

Potential for drug interactions in seniors with osteoarthritis

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ABSTRACT

OBJECTIVE To document the potential for drug interactions in seniors with osteoarthritis and to consider the usefulness of computerized support for detecting clinically important interactions.

DESIGN Self-administered mailed survey. One question requested a list of all medications (prescribed drugs and self-care products, including herbal and "natural" health products) taken in the last 7 days. Interactions among all medications were assessed using an on-line software package.

SETTING Three urban primary care practices in Nova Scotia.

PARTICIPANTS Questionnaires were sent to 244 patients aged 65 years and older with physician-confirmed osteoarthritis.

MAIN OUTCOME MEASURES Number of potential interactions and level of clinical significance associated with each.

RESULTS Response rate was 78% (n = 191); 174 respondents (92%) supplied information on medications. Respondents took an average of 4.7 products of which 2.8 were prescription medications and 1.9 were self-care products. A total of 214 potential interactions were identified; 30 (14%) of these were clinically significant. Most interactions involved nonprescription products, most frequently acetylsalicylic acid. Recommendations in 29 of these 30 clinically significant interactions were cautionary, advising such measures as closer monitoring of blood tests, observation for toxic effects, or making patients aware of side effects. Only 1 interaction prompted a recommendation for avoidance. Respondents reported use of 7 different herbal and natural health products; these products were associated with 5 clinically insignificant interactions.

CONCLUSION Risk of drug interactions in seniors might be high, but few interactions are clinically significant. Only 1 found in our study carried a recommendation for avoidance. The on-line program reported all significant interactions, but the high proportion of insignificant interactions (6:1) also reported could lead physicians to override computer-generated alerts.

EDITOR'S KEY POINTS

- This study documents the potential for drug interactions in seniors and assesses the usefulness of a computerized program for detecting clinically important interactions.
- Patients took an average of 4.7 products concurrently: 2.8 prescription medications and 1.9 self-care products.
- There were a large number of potential interactions, but only a small proportion (14%) were clinically significant. Almost all recommendations were cautionary rather than suggesting the combinations be avoided completely.
- The research highlighted the fact that physicians perceived interaction alerts as frequently irrelevant and became used to overriding them.

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Establishment of the Canadian Patient Safety Institute followed by release of the Canadian Adverse Events Study drew well-deserved attention to the issue of patient safety in Canada.¹ With respect to drug safety, two major concerns are adverse reactions and adverse interactions.² Risk of either of these is correlated with the number of diseases patients suffer from and the number of medications they are taking concurrently.³ Consequently, drug interactions have become an increasing problem for seniors.⁴

Pharmacists now use software programs that electronically screen for drug interactions. The effectiveness of these programs is limited because the software can check only for interactions among drugs (mostly prescription drugs) patients obtain from a particular pharmacy. Pharmacists are alerted to all potential drug interactions, regardless of significance, which results in a tendency to ignore or override the constant alerts.⁵ Electronic screening for drug interactions is one of the components being incorporated into electronic medical records. The clinical relevance of alerts generated by these systems has been identified as an issue,⁶ as has the propensity for physicians to ignore or override them.⁷ In fact, a recent Canadian study evaluating the effectiveness of a computerized decision-making support system limited the system's interaction alerts to those that were agreed upon as clinically important.⁸

In 2002, we conducted a survey of community-living seniors with osteoarthritis (OA) regarding how they managed their treatment of OA.⁹ As part of that survey, we asked participants to list all medications and supplements they were taking for any reason. The purpose of this article is to document the potential for drug interactions among the seniors in our study and to consider the usefulness of computerized support for detecting clinically important interactions. This is the first known study on this topic in Canadian primary care.

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METHODS

Clinical staff initially sought subjects for the survey from electronic billing records where patients had on record at least one of the following International Classification of Diseases (ICD) diagnostic codes between 1999 and 2001: OA (ICD-9 715, 721), joint pain or stiffness (ICD-9 719.5, 719.5), or other types of arthritis and diffuse connective tissue disorders (ICD-9 710-713, 719.2, 719.3, 725). Diagnosis of OA was confirmed by each subject's family physician. These family physicians were asked to exclude patients they believed were too mentally, physically, or emotionally disabled to participate. In total, 244 seniors (65 years or older) were asked to complete the self-administered mailed survey. We used a modified Dillman method to obtain responses.

The "Living with Arthritis" survey used in this study was developed specifically to gather information on medications patients were using to manage OA and was created by the investigative team and others versed in pharmacy and survey design. Face and content validity were assessed by experienced physicians and pharmacists. The survey was pilot-tested in a volunteer sample of seniors. For this article, we focus on the question that asked respondents to list all medications they had taken in the last 7 days. The question explicitly asked respondents to report over-the-counter medicines, including supplements (such as vitamins, natural or herbal products, or painkillers), which we refer to as "self-care products," along with medicines prescribed by their doctors. They were asked to refer to labels on pill containers to ensure correct information on the product name, strength, and daily dose was given. Full details of the survey method have been published by Lawson et al,⁹ and a copy of the survey is available from the authors on request.

