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doi: 10.1093/ageing/afq165
Published electronically 27 January 2011

Association of adverse drug reactions with drug–drug and drug–disease interactions in frail older outpatients

SIR—The most common type of medication-related adverse events in older adults is Type A ('augmented') adverse drug reactions (ADRs) [1–3]. Type A reactions are an exaggeration of the expected pharmacologic effect of a drug. These ADRs are more predictable, dose dependent and potentially preventable than Type B ('bizarre') ADRs (i.e. allergic reactions) [3, 4].

The relationship of different elements of suboptimal prescribing to ADRs in older outpatients has not been adequately explored. Recently, Chrischilles *et al.* [5] examined the association between multiple aspects of potentially inappropriate prescribing (defined by explicit criteria for drugs-to-avoid, drug–disease interactions, drug–drug interactions and therapeutic duplication) with self-reported adverse drug events (ADEs). A recent study used a modified weighting system for the medication appropriateness index (MAI), a validated measure that employs a standardised implicit approach to determining prescribing appropriateness, to examine the association of potentially inappropriate prescribing with self-reported ADEs [6, 7]. Neither of the above studies, however, had a specific focus on Type A ADRs.

Given this background, the objective of this study was to determine whether incorrect dosage, incorrect directions, drug–drug interactions and drug–disease interactions, as measured by the MAI, are associated with the Type A ADRs among frail older veterans transitioning from the hospital to the community.

Methods

Study design and study sample

This retrospective cohort study included a random sample of 400 patients from the Geriatric Evaluation and Management (GEM) Drug Study, which examined the impact of GEM care on drug-related problems in 1,388 older veterans from 11 Veterans Affairs Medical Centers (VAMC) [8]. Details about inclusion and exclusion criteria can be found elsewhere [8]. We further restricted the sample to those 359 patients taking one or more high-risk medications (see Supplementary data available in *Age and Ageing* online; http://www.ageing.oupjournals.org/) [3, 9, 10]. The study was approved by the VAMC Research and Human Subjects Committees at each study site and the Institutional Review Boards of Duke University and the University of Pittsburgh.

Potential drug-related adverse events: data collection, abstracted chart screening and self-report

Detailed information about data collection and screening for potential drug-related adverse events has been previously published [8, 11]. Briefly a trained research assistant at each site prepared an abstract of each patients VAMC inpatient and outpatient medical chart. A trained research nurse reviewed the abstracted charts and screened for potential drug-related adverse events using a standardised approach. In addition, at the 12 month closeout a trained research clinical pharmacist queried patients for self-reports of potential drug-related adverse events using previously validated methods [5]. For each potential drug-related adverse event identified by chart review and/or patient interview, a trained clinical pharmacist created a detailed narrative based on reporting information required by the Food and Drug Administration MEDWatch program [12].

Main outcome

The primary outcome measure was any Type A ADR with a causality rating of at least 'possible' [8]. Blinded geriatrician and geropharmacist pairs evaluated ADR causality using the narrative and the validated Naranjo ADR causality algorithm [13]. These ADRs were also assessed for type of ADR (i.e. Type A or not) [3, 4]. Any discordances among evaluators regarding the presence or type of ADR were resolved by clinical consensus conference.

Primary independent variables

The primary independent variables were inappropriate dosage, directions, drug–drug and drug–disease interactions. Physician–pharmacist pairs evaluated each patient's medication regimen for these potential problems using the MAI [6]. Any discordances among evaluators were resolved by clinical consensus conference.

Covariates

Several factors may confound any relationship between potentially inappropriate prescribing and ADRs and were

controlled for in multivariable analyses [5, 7, 9]. Demographic factors included categorical variables for age, race and marital status. Health status factors included continuous measures for the number of high-risk medications, chronic disease status (Charlson Comorbidity Index) and for basic activities of daily living, and a categorical variable for self-rated health [14, 15].

Statistical analysis

Baseline patient characteristics are presented as either means and standard deviations or frequencies and percents of the respective totals. We used backward selection (alpha = 0.15) multivariate logistic regression to determine covariates to be added along with all four MAI variables in the final model [16]. Hosmer and Lemeshow [16] testing for goodness of fit was conducted. We also conducted collinearity diagnostic testing. Post hoc we reran the final multivariate logistic regression model replacing the two individual variables for drug–drug interactions and drug–disease interactions with one composite variable that summarised the occurrence of either type of drug interaction. SAS 9.1 software (SAS Institute Inc., Cary, NC, USA) was used to perform all analyses.

