Identifying Adverse Drug Events in Older Community-Dwelling Patients

Caitriona Cahir, PhD  
Emma Wallace, PhD  
Anthony Cummins, MRCGP  
Conor Teljeur, PhD  
Catherine Byrne, PhD  
Kathleen Bennett, PhD  
Tom Fahy, MD, FRCGP  
1Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland  
2HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in Ireland, Dublin, Ireland  
3Perdana University-Royal College of Surgeons in Ireland, Selangor, Malaysia  
4Health Information and Quality Authority, George’s Court, Dublin, Ireland

ABSTRACT

PURPOSE To evaluate a patient-report instrument for identifying adverse drug events (ADEs) in older populations with multimorbidity in the community setting.

METHODS This was a retrospective cohort study of 859 community-dwelling patients aged ≥70 years treated at 15 primary care practices. Patients were asked if they had experienced any of a list of 74 symptoms classified by physiologic system in the previous 6 months and if (1) they believed the symptom to be related to their medication, (2) the symptom had bothered them, (3) they had discussed it with their family physician, and (4) they required hospital care due to the symptom. Self-reported symptoms were independently reviewed by 2 clinicians who determined the likelihood that the symptom was an ADE. Family physician medical records were also reviewed for any report of an ADE.

RESULTS The ADE instrument had an accuracy of 75% (95% CI, 77%-79%), a sensitivity of 29% (95% CI, 27%-31%), and a specificity of 93% (95% CI, 92%-94%). Older people who reported a symptom had an increased likelihood of an ADE (positive likelihood ratio [LR+]: 4.22; 95% CI, 3.78-4.72). Antithrombotic agents were the drugs most commonly associated with ADEs. Patients were most bothered by muscle pain or weakness (75%), dizziness or lightheadedness (61%), cough (53%), and unsteadiness while standing (52%). On average, patients reported 39% of ADEs to their physician. Twenty-six (3%) patients attended a hospital outpatient clinic, and 32 (4%) attended an emergency department due to ADEs.

CONCLUSION Older community-dwelling patients were often not correct in recognizing ADEs. The ADE instrument demonstrated good predictive value and could be used to differentiate between symptoms of ADEs and chronic disease in the community setting.

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INTRODUCTION

Drug-related morbidity and mortality are major health care concerns in older populations and exert a significant burden on health care resources. Older people experience greater morbidity with a corresponding increase in drug use, resulting in a greater risk of adverse drug events (ADEs). Aging is also associated with a variety of physiologic changes affecting the pharmacokinetics and pharmacodynamics of drugs, which may increase the potential for drug toxicity and ADEs. The prevalence of ADEs in community-dwelling older populations is underestimated, and there is a need for assessment tools that allow for early detection of ADEs that might develop into more significant adverse effects requiring medical treatment or hospitalization. In outpatient settings, 25% to 50% of ADEs can potentially be detected and mitigated at an early stage. Studies have also indicated that more than one-half of hospital admissions for ADEs are preventable, with only 19% to 28% of ADEs causing hospital admission in older patients considered unavoidable. Patient reporting of suspected ADEs has the potential to increase knowledge regarding the safety of drugs and is an important additional

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CORRESPONDING AUTHOR
Caitriona Cahir, PhD  
Division of Population Health Sciences  
Beaux Lane House  
Mercer Street Lower  
Dublin 2, Ireland  
caitrionacahir@rcsi.ie
source of information for health care professionals.\textsuperscript{11} Health care professionals have been shown to underestimate the prevalence and severity of ADEs among their patients.\textsuperscript{13} In a literature review, health care professionals reported rates of constipation ranging from 0.6% to 1% with the use of blood glucose–lowering drugs in patients with type 2 diabetes mellitus, compared with 21% when reported by patients.\textsuperscript{13} In the United States, a study of 11 common adverse events in cancer treatment found that patients assigned greater severity to their symptoms than did their clinicians.\textsuperscript{14}

To date, few patient-report instruments to assess ADEs exist, and none have been established for use in older populations.\textsuperscript{15-17} Most available patient-report ADE measures focus on specific ADEs such as gastrointestinal ADEs or ADEs specific to a particular drug class (eg, inhaled corticosteroids, psychotropic drugs).\textsuperscript{18-20} Some generic questionnaires have been developed but require further validation.\textsuperscript{15,16} Patient self-report measures of ADEs are also often collected without access to the patients’ medical or health records and depend on self-reporting for information regarding diagnosis, comorbidities, allergies, and other treatments, which limits the accuracy of these measures.\textsuperscript{11}

The aim of this study was to evaluate a patient-report instrument for identifying ADEs in older populations with multimorbidity in primary care. The main objectives were to establish (1) the relation between subjective patient-reported ADEs and the objective presence of ADEs per clinical review and (2) the types of ADEs that require hospital care.

**METHODS**

**Study Population**

This was a retrospective cohort study of 859 community-dwelling patients aged ≥70 years and treated at 15 primary care practices in Ireland. A random sample of practices affiliated with the Royal College of Surgeons in Ireland and Trinity College Dublin were invited to take part in the study (response rate: 81%). Patients aged ≥70 years and treated at the 15 participating practices were assessed for eligibility to take part in the study by the research team and their family physician. A random sample of eligible patients from each of the 15 participating practices was invited to take part in the study using proportionate stratified random sampling (response rate: 63%).\textsuperscript{21} Ethical approval was granted by the Royal College of Surgeons in Ireland.

**Measurement of Patient-Reported Adverse Drug Events**

An ADE was defined as “an event which results in unintended harm to the patient, and is related to the care and/or services provided to the patient, rather than to the patient’s underlying medical conditions.”\textsuperscript{22} This definition is consistent with other studies, and examples of drug and adverse-effect associations include angiotensin-converting enzyme inhibitors and cough, nonsteroidal anti-inflammatory drugs and gastrointestinal tract complaints, and opioids and constipation.\textsuperscript{5,6,21} Each patient’s electronic family physician medical record was reviewed using a standardized form to collate information on their repeat and acute prescriptions, drug allergies, and ongoing medical condition(s), and this information was used as the basis for a phone-based patient interview about potential ADEs in the previous 6 months. The interview began with a general stem question designed to orient patients to the issue under measurement; for example, “In the last 6 months have you noticed any side effects, unwanted reactions, or other problems from medications you were taking?” This question has been used in previous studies and was found to correctly identify 94% of ADEs.\textsuperscript{24-26} Patients were then asked if they had experienced any of a list of 74 symptoms (Yes/No) classified by physiologic system in the previous 6 months.\textsuperscript{5,15} If the patient reported the symptom, more structured questions followed including (1) whether they believed the symptom was caused by their medication(s) (Yes/No), (2) the name of the medication(s), (3) the duration of the symptom, (4) whether the symptom bothered them (Yes/No), (5) whether they had discussed the symptom with their family physician (Yes/No), (6) what action their family physician had taken, and (7) if they were in need of hospital care (emergency department visit, hospital outpatient clinic visit, emergency hospitalization [>24 hours]) because of the symptom. The average duration of the interview was 21 minutes (range: 10-45 min).

Patients’ self-reported symptoms were independently reviewed by 2 academic family physicians (E.W., A.C.) who determined the likelihood that the symptom was an ADE on a 6-point scale (1 = no confidence to 6 = certain). The symptom was not classified as an ADE if the score was <4 (<50% confidence). There was 95% agreement between the 2 reviewers.\textsuperscript{5,21} Each patient-reported symptom that was established as an ADE was also independently rated according to severity by a family physician (E.W.) and a pharmacist (C.B.). The ADE was classified as a (1) mild ADE laboratory abnormality or symptom not requiring treatment (eg, bruising, constipation), (2) moderate ADE laboratory abnormality or symptom requiring treatment by family physician/hospital outpatient clinic or emergency admission to hospital (eg, delirium), or (3) severe ADE laboratory abnormality or symptom that was life-threatening or resulted in permanent disability or death.
(eg, acute renal failure). This taxonomy has been used in several studies to assess the severity of ADEs across different countries and health care settings. Differences between the 2 reviewers’ determinations and severity classification of ADEs were evaluated by a third clinician (T.F.).

Medical Record Reports of Adverse Drug Events

Each patient’s family physician medical record was reviewed for any report of an ADE in the previous 6 months, and this was compared with the patient’s self-report of ADEs.

Data Analysis

The performance characteristics of the patient-report ADE instrument were established by comparing patients’ subjective classification of each symptom as an ADE or not to the objective independent clinicians’ classification (review by 2 academic family physicians). Accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated. For each ADE, we assessed (1) the number (%) of patients who experienced the ADE, (2) the drugs associated with the ADE, (3) the severity of the ADE, (4) the number (%) of patients bothered by the ADE, and (5) whether the patient reported the ADE to their family physician. The number (%) of patients in need of hospital care due to an ADE was calculated and included the drug and severity of the ADE.