For each respondent, all prescribed medications and self-care products listed were entered into the interaction search software, eFacts from **drugfacts.com**.¹⁰ We elected to use this on-line subscription service in lieu of a CD-ROM version to ensure that we accessed an up-to-date resource. Identified interactions were tabulated by level of clinical significance on a scale of 1 to 5.¹⁰ We considered levels 1 (potentially severe or life threatening) and 2 (might cause deterioration in a patient's clinical status) to be of clinical significance and important to physicians and pharmacists at the point of care. The other levels were either "minor," based on "very limited" data, or lacking "good evidence."

Seventy-one of the self-care products mentioned by seniors were not found in the database. We elected not to investigate Aspercreme, "protein," "minerals," or vitamin B of unspecified type. The remaining 67 products were sought in one of seven on-line or print sources and compared manually.¹¹⁻¹⁸ Based on the information

provided by the source, a pharmacist (D.F.) judged it best to categorize any interaction she found by the levels of significance described by **Drugfacts.com**.¹⁰ Interactions were counted and summarized by significance level and clinically significant combinations.

The study was approved by the Research Ethics Board of the Capital District Health Authority in Halifax, NS.

RESULTS

Of 244 patients with a physician-confirmed diagnosis of OA who were mailed the survey, 191 (78%) responded. Average age was 76.5 years (range 65 to 97 years), 66.7% were women, and 94% reported having some form of drug insurance. Details on products taken were provided by 174 respondents (91.6%) who took an average of 4.7 (standard deviation (SD) 3.2, range 0 to 15) drugs, of which 2.8 were prescription drugs (SD 2.5, range 0 to 10) and 1.9 were self-care products (SD 1.9, range 0 to 10).

Table 1 shows the number of potential interactions by significance level for prescription-prescription, self-care-prescription, and self-care-self-care combinations. Thirty interactions (14%) were level 1 or 2, indicating potential clinical significance. Most interactions (187, 87.4%) were discovered by the eFacts program, including all 30 of the clinically significant ones.

The specific drug (or therapeutic group) and self-care product combinations involved in the 30 clinically significant interactions (level 1 and 2) are listed in **Table 2**. Eighteen interactions (60%) involved self-care products, most frequently ASA and angiotensin-converting enzyme inhibitor (ACEI) combinations. Because the hypotensive and vasodilator effects of ACEIs can be reduced by ASA, eFacts¹⁰ recommends monitoring blood pressure and hemodynamic parameters. The action recommended in almost all interactions (29/30) was cautionary, such as closer monitoring of blood tests, observation for toxic effects, or advising patients to be aware of side effects. For example, taking warfarin and vitamin E together required “close observation for signs of excessive hypoprothrombinemic response” although that was unlikely to occur at the 400-IU daily dose our respondent was taking. One patient reported taking acetaminophen in combination with warfarin, which might increase the

Table 2. Number of clinically significant combinations: Self-care products were over-the-counter medicines and included supplements, such as vitamins, “natural” or herbal products, and painkillers.

SELF-CARE PRODUCT WITH PRESCRIPTION MEDICATION	
ASA with ACEI	11
ASA with glyburide	3
ASA with prednisone	1
Acetaminophen with warfarin	1
Vitamin E with warfarin	1
Calcium carbonate with verapamil	1
TOTAL	18
PRESCRIPTION MEDICATION WITH PRESCRIPTION MEDICATION	
Conjugated estrogen with levothyroxine	3
Conjugated estrogen with prednisone	2
Glyburide with hydrochlorothiazide	2
Diltiazem with atorvastatin	1
ACEI with indomethacin	1
ACEI with triamterene	1
Furosemide with hydrochlorothiazide	1
Metoprolol with prazosin	1
TOTAL	12

ACEI—angiotensin-converting enzyme inhibitor, ASA—acetylsalicylic acid.

latter’s antithrombotic effect. Only one recommendation suggested avoidance, because the combination of diltiazem and atorvastatin leads to risk of increased statin toxicity.

Seven herbal and natural health products had been taken by our respondents in the previous week: glucosamine by 21, garlic by six, methylsulfonylmethane by four, *Ginkgo biloba* by two, and St John’s wort, chondroitin, and echinacea by one each. The eFacts interaction software included *Ginkgo biloba* and St John’s wort and reported only one level-4 interaction (based on limited data) between ASA and *Ginkgo biloba* with a recommendation “to avoid concurrent use of aspirin and *Ginkgo biloba* because of the potential for serious bleeding complications.”¹⁰ Four interactions found through a manual search of the *Pharmacist’s Letter*¹³ (for glucosamine, echinacea, and garlic) were all clinically insignificant.

