given (1) the development of catatonic syndrome after exposure to high (haloperidol) and intermediate (loxapine) potency D2-receptor antagonists, (2) the absence of any catatonic sign before the introduction of the D2-receptor antagonists, (3) the occurrence of extrapyramidal features (ie, sialorrhea, cogwheel rigidity, tremors) concomitant with catatonic syndrome, and (4) the replication of the catatonic-extrapyramidal syndrome each time these antipsychotics were readministered, we are confident that the diagnosis of NRC best accounts for the array of findings in our patient. The efficacy of zolpidem and benzodiazepines, notably lorazepam and to a lesser degree diazepam, clonazepam, and oxazepam, is well documented in the treatment of simple noninduced catatonia. It seems that benzodiazepines are an effective treatment for NRC as well.[8,9] However, we did not find any study using zolpidem in the treatment of NRC after a thorough PubMed research in October 2018. In our case report, lorazepam (4 mg) effectively treated the first NRC episode, and zolpidem (10 mg) effectively treated the second and third NRC episodes. It is also to be noted that low-dose diazepam in combination with loxapine did not prevent its occurrence. This could point to possible nonequivalent efficacy of all benzodiazepines in the treatment of NRC.

However, the simultaneous rapid resolution of both NRC and psychosis after zolpidem administration, but not low-dose lorazepam and diazepam, is quite surprising and intriguing. Although there are no internationally agreed standards or criteria for assessing causality in individual cases, the rapid resolution of psychosis in our patient can nevertheless be strongly attributed to zolpidem given (1) the complete resolution of the psychotic syndrome within 30 minutes after zolpidem administration, (2) the replication of this phenomenon twice in succession, (3) the psychosis relapse after zolpidem discontinuation, and (4) the absence of other more likely explanations of psychosis resolution (ie, the psychotic syndrome was resistant to antipsychotic and immunosuppressant treatments). Zolpidem is a Z-drug acting preferentially at α1-containing GABA A receptors. Little evidence exists regarding its efficacy as an antipsychotic medication or add-on treatment to antipsychotic drugs. In a single case report, Wong et al[10] have shown that zolpidem augmented the effects of antipsychotic medications in a patient presenting treatment-resistant schizophrenia. Certain limitations that may moderate the plausibility of our hypothesis concerning zolpidem's antipsychotic effect, should be taken into account: (1) no other similar cases have been reported in the literature; (2) the patient received multiple medications, which could be a confounding factor; and (3) the involved underlying biological mechanism is unknown. Further evaluation of the zolpidem effect on psychosis is needed, as well as exploration of its underlying possible mechanism of action.

Through our case report and literature review, it seems that (1) psychosis and mania are rare but severe NP manifestations in SLE; (2) zolpidem and low-dose lorazepam, but not low-dose diazepam, were rapidly effective in the treatment of NRC in our patient; and (3) surprisingly, treatment-resistant SLE-related psychosis completely and rapidly resolved with the use of zolpidem, but not low-dose lorazepam or low-dose diazepam. To our knowledge, this is the first case in the literature in which zolpidem most likely allowed resolution of both NRC and aggressive immunosuppressive and psychopharmacological treatment-resistant SLE-related psychosis. It would be interesting to further try zolpidem to treat SLE-related psychosis even in the absence of NRC.

Oral informed consent for publication of her clinical details was obtained from the patient.

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# Detoxification of a Patient With Comorbid Dependence on Phenibut and Benzodiazepines by Tapering With Baclofen

*Case Report*

***To the Editors:***

Recreational use of phenibut is an emerging public health issue in Western

countries.[1] Phenibut was originally designed as an anxiolytic for astronauts and is currently being used clinically in some countries (eg, Russia, Ukraine, and Latvia) to treat a wide range of psychiatric disorders including anxiety and depression[2] in which generally a therapeutic dosage of 0.25 to 0.5 g 3 times daily is used.[2] In most Western countries, phenibut is not approved for clinical use. Nevertheless, it can be legally purchased online as a dietary supplement.[3,4]