RESULTS

Study Population

The median age of the cohort was 77 years (interquartile range [IQR]: 73-81 years), and 471 (55%) participants were female. A total of 41% (n = 356) of patients had 5 or more chronic conditions and were dispensed (median deprivation score 2.95; range −1.04 to 4.86). 21 had above average deprivation in their catchment area family physician practices taking part in the study.

Table 2 presents details on the attributes of the more common patient-reported ADEs. Antithrombotic agents were the drugs most commonly associated with ADEs, with 86% of patients prescribed aspirin or warfarin reporting bruising, bleeding, or indigestion. A number of cardiovascular-system drugs, including diuretics, beta-blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, and serum lipid-reducing agents, were also associated with ADEs. These ADEs were all classified as mild in severity. Patients were most bothered by muscle pain or weakness (75%), dizziness or lightheadedness (61%), cough (53%), and unsteadiness while standing (52%) but did not associate these symptoms with their medication(s); sensitivity for these was low (Table 2). Patients were less bothered by the more prevalent ADEs; 21% were bothered by bruising and 26% by minor hemorrhages, and 28% and 22% reported these symptoms to their family physician, respectively. On average, patients reported 39% of ADEs to their family physician. Patients who did not report the ADE to their family physician felt the symptom was a result of old age and did not want to bother their family physician.

| Table 1. Performance Characteristics of the Self-Report ADE Measure (N = 859 Patients) |
|---|---|---|
| Estimated Value | 95% CI |
| Sensitivity | 29% | 27%-31% |
| Specificity | 93% | 92%-94% |
| PPV | 57% | 54%-60% |
| NPV | 81% | 80%-81% |
| LR+ | 4.22 | 3.78-4.72 |
| LR− | 0.76 | 0.74-0.78 |

ADE = adverse drug effect; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

Note: Based on the number of patients with an ADE (reported symptom established as an ADE, true and false positive and true and false negative).
mild, with 21 patients (26%) experiencing moderate or severe ADEs. All of the family physician reports of ADEs were also reported as ADEs by patients in the patient self-report instrument of ADEs.

**Adverse Drug Events and Hospital Care**

Twenty-six (4%) patients who reported an ADE attended a hospital outpatient clinic or met with a hospital consultant due to an ADE, and 32 (5%) attended an emergency department (Table 3). The majority of emergency department visits were for central nervous system symptoms (n = 13, 41%) and gastrointestinal symptoms (n = 11, 34%). Central nervous system symptoms included dizziness and light-headedness and unsteadiness while standing associated with beta-blocking agents, diuretics, psychoanaleptics, psycholeptics, and analgesics and were rated as moderate in severity. Gastrointestinal symptoms included abdominal pain associated with anti-inflammatory and antirheumatic products (diclofenac and aspirin) and diarrhea associated with proton-pump inhibitors and were rated as mild in severity.

In the family physician medical record reports of ADEs (n = 82 patients, 10%), 7 patients (9%) attended a hospital outpatient clinic or met with a hospital consultant due to a mild or moderate ADE. Six patients (7%) visited an emergency department with a moderate or severe ADE.

