known adverse effects of ginseng.[1] We present a case of menstrual alterations related to ginseng consumption.

Case Report. A 48-year-old woman was admitted to the hospital with a three-week history of metrorrhagia. The patient had never experienced menstrual disorders before. On questioning, she described self-medication with three daily capsules of Pharmaton Complex (dimethylaminoethanol bitartrate; standardized ginseng G115 extract equivalent to 120 mg/d; vitamins A, B_1, B_2, B_6, B_{12}, C, D_3, and E; nicotinamide; calcium pantothenate; rutoside; iron; calcium; phosphorus; sodium fluoride [Fluor]; copper; potassium; manganese; magnesium; zinc) for two months because a companion advised her to take it to improve her work performance. She was not taking any other medication, including over-the-counter products and cosmetics, that might contain hormonal compounds. The physical examination, echography, gynecologic study, sex hormones, complete blood count, coagulation, and biochemical tests were normal. The metrorrhagia disappeared four days after discontinuing Pharmaton Complex administration. The patient experienced no menstrual alteration in the following six months and declined taking the medication again.

Discussion. The causal relation between Pharmaton Complex and metrorrhagia is probable in this case,[2,3] because (1) isolated cases of vaginal bleeding have been reported[4-7] in women taking ginseng (an active component of Pharmaton Complex), apparently as a result of its estrogenic effect; (2) a clear temporal relationship was observed; (3) the bleeding stopped after withdrawing the medication; (4) other alternative causes were discarded, including a possible influence of the other active components associated to ginseng, for which no such reactions have been reported; and (5) the objective evidence of the adverse reaction was that the patient had never experienced menstrual disorders before taking the medication and presented no further such problems in the six months following withdrawal of the drug.

In Spain, ginseng is commercialized in the form of *Panax* ginseng or Korean ginseng, as well as in the form of Siberian ginseng or *Electherococcus senticosus*. In terms of Spanish drug formulation,[8,9] 16 medications presently contain ginseng. The technical specifications provided for most of these products make no mention of menstrual alterations as a potential adverse effect; Pharmaton Complex is no exception to this. Although this adverse effect may be infrequent, the growing consumption of products containing ginseng suggests the need to include this substance as an etiologic factor in menstrual disorders.

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Comment: potential risk of valproic acid therapy in patients who are HIV-positive

TO THE EDITOR: We read with great interest the case report by Hugen et al., entitled Carbamazepine–Indinavir Interaction Causes Antiretroviral Therapy Failure (2000;34:465-70). We commend the authors on their report of a timely topic that is problematic for many neurologists and HIV clinicians; that is, the treatment of neurologic disorders in the HIV-positive patient.[1] We agree with the authors that HIV disease is often associated with multiple neurologic manifestations that occur secondary to disease progression, adverse effects from highly active antiretroviral therapy (HAART), or opportunistic infections, as presented in the case that they describe. Disorders such as seizures, headaches, depression, bipolar disorders, and neuropathies are common in patients who are HIV-positive. As the authors stated, these conditions are frequently refractory to traditional therapy, yet responsive to treatment with antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, and phenobarbital. Unfortunately, however, these drugs are inducers of the cytochrome P450 (CYP-450) enzyme system and, therefore, have the potential to compromise HAART therapy, as occurred in this case.

Additionally, we agree with the authors' call for additional studies evaluating these potentially therapy-compromising drug–drug interactions, as well as their recommendations of using alternative agents until the safety of combining these AEDs with HAART can be established. However, we do question the authors' recommendation of using valproic acid (VPA) as an alternative anticonvulsant agent in these patients.[1,2] It has been demonstrated in small in vitro studies[1-6] that replication of HIV was stimulated in the presence of VPA. This phenomenon may occur secondary to VPA-mediated decreases in red blood cell glutathione reductase. As intercellular concentrations of reduced glutathione drop, T-cell activation is affected, and HIV replication subsequently increases.[3,4] Alternatively, it has also been demonstrated[5,6] that VPA plays a direct role in HIV transcription and expression, an effect that seems to be independent of its ability to alter glutathione synthesis. These effects are, interestingly, not unique to HIV, as valproate has also been demonstrated[7] to stimulate cytomegalovirus (CMV) replication. The mechanism of its effect on CMV replication is unclear; however, VPA is a short-chain fatty acid that does not affect the CMV promoter and may be analogous to sodium butyrate in its potentiation of CMV replication.[6,8,9]

We concede that no immediate clinical correlation has been established with these in vitro studies. However, the potential ramifications of VPA-induced viral replication may be analogous to the results observed with nonadherent or subtherapeutic HAART therapy. Given even the theoretical risk of this phenomenon, we are reluctant to recommend the use of VPA in any HIV-infected individual. Additionally, we believe that this interaction deserves attention equal to that given to possible therapy-compromising CYP450 drug–drug interactions, as both may contribute to the emergence of viral resistance and HAART failure. Further research may also be necessary to evaluate the safety and efficacy of other AEDs, such as lamotrigine and gabapentin.

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.

We recommend that clinicians carefully consider the risk versus benefit of any new therapy to be added to or removed from the patient medication regimens for HIV-positive patients. Careful monitoring of pharmacodynamic and, possibly, pharmacokinetic end points is appropriate to evaluate the efficacy and toxicity of therapy. At this time, we encourage clinicians to consider all aspects of the patient's health, including current virologic suppression and immune response, concurrent medications and diseases, and quality of life when considering medication regimen changes.

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AUTHORS' REPLY: We are aware of the concern raised by Jennings and Romanelli regarding valproic acid in the treatment of neurologic disorders in HIV-infected patients.[1] We agree with them that recommendations for alternative therapies for CYP450–inducing antiepileptic drugs, such as phenytoin, phenobarbital, and carbamazepine, must be made with care.

However, at this time we do not think that the information is conclusive enough to withdraw our recommendation to use valproic acid as an alternative antiepileptic drug for HIV-positive patients treated with protease inhibitors. As Jennings and Romanelli stated, it is difficult to extrapolate in vitro data to the in vivo situation, and the data from the three studies described[2-4] are, in part, contradictory. Therefore, the clinical implications of increased viral replication by valproic acid as seen in the in vitro studies are very uncertain. Even if replication is stimulated in vivo, it is highly questionable whether combination antiretroviral therapy is unable to suppress that replication. So far, we do not have indications that the use of valproic acid in HIV-infected patients causes unwanted viral load increases, although no formal studies have been performed.

Induction of CYP450 is a far more thoroughly established problem, and lowered plasma concentrations of protease inhibitors are a serious risk factor for decreased levels of antiretroviral therapy. Therefore, we do not recommend combining these groups of drugs; thus, looking for alternatives is of great importance. We agree with Jennings and Romanelli that the risks and benefits of changes in medication regimens in HIV-infected patients must be carefully weighed but, in our opinion, the risk of viral replication induced by valproic acid is lower than the risks of using CYP450-inducing agents. Nevertheless, further in vivo research on this topic is needed.

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