Phenibut (4-amino-3-phenyl-butyric acid) was synthesized as an organic derivative of gamma amino butyric acid (GABA), with an extra phenyl ring attached to its second carbon. It has a half-life of approximately 5 hours and acts as a GABA-mimetic, primarily at GABA-B receptors.[5] Systemic administration of phenibut causes a great variety of effects such as anticonvulsant, nootropic or cognitive enhancing, tranquilizing, and anxiolytic effects.[5,6] The structure and pharmacodynamics of phenibut are similar to baclofen (β-(4-chlorophenyl)-GABA). Regarding the effective doses, those of baclofen are 10 to 12 times lower than those of phenibut.[5] The reported average oral dose for recreational purpose of phenibut is 2.43 g (SD, 1.62 g) with a wide range varying from 500 mg up to 9 g.[1,2,4]

The regular use of phenibut has been associated with the development of dependence, which may occur rapidly, even within several days.[7–9] Reported intoxication symptoms include reduced level of consciousness, lethargy, and agitation.[4,10] Withdrawal symptoms mimic those of alcohol, benzodiazepine, and gamma-hydroxy butyrate (GHB) withdrawal including anxiety,[2,6,7,11,12] sweating,[6] and insomnia[6–8] as well as visual hallucinations,[6,7,9] disorientation,[7] and confusion.[9] There are virtually no data on prevalence of phenibut dependence, and there are currently no guidelines available on detoxification and relapse prevention.

Here, we present a patient with dependence on both phenibut and benzodiazepines, who was successfully detoxified using baclofen. To our knowledge, there is only 1 case report in which phenibut was substituted by baclofen and then gradually tapered off.[2] We provide a detailed course of the medication regime with baclofen and diazepam, withdrawal symptoms and 12-month follow-up together with a literature review and discussion on treatment of phenibut withdrawal.

## CASE REPORTS

A 25-year-old man dependent on both phenibut and benzodiazepines was admitted to our psychiatric unit for detoxification. His psychiatric history included cocaine and GHB dependence, which were successfully treated through detoxification and cognitive behavioral therapy in addiction care. Furthermore, he had a history of attention-deficit hyperactivity disorder with features of oppositional defiant disorder, obsessive-compulsive disorder (OCD), and intellectual disability. He was successfully treated with cognitive behavioral therapy for OCD. He used the GABA analog pregabalin (75 mg 3 times a day) as well as the GABA-A agonist diazepam for persisting symptoms of anxiety. There was no history of physical conditions. His family history included attention-deficit hyperactivity disorder, OCD, and alcohol dependence.

He reported using phenibut 11 to 12 g 3 times a day (with a maximum of 34.5 g per day). He started using phenibut at the age of 23 years, purchased as online supplement, because of insomnia. He gradually increased the dose of phenibut, to maintain the euphoric effects. He reported withdrawal symptoms that appeared 5 to 6 hours after the last use of phenibut. These symptoms included sudden changes in body temperature, depersonalization, locking of the jaw, paranoid delusions, insomnia, and decreased appetite. He also experienced craving, which worsened during times of tension or stress. Attempts to reduce the dose of phenibut were followed by fear and dysphoria. He had not used other substances than phenibut and benzodiazepines (diazepam [20 mg] 4 times daily) over the past year.

On psychiatric examination, no abnormalities were observed, except for the patient being easily distracted and being long-winded, as he had some difficulties maintaining his storyline as well as global impression of intellectual functioning below average. No affective signs or symptoms were described. He did show difficulty regulating his emotions and impulses. Mild psychomotor agitation, and strong gestures and facial expression were observed. Physical examination and blood tests (included general blood count, liver enzymes, kidney, and thyroid function) did not show any alterations. He had a rhythmic heart rate of 87 beats per minute, blood pressure of 117/69 mm Hg, and body temperature of 37. 1°C.

Given the similar structure and similar mechanism of action, we started detoxification of phenibut with the GABA-B agonist baclofen (25 mg) 4 times a day, with baclofen (5 mg) as needed in case of withdrawal symptoms. Withdrawal symptoms were closely monitored using 2 commonly used clinical monitoring scales for objective withdrawal symptoms (OWSs) and subjective withdrawal symptoms (SWSs)[13] 2 times a day (Fig. 1). The OWSs and SWSs measure withdrawal symptoms according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[13] For these scales, no strict cutoff points are available. An increase in withdrawal symptoms can either be followed by reduction of the pace of tapering or additional pharmacotherapy. The first 2 days the patient used 5 mg of baclofen extra per day.

After day 2, an increase in withdrawal symptoms was observed (Fig. 1). The patient reported increased sadness, irritability, insomnia, and psychomotor agitation. He used 10 mg of baclofen on top of the fixed dose of baclofen and received 2.5 to 5 mg of olanzapine as needed at night against insomnia, with good effect. He used baclofen (5 mg) as needed as well as olanzapine (2.5 mg) as needed regularly over the subsequent weeks. Thereafter, diazepam tapering was started with 2.5 mg per day (about −20% per week). Withdrawal symptoms and craving improved over the subsequent weeks with anxiety, tension, and flulike symptoms (headache, myalgia) being the most reported symptoms.

After approximately 4 weeks, the dose of diazepam was kept stable at 2.5 mg 4 times per day, as requested by the patient. Next, baclofen was tapered with 10 mg every 2 days (approximately −50% per week). During this period, we observed a slight increase in craving and withdrawal symptoms, with vivid dreaming, restlessness, and agitation being the most reported (Fig. 1). After about 2 weeks, the dose of baclofen was kept on 5 mg 4 times daily, because of increasing craving for phenibut. Because of persisting anxiety, the dosage of pregabalin was increased to 125 mg 3 times daily, in line with national guidelines. After a subsequent stabilization period of 2 weeks, the patient was discharged without any psychiatric or withdrawal symptoms. He received baclofen (5 mg) 4 times daily, diazepam (2.5 mg) 4 times daily, and pregabalin (125 mg) 3 times daily.

At 6 and 12 months of follow-up, the patient remained abstinent from phenibut and other substances. The dose of baclofen had been increased by the addiction care physician to 40 mg per day, owing to craving for phenibut with good effect on craving. Diazepam had been reduced to 9 mg per day, whereas the dose of pregabalin remained unaltered during outpatient treatment.

## DISCUSSION

To the best of our knowledge, we report the first case of detoxification of a patient with dependence on both phenibut and benzodiazepines. We describe a safe detoxification procedure, using gradual tapering of baclofen over approximately 7 weeks, without severe withdrawal symptoms or other complications. Titration of baclofen was in line with a previous case report using baclofen to counteract phenibut withdrawal.[2] However, where they required about 10 mg of

