Identifying Adverse Drug Events in Older Community-Dwelling Patients

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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).[1] 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.[2] 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.[3,4] In outpatient settings, 25% to 50% of ADEs can potentially be detected and mitigated at an early stage.[5-8] 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.[9,10]

Patient reporting of suspected ADEs has the potential to increase knowledge regarding the safety of drugs and is an important additional

source of information for health care professionals.[11] Health care professionals have been shown to underestimate the prevalence and severity of ADEs among their patients.[12] 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.[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.[14]

To date, few patient-report instruments to assess ADEs exist, and none have been established for use in older populations.[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).[18-20] Some generic questionnaires have been developed but require further validation.[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.[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%).[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."[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.[5,6,23] 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.[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.[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.[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).[9] This taxonomy has been used in several studies to assess the severity of ADEs across different countries and health care settings.[9,27] 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.[21] A total of 41% (n = 356) of patients had 5 or more chronic conditions and were dispensed on average ≥6 different drug classes. The most common conditions were hyperlipidemia, cerebrovascular disease, and heart disease.[28] The majority of the 15 family physician practices taking part in the study had above average deprivation in their catchment area (median deprivation score 2.95; range –1.04 to 4.86).[21]

Patient Self-Reported Adverse Drug Events

In total, 674 patients (78%) were classified as having at least 1 ADE during the study period (symptom established as an ADE per patient self-report and independent clinician review). The median number of ADEs per patient was 2 (IQR: 1-4). The accuracy of the patient-report ADE instrument in differentiating between ADEs and non-ADEs was 75% (95% CI, 77%-79%). The ADE instrument had a sensitivity of 29% (95% CI, 27%-31%) and a specificity of 93% (95% CI, 92%-94%) (Table 1). The PPV of the instrument was 57%, with older people who reported a symptom having an increased likelihood of an ADE (LR+: 4.22; 95% CI, 3.78-4.72).[29] From the clinical perspective, 24% (95% CI, 23%-25%) of patient-reported symptoms were established as a true ADE per clinician review.

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.

Medical Record Reports of Adverse Drug Events

Family physician reports of ADEs in the previous 6 months were documented in the medical records for 82 (10%) patients during the study period. Twenty-two (27%) of these patients experienced more than 1 ADE. The majority of these ADEs were classified as

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 lightheadedness 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

ADE[a]	Patients Self-Reporting ADE, No. (%)	Main Therapeutic Drug Group Associated With ADE	No. (%) of Therapeutic Drug Group With ADE[b]	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 lightheadedness	117 (14)	Diuretics (eg, furosemide, bendroflumethiazide)	19 (6)	Mild
		Beta-blocking agents (eg, bisoprolol, atenolol, metoprolol)	32 (13)	
		Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone)	32 (31)	
		Psychoanaleptics (eg, amitriptyline, doxepin)	10 (15)	
		Psycholeptics (eg, benzodiazepine derivatives, trifluoperazine)	15 (31)	
Unsteadiness while standing	75 (9)	Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone)	28 (27)	Mild
		Psychoanaleptics (eg, amitriptyline, doxepin)	10 (15)	
		Psycholeptics (eg, benzodiazepine derivatives, trifluoperazine)	20 (42)	
Constipation	137 (16)	Calcium channel blockers (eg, amlodipine, lercanidipine, diltiazem)	28 (21)	Mild
		Analgesics (eg, codeine combinations, tramadol, buprenorphine, oxycodone)	40 (39)	
		Psychoanaleptics (eg, amitriptyline, doxepin)	11 (17)	
Indigestion or heartburn	115 (13)	Antithrombotic agents (eg, aspirin, warfarin)	92 (18)	Mild
		Anti-inflammatory and antirheumatic products (eg, diclofenac, ibuprofen, etoricoxib)	23 (32)	
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)	
Dry mouth	84 (10)	Diuretics (eg, furosemide, bendroflumethiazide)	50 (15)	Mild
		Psychoanaleptics (eg, amitriptyline, doxepin)	12 (18)	
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.

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

[b] 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%.[30] 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.[15] 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).[27]

Bothered, No. (%)	Reported to Physician, No. (%)	Sensitivity, %	Specificity, %
55 (21)	74 (28)	53	90
26 (26)	22 (22)	73	72
43 (28)	33 (22)	18	95
71 (61)	73 (62)	28	84
39 (52)	33 (44)	4	100
69 (50)	73 (53)	22	89
38 (33)	57 (50)	12	89
43 (49)	24 (28)	17	92
28 (33)	17 (20)	33	77
25 (37)	44 (65)	27	90
35 (53)	37 (56)	18	90
43 (75)	27 (47)	18	96

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.[31]

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.[32] 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.[5,33] 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.[15] 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.[34] Research has shown that patient-reported ADEs are associated with a lower quality of life and medication nonadherence.[35,36]

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.[5,15,37] As indicated in the present study, patients may be less bothered by the more prevalent or

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

Physiologic System	ADE[a]	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.

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

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.[38,39] 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 or contributory ADEs to hospital admission among older patients.[40,41] Patients in the present study were bothered by dizziness or lightheadedness (61%) and unsteadiness while standing (52%), and the majority (62% of those with dizziness or lightheadedness) reported symptoms to their family physician. Failure of physicians to respond appropriately to patient-reported symptoms has been reported to account for 63% of ameliorable ADEs.[5] 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.[3]

This study has a number of limitations. Patient self-report has inherent limitations, owing to its dependence on patients' accurate recall of events.[4] 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.[42] Extensive checklists of symptoms organized by physiologic system, as applied in this study, have been advocated for drug safety reporting in clinical trials.[27] 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.[43,44] 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.[45]

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.[8] Patients could be provided with

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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References

1. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. *Am J Ther.* 2007;14(5):488-498.
2. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab.* 2011;12(7):601-610.
3. Foster JM, van der Molen T, Caeser M, Hannaford P. The use of questionnaires for measuring patient-reported side effects of drugs: its importance and methodological challenges. *Pharmacoepidemiol Drug Saf.* 2008;17(3):278-296.
4. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 2006;29(5):385-396.
5. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med.* 2003;348(16):1556-1564.
6. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289(9):1107-1116.
7. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. Adverse drug events occurring following hospital discharge. *J Gen Intern Med.* 2005;20(4):317-323.
8. Steinman MA, Handler SM, Gurwitz JH, Schiff GD, Covinsky KE. Beyond the prescription: medication monitoring and adverse drug events in older adults. *J Am Geriatr Soc.* 2011;59(8):1513-1520.
9. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ.* 2004;329(7456):15-19.
10. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf.* 2008;31(6):545-556.
11. Basch E. Systematic collection of patient-reported adverse drug reactions: a path to patient-centred pharmacovigilance. *Drug Saf.* 2013;36(4):277-278.
12. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *Br J Clin Pharmacol.* 2007;63(2): 148-156.
13. Hakobyan L, Haaijer-Ruskamp FM, de Zeeuw D, Dobre D, Denig P. Comparing adverse event rates of oral blood glucose-lowering drugs reported by patients and healthcare providers: a post-hoc analysis of observational studies published between 1999 and 2011. *Drug Saf.* 2011;34(12):1191-1202.
14. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol.* 2006;7(11):903-909.
15. