

# Letter to the Editor

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## Interaction of duloxetine with warfarin; a cautionary report

Dear Editor,

Drug-drug interactions are common in older adults. Four out of five people aged over 75 years take at least one medicine and thirty-six percent of this age group take four medicines or more.<sup>1</sup>

Warfarin is primarily cleared by the liver through the cytochrome P450 system. Many of the isoenzymes involved are also involved in the metabolism of psychotropic agents.<sup>2</sup> Drug interactions with Warfarin are generally well described. Data regarding the interaction of warfarin with duloxetine are limited. There are only two case reports in the literature which report conflicting findings.<sup>3,4</sup> Additionally, a small open-label study reported no significant interaction between the two agents.<sup>5</sup>

Warfarin is normally indicated for serious vascular conditions. So an elderly patient who is attending the psychiatric service and is on warfarin will have higher risk for serious interactions. This is exactly the subject of this case report.

### Case Report

An eighty seven year old gentleman was admitted for treatment of a severe depressive episode with prominent anxiety symptoms. Relevant medical co-morbidities included paroxysmal atrial fibrillation, for which he was on lifelong warfarin prophylaxis. Notably, his warfarin dose had been stable for several months prior to admission. He presented with a treatment resistant depression and failed to respond to trials of antidepressant medications (including venlafaxine, bupropion, SSRI's, mirtazapine and agomelatine) and to augmentation with several different agents (including risperidone, lithium, olanzapine, amisulpride and aripiprazole). He refused the option of ECT. A trial of duloxetine was moderately successful. The dose was increased cautiously to 90 mg with good effect. At this point it was noted that his INR had increased significantly. This was temporally related to an increase in duloxetine from 60 to 90 mg daily. There had been no other significant changes in his management or his medical condition that would explain the increased INR. Review of his INR readings and comparison with his duloxetine treatment revealed a stepwise increase in INR which coincided with the increase in duloxetine.

As this patient's treatment resistant depression had responded to duloxetine, a decision was made to continue duloxetine treatment at this higher dose. This necessitated a forty percent dose reduction in warfarin to stabilise the INR at a safe therapeutic level.

In light of the temporal relationship between the increase in duloxetine and the rise of INR, the most likely explanation lies at the cytochrome P450 level. It is likely that duloxetine may potentiate the anticoagulant effect of warfarin through displacing warfarin from CYP 1A2 isoenzymes.<sup>6</sup> This would result in a net increase in bioactive warfarin and a consequent increase in INR.

### Discussion

A higher number of people enter old age nowadays thanks for recent advances in health measures.<sup>7</sup> Therefore, more people over the age of 65 are expected to be on combination of warfarin plus another one or more medications, especially psychiatric medications. This report adds to the scarce evidence that currently exists for possibility of drug-drug interactions between duloxetine and warfarin. It is the first report, we know of, to describe a potentiating effect for duloxetine upon the action of warfarin in older adults. It stresses the need to closely monitor INR levels for elderly patients on warfarin, especially if it is combined with duloxetine for treatment of depressive illness or other psychiatric or non-psychiatric disorder. It appears that duloxetine can synergistically potentiate the effect of warfarin, thereby, leading to a bleeding hazard. Further research is urgently needed in this area.

### References

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