Table 1. Number of interactions by level of clinical significance

INTERACTION	LEVEL 1 N (% OF TOTAL)	LEVEL 2 N (% OF TOTAL)	LEVEL 3 N (% OF TOTAL)	LEVEL 4 N (% OF TOTAL)	LEVEL 5 N (% OF TOTAL)	TOTAL
Drug-drug	1 (0.5)	11 (5.1)	8 (3.7)	25 (11.7)	30 (14.0)	75 (35.0)
Drug-SC	1 (0.5)	17 (7.9)	7 (3.3)	39 (18.2)	60 (28.0)	124 (57.9)
SC-SC	0	0	1 (0.5)	3 (1.4)	11 (5.1)	15 (7.0)
Total	2 (0.9)	28 (13.1)	16 (7.5)	67 (31.3)	101 (47.2)	214 (100)

Drug—prescription medication, SC—self-care product (over-the-counter medicines, including supplements such as vitamins, “natural” or herbal products, and painkillers).

DISCUSSION

There were a large number of potential interactions, 214 in 190 respondents, but only a small proportion of these (14%) were clinically significant. Equally important, almost all recommendations

for action were cautionary rather than suggesting that the combinations be avoided completely. The largest number of potential interactions was between ACEIs and anti-inflammatory medications (11 with ASA and one with indomethacin). Physicians who care for patients taking ACEIs need to be aware that they might need to increase doses if patients begin taking commonly used anti-inflammatory medications. The authors suggest that many patients taking ASA are doing so at a physicians' request for ischemic heart disease. More troublesome is the potential for an enhanced anti-thrombotic effect of warfarin if a patient starts taking either acetaminophen, a very commonly used nonprescription medication, or large doses of vitamin E.

Physicians and pharmacists both need to be alert to the fact that most clinically significant interactions involved self-care products. Health professionals could be unaware of the risk of harm if they do not regularly ask patients about other products they are taking. Patients might not realize that they should mention vitamins (considered safe at recommended daily doses) when they tell their physicians or pharmacists what medications they are taking.

Our respondents were taking more herbal and natural health products than had been reported in previous articles based on Canadian data,¹⁹ but comparable amounts to those reported in an American study.²⁰ The very few, all clinically insignificant, potential interactions found might be owing to the paucity of reliable data in the literature. Brazier and Levine have documented thoroughly how little solid evidence there is for clinically significant drug-herb interactions.²¹

The on-line search program yielded a high proportion (87.4%) of all interactions ultimately found, including all the clinically significant interactions. Six clinically insignificant interactions were identified for every significant one (184:30). Our data suggest that the risk outlined by Magnus et al⁷ is real: "...the perception that interaction alerts were frequently irrelevant so that GPs had become used to overriding them." Interaction program developers and clinician users should collaborate to ensure that computerized support for prescribing decisions clearly flags the clinically important "must see" potential interactions so they do not get ignored during patient visits.

One serious limitation to any system for identifying potential interactions is double-doctoring and patients' use of many different pharmacies to fill their prescriptions. We did not ask patients whether their medications were prescribed by more than one physician or whether they were receiving medications from more than one pharmacy. Tamblyn et al showed that the most important risk factor for potentially inappropriate drug combinations was patients having more than one prescribing physician and that using a single dispensing pharmacy could lower this risk.²²

Limitations

Our results have several limitations. We asked seniors to list products taken in just the 7 days before they completed the form. We acknowledge there might be seasonal variation in use of herbal and natural health products and that the timing of our survey in warm weather might have given us a biased view. Knowledge about potential interactions is increasing slowly, and a search of eFacts at the time of writing found interactions for glucosamine, garlic, and chondroitin in "Herbal Interaction Facts," although not in "Drug Interaction Facts."¹⁰ We recognize that self-report surveys, such as ours, are vulnerable to underreporting or over-reporting, and we have no means of confirming the accuracy of our data. Finally, our earlier paper listed several limitations that apply to these data as well: our sample was taken from urban practices, our respondents might have been heavier users of medication than patients who were not caught by our recruitment method, and we of course have no data from seniors with OA who did not report the OA to their physicians.⁹

Conclusion

Seniors who take an average of five prescription medications or self-care products (2.8 medications plus 1.9 self-care products) concurrently are at low risk of clinically significant interactions. Most potential interactions require caution, not absolute avoidance, but physicians and pharmacists need to be particularly alert to the possibility that self-care products could interact with prescribed medications or other self-care products. Computerized support systems offer great potential for identifying clinically important interactions at the point of care for physicians and pharmacists, but care must be taken to highlight or flag them to separate them from the much larger number of insignificant interactions. Herbal and natural health products must be included in these computerized systems as reliable data become available. 

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Contributors

Dr Putnam, Ms Lawson, Ms Frail, and Ms Bower contributed to concept and design of the study, analysis and interpretation of data, drafting the article, revising the manuscript for important intellectual content, and approving the final version of the article submitted. **Drs Archibald, Conter, and MacKillop** contributed to design of the study, interpretation of data, revising the manuscript for important intellectual content, and approving the final version of the article submitted.

Competing interests*None declared*

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