Results

Table 1 displays the characteristics of the study sample and Supplementary data available in *Age and Ageing* online (http://www.ageing.oupjournals.org/) display the rate of high-risk medication use.

Overall, 31.8% of patients experienced one or more Type A ADRs during the follow-up period (median = 1; range 1–7). Only 14% of those with ADRs had more than two.

Table 2 provides information about the frequency of the four MAI prescribing problems and the univariate and multivariate results. Neither dosage nor directions problems were significantly associated with Type A ADRs ($P > 0.05$). However, there was some evidence ($P < 0.10$) that both drug–drug interactions (adjusted odds ratio [AOR] 2.37, 95% confidence interval [CI] 0.91–6.11) and drug–disease interactions (AOR 1.93, 95% CI 1.00–3.72) separately were associated with Type A ADRs. Moreover, post hoc analyses revealed that having either type of drug interaction problem increased the risk of Type A ADRs nearly 2-fold (AOR 1.83, 95% CI 1.03–3.25).

Table 1. Patient characteristics of frail older patients taking high-risk medications at hospital discharge ($n = 359$)

Variables	*n*	Per cent	Mean (SD)
Demographic factors			
Age			
>75	165	46.0	
65–74	194	54.0	
White race	258	71.9	
Married	157	52.1	
Health status factors			
Number of high-risk medications			3.86 (2.08)
Charlson Comorbidity Index			2.51 (1.93)
Basic activities of daily living			2.71 (1.99)
Fair/poor self-rated health	228	63.5	

SD, standard deviation.

Table 2. Prevalence of prescribing problems at hospital discharge and their relationship with Type A ADRs in the subsequent 12 months ($n = 359$)

Prescribing problems	*n*	Per cent	Unadjusted odds ratio (95% CI)	Adjusted odd ratio (95% CI)[a]
Any dosage problem	148	41.2	0.89 (0.57–1.39)	0.72 (0.44–1.17)
Incorrect directions	159	44.3	0.85 (0.548–1.33)	0.72 (0.44–1.16)
Any drug–drug interaction	21	5.9	2.70 (1.11–6.55)	2.37 (0.91–6.11)
Any drug–disease interaction	48	13.4	2.09 (1.14–3.85)	1.93 (1.00–3.72)

[a]Controlling for basic activities of daily living score and self-rated health. Neither the number of high-risk medications nor the comorbidity index were retained in the backward selection (alpha = 0.15) multivariable logistic regression model. Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 7.05$; df = 8; $P = 0.53$) suggests adequate model fit. No collinearity problems were detected with the final multivariable model.

Discussion

To the best of our knowledge this is one of the first studies using standardised implicit methods to examine types of inappropriate prescribing and their association with Type A ADRs as determined by a structured causality algorithm. Our findings provide some evidence of an association of the occurrence of Type A ADRs with both drug–drug and drug–disease interactions. Chrischilles *et al.* [5] reported that the use of drugs to avoid, and the occurrence of drug–disease interactions both independently and significantly increased the risk of the occurrence of one or more self-reported ADE. They also reported a trend towards increased risk of ADEs with drug–drug interactions and therapeutic duplication. When these four explicit measures of inappropriate prescribing were combined, a statistically significant relationship with ADEs was demonstrated [5]. Lund *et al.* [7], found that a modified summated MAI score, with the highest weights applied to drug–drug and drug–disease interactions, increased the risk of self-reported ADEs.

We did not find a significant relationship between dosage and direction problems and Type A ADRs. One possible explanation is that these two items measured by the MAI only assess whether they are incorrect. Therefore some of these incorrect ratings were due to dosage being too low or directions for use too infrequent which in both cases could lead to decreased drug concentrations and be more likely to be associated with therapeutic failure than with ADRs. This is consistent with the results from the Lund *et al.* [7], who assigned these two items a weight of zero and found they were not associated with ADRs.

This study has a number of limitations. First, the association did not achieve statistical significance. Second, the study relied primarily on chart review of information to assess prescribing and ADR causality. We may have underestimated problems if the information was not recorded or was erroneously recorded in the medical chart.

Third, we utilised a modification of the MAI incorporating only four of the original 10 items. This modification has not been independently validated. Moreover, our rate of ADRs discovered only by self-reported potential ADEs may be an underestimate especially in those with cognitive impairment and those who died (nearly 8% of subjects) before the 12 month follow-up period. It is reassuring that a previous study by our group found that nearly 60% of self-reported ADEs were also found during chart screening [11]. It is also possible that we overestimated the use of high-risk drugs as only prescribing and not adherence was assessed. Also the generalisability of our findings is unknown as it involved mostly male frail older veteran outpatients recently discharged from hospital and thus may differ from other ADR studies of older outpatients who were not hospitalised.

