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## **Abstract**

This report presents the case of a 78-year-old man residing in a nursing home who presented with a 2-month history of increasing lethargy and confusion. These symptoms coincided with the initiation of sertraline in the patient. Among other medications, he was also taking phenytoin. The medical team concluded that the cause of the patient's lethargy and confusion was a drug interaction between sertraline and phenytoin. Phenytoin was held, while the sertraline was slowly tapered to discontinuation. The patient's symptoms resolved soon thereafter. Future research is needed to better guide clinicians in appropriate selection, dosing, and monitoring of selective serotonin reuptake inhibitors with concomitant phenytoin use.

Key words: phenytoin, sertraline, SSRIs, drug interaction

## **Disciplines**

Pharmacy and Pharmaceutical Sciences

## **Comments**

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# Sertraline and Phenytoin Drug Interaction in a Geriatric Patient

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**Abstract:** This report presents the case of a 78-year-old man residing in a nursing home who presented with a 2-month history of increasing lethargy and confusion. These symptoms coincided with the initiation of sertraline in the patient. Among other medications, he was also taking phenytoin. The medical team concluded that the cause of the patient's lethargy and confusion was a drug interaction between sertraline and phenytoin. Phenytoin was held, while the sertraline was slowly tapered to discontinuation. The patient's symptoms resolved soon thereafter. Future research is needed to better guide clinicians in appropriate selection, dosing, and monitoring of selective serotonin reuptake inhibitors with concomitant phenytoin use.

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Depression affects approximately 16% of patients who are older than 65 years of age.<sup>1</sup> Various nonpharmacologic and pharmacologic treatment options are available for the treatment of depression. Notably, second-generation antidepressants, which include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, and other agents, have been the standard treatment option for depression given their efficacy, tolerability, and safety profile.<sup>2</sup>

However, clinically significant drug-drug interactions between SSRIs and other pharmaceutical agents have been well documented. All SSRIs are hepatically metabolized via the cytochrome P450 (CYP) enzyme pathway and have inhibitory effects on these enzymes. When these agents are taken concurrently with other agents that are substrates of CYP isoenzymes, significant drug interactions can occur.<sup>2-4</sup> This case report outlines a potential clinically significant drug interaction in a nursing home (NH) resident who was receiving sertraline, an inhibitor of the isoenzymes CYP2C19, CYP2C9, and CYP2D6,<sup>5-7</sup> at the same time as phenytoin, a substrate of the isoenzyme CYP2C9.

## Case Report

The case is a 78-year-old man who was residing in a NH, was deaf, and weighed 179.9 lb. Pertinent medical history was notable for osteoporosis, hypertension, coronary artery disease, depression, frequent falls, mild vascular dementia, hypothyroidism, hidradenitis suppurativa, and remote his-

tory of seizures (he had had no seizures for more than 40 years). He had no history of alcohol or substance use. His was taking levothyroxine, ergocalciferol, docusate sodium, atorvastatin, doxycycline (hidradenitis suppurativa), aspirin, and phenytoin, all of which had been at stable dosing. The phenytoin dose, at 100 mg by mouth 4 times daily, had been unchanged for the past 5 years. He had no allergies to medications.

In January 2016, he had reported increased depression symptoms to NH staff, specifically to the nursing assistants and to the medical provider treating him. At that time, his medication was changed from citalopram 20 mg by mouth daily to sertraline 100 mg by mouth daily.

In March 2016, he reported symptoms of lethargy and confusion of unclear etiology since January to NH staff. Also at this time, his friends reported to NH staff that he was increasingly withdrawn, not engaging in conversation, lethargic, and delayed in responses. Examination was notable for slow responses to questions and commands. The patient had no nystagmus or tremors upon exam. Laboratory values showed stable renal function with creatinine of 0.5 mg/dL, albumin level of 3.1 g/dL, normal liver function tests, and normal thyroid function tests. During the course of his confusion, he was treated for urinary tract infections without improvement in his cognitive function.

Psychiatry service was consulted and recommended tapering sertraline with intent to discontinue this medication. Free phenytoin level was measured to be 4.9 µg/mL at initiation of sertraline taper. Archived health record data from 2015 was consulted for previous phenytoin levels and showed that the patient’s free and total phenytoin levels were not elevated prior to sertraline initiation (0.5 µg/mL and 3.8 µg/mL, respectively) (Table 1). Phenytoin was discontinued, and levels decreased back to his previous normal values. After tapering, sertraline was also discontinued.

Neurology was consulted and recommended monitoring for seizure recurrence before introducing another antiepileptic medication. His cognitive status returned to his baseline 2 months prior.

**Discussion**

In this case, the medical team concluded that the cause of the patient’s lethargy and confusion was a drug interaction between sertraline and phenytoin. The patient’s symptoms resolved soon after phenytoin was held and sertraline was slowly tapered to discontinuation.

Sertraline selectively and potently inhibits neuronal serotonin reuptake while having no effect on adrenergic, cholinergic, γ-aminobutyric acid, dopaminergic, histaminergic, or benzodiazepine receptors.<sup>8</sup> The agent is primarily metabolized via N-demethylation to N-desmethylsertraline, a less active metabolite. Multiple CYP isoenzymes participate in the demethylation pathway, including CYP2C9, CYP2C19, CYP2D6, and CYP3A4.<sup>3,5,9</sup> Some studies suggest that sertraline displays fewer clinically significant drug interactions compared to its other counterparts in the SSRI family.<sup>10</sup> However, it is notable that interpatient variability in the activity of CYP isoenzymes does exist and may account for overt drug interactions in some patients, necessitating the need for dose adjustment or cessation of the agent.