### Table 2. Attributes of the More Prevalent Patient-Reported ADEs

| ADEa | Patients Self-Reporting ADE, No. (%) | Main Therapeutic Drug Group Associated With ADE | No. (%) of Therapeutic Drug Group With ADEb | Severity |
|------|-------------------------------------|-----------------------------------------------|--------------------------------------------|----------|
| Bruise easily | 266 (31) | Antithrombotic agents (eg, aspirin, warfarin) | 249 (49) | Mild |
| Difficulty stopping a small cut from bleeding | 101 (12) | Antithrombotic agents (eg, aspirin, warfarin) | 97 (19) | Mild |
| Up at night to urinate | 153 (18) | Diuretics (eg, furosemide, bendroflumethiazide) | 147 (44) | Mild |
| Dizziness or light-headedness | 117 (14) | Diuretics (eg, furosemide, bendroflumethiazide) | 19 (6) | Mild |
| | | Beta-blocking agents (eg, bisoprolol, atenolol, metoprolol) | 32 (13) | Mild |
| | | Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone) | 32 (31) | Mild |
| | | Psychoanaleptics (eg, amitriptyline, doxepin) | 10 (15) | Mild |
| | | Psycholeptics (eg, benzodiazepine derivatives, trifluoperazine) | 15 (31) | Mild |
| Unsteadiness while standing | 75 (9) | Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone) | 28 (27) | Mild |
| | | Psychoanaleptics (eg, amitriptyline, doxepin) | 10 (15) | Mild |
| | | Psycholeptics (eg, benzodiazepine derivatives, trifluoperazine) | 20 (42) | Mild |
| Constipation | 137 (16) | Calcium channel blockers (eg, amlodipine, lercanidipine, diltiazem) | 28 (21) | Mild |
| | | Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone) | 40 (39) | Mild |
| | | Psychoanaleptics (eg, amitriptyline, doxepin) | 11 (17) | Mild |
| Indigestion or heartburn | 115 (13) | Antithrombotic agents (eg, aspirin, warfarin) | 92 (18) | Mild |
| | | Anti-inflammatory and antirheumatic products (eg, diclofenac, ibuprofen, etoricoxib) | 23 (32) | Mild |
| Fatigue or unusual tiredness | 87 (10) | Beta-blocking agents (eg, bisoprolol, atenolol, metoprolol) | 38 (15) | Mild |
| | | Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone) | 30 (29) | Mild |
| Dry mouth | 84 (10) | Diuretics (eg, furosemide, bendroflumethiazide) | 50 (15) | Mild |
| | | Psychoanaleptics (eg, amitriptyline, doxepin) | 12 (18) | Mild |
| Ankle swelling | 68 (8) | Calcium channel blockers (eg, amlodipine, lercanidipine, diltiazem) | 68 (52) | Mild |
| Cough | 66 (8) | Agents acting on the renin-angiotensin system (eg, ramipril, perindopril, lisinopril) | 62 (52) | Mild |
| Muscle pain or weakness | 57 (7) | Serum lipid–reducing agents (eg, atorvastatin, pravastatin, rosuvastatin, simvastatin) | 48 (43) | Mild |

ADE = adverse drug effect.

1 ADE is a patient-reported symptom that was established as an ADE per independent clinician review.

2 The proportion of patients with an ADE to this therapeutic drug group as a percentage of the overall number of patients prescribed medication from this therapeutic group during the study period.
DISCUSSION

The patient-report ADE instrument compared with the objective presence of ADEs per clinical review had 75% accuracy, low sensitivity (29%), and high specificity (93%). Older community-dwelling patients were often not correct in recognizing a symptom as an adverse effect of their medication. Previous research on self-reported ADEs in older hospitalized patients reported a sensitivity of 70% and specificity of 85%. Unlike the present study, however, ADEs were based on a single question of whether patients had complaints caused by their medication. Given the complexity of identifying ADEs in older people with several comorbidities and medications, patients may have been unable to discriminate effectively between symptoms attributable to individual medications or their underlying medical conditions. Older patients are also at increased risk of misclassification, given that old age is associated with increased illness, frailty, and disability, which may overlap with symptoms of ADEs (eg, fatigue, muscle pain, etc).

The patient-report ADE instrument is not suitable for use as a screening tool by family physicians or pharmacists to identify older people at risk of an ADE in the community setting. The instrument demonstrated good predictive value, however, and may be useful for confirmation of an ADE, or not, in symptomatic older people for whom their symptoms might be attributable to an ADE or to chronic disease. Whereas older patients may be regarded as unable to discriminate effectively between symptoms that are attributable to individual drugs or diseases, there are similar problems with health professionals. Family physicians are often unable to evaluate the risk/benefit of all potential options for a patient with multimorbidity, given the deficiencies in evidence-based medicine and the time available for making decisions, and have been shown to preserve the doctor-patient relationship ahead of medication rationalization.

Indeed, only a small proportion of patient-reported ADEs (9%) in the present study were documented in their family physician record. This poor documentation of ADEs in the primary care setting reflects the difficulties of differentiating between symptoms associated with aging, frailty, and multiple medical conditions, as well as the low reporting of symptoms (39%) by patients to their family physician. A study of ADEs in 4 primary care practices in the United States identified 92% of ADEs by interviewing patients, 28% by reviewing charts, and 19% by both means. In 79 medical practices in Scotland, only 22% of ADE symptoms associated with newly marketed drugs and reported using a generic patient questionnaire were found documented in primary care medical records. In practice, there are many difficulties in assessing ADEs in primary care. Family physicians may record and focus more on severe ADEs that directly affect patient morbidity or mortality and underestimate the impact of nonserious symptomatic ADEs on patients’ quality of life and adherence. Research has shown that patient-reported ADEs are associated with a lower quality of life and medication nonadherence.