Despite these limitations, our results confirm that Type A ADRs are common in frail older outpatients, and provide evidence of an association with drug interactions. Further studies, possibly with larger cohorts, are required to test the reproducibility of these findings. In the meantime, quality improvement activities to reduce ADRs by improving prescribing appropriateness should continue to include a focus on the identification of potential drug–drug and drug–disease interactions.

Key points

- Type A ADRs are common in frail older outpatients.
- This study provides evidence of an association between drug interactions and Type A ADRs in frail older outpatients.
- Future quality improvement activities should include a focus on clinically important drug interactions.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

Conflicts of interest

None declared.

Funding

This study was not funded by outside sources. The original GEM Drug Study [8] was supported by the National Institutes of Health [R01-AG-15432] and the Veterans Affairs Cooperative Study Program 006. J.T.H. was supported by the following: National Institute of Aging grants (P30AG024827, T32 AG021885, 3U01 AG012553 K07AG033174, R01AG034056, 2R56AG027017), a National Institute of Mental Health grant (R34 MH082682), a National Institute of Nursing Research grant (R01 NR010135), an Agency for Healthcare Research and Quality grants (R01 HS017695 and R01HS018721) and a VA Health Services Research grant (IIR-06-062).

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doi: 10.1093/ageing/afq158
Published electronically 21 December 2010

Comparison of retrospective interviews and prospective diaries to facilitate fall reports among people with stroke

SIR—Monitoring falls is an important aspect of stroke rehabilitation. Retrospective methods include face-to-face or telephone interviews, postal questionnaires and medical note reviews [1–4]. Prospective methods include post cards, medical records, diaries and calendars as well as surveillance systems [1, 5–7]. Although prospective methods are considered preferable [1, 8, 9], it remains difficult to ascertain the accuracy of reporting methods as both may lead to over- or under-reporting [8, 10–17] and many factors influence recall [1, 8, 18–20].

Recall of falls in the previous year has reasonable sensitivity (80–89%) and specificity (91–95%) [5, 11, 16, 18] and produced better results than recall over shorter periods [16, 18] but recent studies have advocated short recall periods and intensive prospective (weekly or monthly) follow-up over longer periods [1, 5]. Little is known about the accuracy of fall reports among people with stroke. The present study examined the agreement between two fall-reporting methods (retrospective interviews and prospective fall diaries) over a 12-month period.

Methods

This study formed part of a larger project predicting fall risk among stroke patients [21]. Ethical approval was obtained from the Southampton and South West Hampshire Local Research Ethics Committee. Consecutively hospitalised patients were recruited if they were independently mobile prior to stroke, able to give consent: those who failed a cognitive function test [22] which might have affected fall recall, were excluded. Two researchers carried out assessments: the first carried out tests of balance, function, mood and attention and was kept blind to participants' fall status; the second collected data concerning falls, the focus of this paper.

Retrospective falls data were collected during an interview with participants and significant others at 12 months following discharge from hospital to the community, using an interview schedule [23]. Over the same time period, prospective falls data were self-completed in a diary: participants (and significant others) were asked to record falls as and when they occurred and were reminded to do so by regular telephone calls and letters. We defined a fall as an event that resulted in a person coming to rest unintentionally on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard [24]: participants were asked to adhere to this definition when reporting falls for either method. Participants were classified as fallers if they experienced one or more falls and as repeat fallers if they experienced two or more.

Agreement between the retrospective and prospective methods of collecting numbers of falls was examined using kappa statistics and Bland and Altman limits [25], which give a range of values in which the difference is expected to lie 95% of the time. Response and falling rates are presented with 95% confidence intervals calculated in CIA [26].

Results

Of the 122 participants recruited to the main study, retrospective falls information during the 12-month period following hospital discharge was available for 112 (93%, confidence interval 85–95%). Of these, 62 (55%, confidence interval 46–64%) reported one or more falls, and 45 (40%, confidence interval 32–49%) reported repeat falling. Using the prospective diary method, data for 76 (62%, confidence interval 53–70%) cases were available. Missing prospective information was due to the diary being lost ($n = 26$), death ($n = 4$) and no reason was recorded for the remaining 16.