Grapefruit–medication interactions

We are very concerned that statements made in a review article that appeared in *CMAJ*[1] do not correctly reflect the current state of medical and scientific understanding of the topic of grapefruit–medication interactions.

We know of no validated evidence that coadministration of grapefruit juice with a drug has caused a dangerous interaction, resulting in serious adverse effects or actual harm to a patient's health. We point readers to 2 extensive review articles on grapefruit juice–drug interactions that have appeared in peer-reviewed medical literature.[2,3] These articles provide a review of primary research literature, a compilation of the extent of interactions with specific drugs, and an evaluation of their clinical importance; however, neither of these publications is cited in the *CMAJ* article.

We emphasize that Table 1 of the *CMAJ* review[1] shows theoretically predicted risks of grapefruit juice–drug interactions, as opposed to actual documented interactions. We are concerned that this generalized information may lead *CMAJ* readers to conclude incorrectly that grapefruit juice coadministration should be avoided for many more drugs than is supported by the scientific data. As a specific example, the interaction of grapefruit juice with atorvastatin is listed as high risk, with a dose-related adverse event of rhabdomyolysis. The authors go on to cite elsewhere in the article a published clinical study of addition of grapefruit juice co-treatment to patients taking atorvastatin for hyperlipidemia.[4] The study results show a trivially small interaction of grapefruit juice with atorvastatin, with no evidence of adverse effects, let alone rhabdomyolysis. Other examples of incorrect information in Table 1 of the review include the purported interactions of grapefruit juice with quinine, quinidine, erythromycin, dextromethorphan, oxycodone, tolvaptan, nilotinib, and sunitinib, all of which are negligible and/or clinically unimportant in magnitude.

Table 2 of the *CMAJ* review presents case reports of adverse events supposedly related to grapefruit juice–drug interactions. In connection with the MedWatch system for spontaneous reporting of medication-related adverse events, the United States Food and Drug Administration is explicit in emphasizing the limitations of such reports.[5,6] Unvalidated anecdotal reports do not establish cause and effect, and cannot be used to determine absolute or relative incidences of specific events. Adverse event case reports are to be used as "signals" to define whether further controlled scientific research is required to address a specific hypothesis.[5–7] Looking again at the example of atorvastatin, the actual controlled study with chronic concomitant use of grapefruit juice and atorvastatin showed that there was no clinically significant interaction.[4] In patients on extended stable atorvastatin treatment, addition of daily grapefruit juice in typical quantities slightly elevates serum atorvastatin concentrations, but has no meaningful effect on the serum lipid profile, and causes no detectable adverse liver or muscle effects. Modification of atorvastatin dosage when moderate amounts of grapefruit juice are co-ingested does not appear to be necessary.

We agree that grapefruit juice may produce clinically significant interactions with a few drugs. These include: simvastatin, buspirone, felodipine, and possibly cyclosporine. However, the number of affected drugs does not approach 85. We encourage readers to visit www.DrugInteractionCenter.org, which provides a listing of drugs that are known to interact with grapefruit juice, the magnitude and clinical importance of the interaction, and citation of primary scientific documentation.

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Competing interests: David Greenblatt and Hartmut Derendorf are clinical research advisors to the Florida Department of Citrus, Bartow, Fla.

References

1. Bailey DG, Dresser G, Arnold JMO. Grapefruit–medication interactions: Forbidden fruit or avoidable consequences? *CMAJ* 2013;185-309-16.
2. Mertens-Talcott SU, Zadezensky I, De Castro WV, et al. Grapefruit–drug interactions: can interactions with drugs be avoided? *J Clin Pharmacol* 2006;46:1390-416.
3. Hanley MJ, Cancalon P, Widmer WW, et al. The effect of grapefruit juice on drug disposition. *Expert Opin Drug Metab Toxicol* 2011;7:267-86.
4. Reddy P, Ellington D, Zhu Y, et al. Serum concentrations and clinical effects of atorvastatin in patients taking grapefruit juice daily. *Br J Clin Pharmacol* 2011;72:434-41.
5. Goldman SA. Limitations and strengths of spontaneous reports data. *Clin Ther* 1998;20 (Suppl C): C40-4.
6. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *J Gen Intern Med* 2003;18:57-60.
7. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. *Br Med J (Clin Res Ed)* 1982;284:249-52.

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The authors respond

Greenblatt and Derendorf[1] have previously acknowledged their conflict of interest as clinical research advisors to the Florida Department of Citrus. That there is "no validated evidence" of "serious adverse effects" of an interaction of grapefruit with any affected medications is their opinion. We have documented published reports in the medical literature that are noted in our recent article.[2]

That a serious adverse event has not been reported should not be interpreted to mean that it has not happened. To recognize an adverse event, there first must be an awareness of the possibility of such an adverse event. Otherwise, the likelihood that it will be investigated is extremely low. This is mentioned in our article[2] and is one of the major reasons why we were compelled to identify and inform the profession and public about this interaction.

Our article[2] focuses on the number of new drugs now on the market that have the potential for serious toxicity if administered with grapefruit. The relevance of this aspect is highlighted by a recent publication showing that nearly one-quarter of the new drugs approved in Canada will eventually get a serious safety warning or have to be pulled