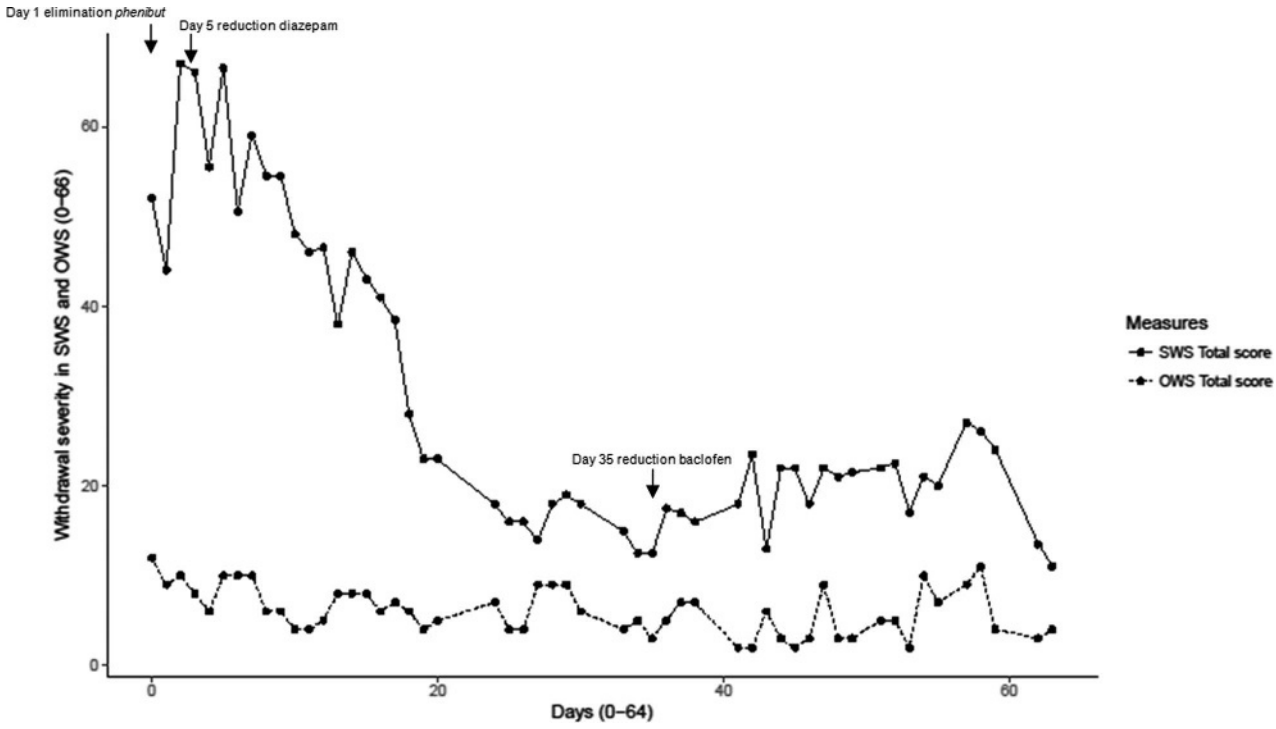


**FIGURE 1.** Withdrawal severity from phenibut, measured in Subjective and Objective Withdrawal Scale (SWS and OWS).

baclofen per gram of phenibut,[2] our case needed only about 3 mg baclofen per gram of phenibut. After stabilization, we performed a successful 2-phase detoxification, starting first with tapering of diazepam (about −20% dosage reduction per week), followed by baclofen (about −50% dose reduction per week). The patient remained abstinent for phenibut, benzodiazepines, and other drugs after 1-year follow-up, treated with baclofen (40 mg) daily and diazepam (9 mg) daily. This suggests that baclofen might be useful for relapse prevention or substitution in case of phenibut dependence.

In this case, several sedative drugs were used simultaneously: phenibut, diazepam, and pregabalin, with different main mechanisms of action (GABA-B, GABA-A, glutamate, respectively). It is possible that phenibut withdrawal was diminished by cross-tolerance with diazepam and pregabalin in combination with the GABA-B agonist baclofen. Such synergistic effect may explain the relatively lower dose of baclofen needed in comparison with a previous case report, despite the relatively high dosage of phenibut our patient reported to use (more than 10 g versus on average 2.4 g in literature).[1] Notably, the purity of commercially available phenibut varies widely (40%–98%),[7] which might also explain variation in withdrawal severity and dosages of baclofen required. Nonetheless, based on our experience we consider well-monitored baclofen tapering as a relatively safe and easy detoxification strategy in case of phenibut dependence.

The clinical cases published until now regarding phenibut misuse mostly report phenibut toxicity,[4,7,10,14,15] except for a couple of cases describing phenibut dependence.[2,6,11] Reported withdrawal symptoms are in line with our observations and include intermittent anxiety, irritability, mood liability, psychomotor agitation, and insomnia, which occur rapidly after the last ingestion of phenibut.[2,7] The addictive properties of phenibut are attributed to its euphoric and anxiolytic effects, primarily mediated by GABA-B receptors. However, activation of GABA-A and dopamine receptors and antagonizing effects of β-phenethylamine, a putative endogenous anxiogenic, have also been described.[5] The GABA-B activity is conferred to the R-enantiomer of phenibut. R-phenibut is known to have a 10- to 15-fold lower affinity for GABA-B receptors than baclofen ($K_d$ 25–90 μM vs 2.5–6 μM).[1]