Research has also shown that 30% to 50% of patients do not spontaneously report adverse effects of their medication to their physician or any resulting modifications they make to their treatment regimen. As indicated in the present study, patients may be less bothered by the more prevalent or
established ADEs (eg, minor hemorrhages from antithrombotic therapy) and unlikely to report those to their family physician. Patients may find drug-related adverse symptoms to be more tolerable than the severe symptoms associated with untreated underlying disease or condition. They might tolerate urinary frequency associated with diuretics if there is good symptomatic relief from heart failure–related shortness of breath or fatigue, and constipation in order to manage chronic pain. Asking patients explicitly about their perceived adverse drug symptoms is probably the only way to obtain a comprehensive understanding of ADE incidence and burden.

Only a small number of ADEs (9%) in the present study resulted in hospitalization. Previous studies have reported similar findings, with falls/unsteadiness while standing when taking benzodiazepines, neuroleptics, opiates, or sedative hypnotics, and acute kidney injury when taking diuretics as the most common causal factors. They might otherwise develop into more significant adverse effects requiring medical treatment or hospitalization. There is a need for patient-centered measurement tools in the primary care setting, which allow for early detection of ADEs that might otherwise develop into more significant adverse effects requiring medical treatment or hospitalization.

This study has a number of limitations. Patient self-report has inherent limitations, owing to its dependence on patients’ accurate recall of events. This study was conducted across 15 practices in 1 region in Ireland, and the results may not be generalizable to different regions or to the general older population. In Ireland, 94% of family physicians are using electronic medical records, but there may be differences in the quality of the data recorded across practices. Extensive checklists of symptoms organized by physiologic system, as applied in this study, have been advocated for drug safety reporting in clinical trials. They are not convenient as a screening tool, however, in the primary care setting. Only 24% of the symptoms reported in this study were ADEs. The measure needs to be adapted to focus only on the more prevalent and bothersome symptoms (Table 2); this would be a more efficient and clinically relevant method of confirming a symptom as an ADE, or not, in practice.

Notwithstanding the limitations, this study is the first to assess a patient-report instrument for systematic reporting of ADEs in older community-dwelling patients with multimorbidity. The results suggest that older patients do not report all symptoms they suspect to be ADEs to their family physician, and family physicians do not record all ADE-related symptoms that may be reported to them. The study also identified common ADE-related symptoms patients found bothersome. Improvements in monitoring and responding to symptoms in community settings are important to prevent ADEs. Recent reviews of the literature on deprescribing have highlighted the importance of patient involvement and shared decision making but recognized that its implementation in clinical practice is complex. Interventions and techniques need to be developed that facilitate communication with patients on their potential options for treatment and provide family physicians with a means of collaborative decision making and treatment planning.

Health information technology and patient outreach programs might provide an effective method of managing and tracking patient-reported drug symptoms and engaging patients in monitoring their medications in the future. Patients could be provided with

### Table 3. Description of the Most Common ADEs Leading to Hospitalization (N = 859 Patients)

| Physiologic System | ADEa | Main Therapeutic Drug Group Associated With ADE | Severity Rating | Hospital A&E (n = 32), No. (%) | Hospital Outpatient (n = 26), No. (%) |
|--------------------|------|-----------------------------------------------|-----------------|-------------------------------|-------------------------------------|
| Central nervous system | Dizziness/unsteadiness on feet/falls | Beta-blocking agents, diuretics, psychoanaleptics, psycholeptics, analgesics | Moderate | 13 (41) | 3 (12) |
| Gastrointestinal | Pain in abdomen, diarrhea | Anti-inflammatory and antirheumatic products, proton-pump inhibitors | Mild | 11 (34) | 8 (31) |
| Cardiovascular | Fainting | Beta-blocking agents, diuretics | Moderate | 3 (9) | 1 (4) |
| Genitourinary | Up at night to urinate, urinating more or less often | Diuretics | Mild | 2 (6) | 5 (19) |
| Musculoskeletal | Muscle pain or weakness | Serum lipid–reducing agents | Mild | 0 | 3 (12) |

A&E = accident & emergency department; ADE = adverse drug effect.

1 ADE is a patient-reported symptom that was established as an ADE per independent clinician review.
concise information resources that describe the purpose of their medication and help them anticipate and recognize ADEs and seek appropriate treatment.7,46 Adverse drug event interviews with a nurse or pharmacist could be incorporated into patient medication reviews as part of a patient’s ongoing pharmacologic care.47 Enabling health care providers and patients to consider drugs as a possible cause of adverse symptoms, and to differentiate them from symptoms of chronic disease or frailty, may ultimately help in enhancing monitoring and discontinuation of drugs. This approach may also help in avoiding unnecessary, more serious ADEs that cause death or disability and may also aid health care providers in recognizing symptoms and avoiding potentially harmful prescribing cascades.

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Key words: adverse drug events; older populations; primary care; patient reported outcomes

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