Phenytoin’s mechanism of action seems to be centered on the motor cortex, and it is postulated that the spread of seizure activity is inhibited at this location.<sup>11</sup> As with all antiepileptic agents, there is wide interpatient variability with regard to optimum phenytoin dosing requirements, and treatment must be individualized. Sustained low plasma levels may suggest nonadherence to medication therapy or hypermetabolization of phenytoin. Sustained high plasma levels may indicate genetic polymorphism pertaining to CYP2C9 and CYP2C19 alleles, or drug-drug interactions.

**Table 1. Trend in Phenytoin Laboratory Values**

	10/7/15	11/9/15 <sup>a</sup>	3/4/16 <sup>b</sup>	3/5/16 <sup>c</sup>	3/6/16 <sup>d</sup>	3/7/16	3/9/16	3/14/16 <sup>e</sup>
<b>Total phenytoin (µg/mL)</b>	3.8	Not ordered	Not ordered	32.7	25.5	19.9	11.7	< 1.5
<b>Free phenytoin (µg/mL)</b>	0.5	0.8	4.9	4.2	3.8	Not ordered	1.6	Not ordered

<sup>a</sup>Patient’s baseline free phenytoin levels before start of sertraline usually < 1.0 µg/mL, based on 2015 health record data.

<sup>b</sup>Sertraline 100 mg daily was initiated in January 4, 2016, then tapered beginning March 1, 2016.

<sup>c</sup>Phenytoin held, stat levels ordered.

<sup>d</sup>Somnolence and lethargy resolving.

<sup>e</sup>Medical team to assess if phenytoin still needed; lorazepam for rescue ordered.

Phenytoin is also highly protein bound (90%-95%), and this pharmacokinetic parameter is of paramount importance when planning and administering a medically appropriate pharmaceutical care plan for geriatric patients, many of whom are frail, lack body mass, or have hypoalbuminemia due to comorbidities and/or general clinical status. Notably, clearance of phenytoin decreases with increasing age. Patients older than 70 years of age have 20% less drug clearance compared with patients 20 to 30 years of age.<sup>11</sup> In such patients, it would be prudent to obtain free phenytoin levels, since total phenytoin levels may not reflect accurately on the clinical status of the patient.

Since phenytoin is a substrate of CYP2C9 and CYP2C19, its metabolism may be inhibited by sertraline when both agents are used concurrently.<sup>10,12</sup> Haselberger and colleagues discuss two case reports in which they observed elevated phenytoin levels in patients who were administered sertraline and phenytoin.<sup>13</sup> In both cases, phenytoin plasma concentrations decreased when sertraline was discontinued, and the patients were discharged with no further complications. In our case report, the patient showed a similar reduction in phenytoin plasma concentration when sertraline was removed from his regimen. Although he did not exhibit signs of phenytoin toxicity, there was concern for a clinically significant drug interaction through observation of his increasing lethargy and delay in processing response.

Notably, phenytoin's nonlinear pharmacokinetics and narrow therapeutic index added another layer of salience to the medical team's assessment of his clinical status. To further add relevance to the possibility that our patient's somnolence and delayed responses was secondary to the initiation of sertraline, the Drug Interaction Probability Scale (DIPS) was used.<sup>14</sup> The DIPS assesses the probability of a causal relationship between a potential drug interaction and an adverse event. The score for our patient was a "6," suggesting that the likelihood of the drug interaction was probable between the two drugs. Additionally, it is worth noting that the patient's mood and psychomotor slowing improved with discontinuation of his antidepressant. This indicates that his symptoms were related to phenytoin levels rather than depression symptoms.

It is recommended that providers pay particular attention to the possibility of clinically relevant drug interactions, especially when prescribing SSRIs in combination with other agents that are metabolized by the CYP2C subfamily of isoenzymes. Of note, initial and periodic monitoring of phenytoin plasma levels is warranted, combined with appropriate clinical

and neurological assessment for phenytoin toxicity.

This case also highlights the need to review indications for antiepileptic medications in older adults. If a patient has been seizure free for years, coordinating dose reduction or discontinuation of an antiepileptic with the neurology team may help reduce unnecessary side effects and polypharmacy in older adults.

### Conclusion

This case report suggests that a clinically significant drug interaction may exist between phenytoin and sertraline in some patients, especially if they are at risk for such events due to poor clinical status or a genetic predisposition. Hence, providers are encouraged to observe their patients for neurological and clinical changes. Phenytoin plasma levels should be closely monitored at initiation of SSRIs and periodically during treatment. Apart from a few documented case studies, there is a paucity of data elucidating this clinically significant drug interaction. Future research is warranted to investigate the relationship between specific doses of each agent and the onset of symptoms in a more diverse patient sampling. Clinicians will then be able to apply this knowledge to aid them in the proper selection and dosing of SSRIs while monitoring for drug interactions and signs of toxicity. ♦

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