As in our case, presumed self-medication for anxiety and dysphoria is the most reported reason to start using phenibut.[1–4,16] Although evidence for effectiveness of phenibut for anxiety and depression is limited, several placebo-controlled studies showed some positive effects on affective symptoms, including mood and fatigue (dose of phenibut, 0.25–0.5 g 3 times daily) over a period of 1 to 2 weeks.[5] A major limitation of these studies is that they were conducted in either neurotic or psychotic patients and phenibut was only given for a maximum of 2 weeks.

Based on the present case, the GABA-B agonist baclofen might be considered as a substitute for phenibut, helping to reduce craving and relapse risk. Baclofen has shown similar potential as an anticraving drug in alcohol use disorders[17] and GHB use disorder.[18,19] It can be speculated that baclofen acts as a more long-acting substitute for other short-acting GABA-ergic substances of abuse, including phenibut, GHB, or alcohol.[17–19] It is unclear whether there is cross-tolerance between baclofen, mainly acting at GABA-B, and substances of abuse mainly acting at GABA-A, such as benzodiazepines. Similarly, it remains to be investigated whether other GABA-analogs, such as gabapentin or pregabalin, might also prove useful for the treatment of phenibut dependence.

Finally, epidemiological data on phenibut dependence are currently lacking. Although several case reports[2,6,10] do underscore the addictive potential of phenibut, little is known about its potential threat for public health. Systematic monitoring of phenibut use seems warranted. Because phenibut is a relatively new drug of abuse, information on therapeutic strategies for the treatment of

withdrawal and prevention of relapse is essential.

Taken together, we show that detoxification of phenibut using baclofen in combination with diazepam might be a safe and effective option for patients with combined phenibut and benzodiazepine dependence. Monitoring withdrawal symptoms, especially mood, anxiety, and irritability, is of major importance. Given the pharmacological profile of baclofen, one might speculate that substitution therapy with baclofen could be a safe option for patients failing to maintain abstinence, as we recently showed for GHB-dependent patients.[18,19] Further studies are needed to confirm the potential of baclofen for treating phenibut dependence.

Written informed consent was obtained.

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# Restless Legs Syndrome Related to Vortioxetine
## *A Case Report*

***To the Editors:***

Vortioxetine (1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]-piperazine) is a new antidepressant (AD). In 2013, it was approved by the Food and Drug Administration and the European Medicines Agency to treat major depressive disorders in adults. Vortioxetine shows multimodal mechanisms on different 5-hydroxytryptamine (5-HT) targets.[1–3] Although studies on microdialysis in free-moving rats reveal that vortioxetine increases extracellular 5-HT, noradrenaline (NA), and dopamine (DA) levels in brain regions relevant for depression,[4] recent animal findings have demonstrated that sustained use of vortioxetine induces a significant reduction of DA firing resulting in a suppression of DA and NA neuronal activity similar to that obtained with escitalopram even though less evident.[3]

Restless legs syndrome (RLS) is characterized by discomfort in the limbs associated with an urge to move the limbs and to gain temporary improvement with movement, as well as worsening symptoms at rest and in the evening.[5] Periodic limbs movements of sleep (PLMS) were described in about 70% of patients with RLS.[6] The prevalence of RLS was about 2.1% to 5% of the general population[6]; nevertheless, patients with depressive symptoms, anxiety, and fibromyalgia showed higher rates.[7] These patients were frequently treated with AD medications. Restless legs syndrome was described in 27% of patients with unipolar depression,[8] whereas patients with RLS were often depressed.[7,9] Besides this, sedating AD may impair insomnia symptoms owing to untreated RLS and PLMS.[6] The use of AD has been associated with the onset or worsening of RLS and/or PLMS,[7,10–12] in particular, the use of selective serotonin reuptake inhibitors (SSRIs) medications has been significantly associated to RLS.[7] Therefore, the International Restless Legs Syndrome Study Group recommended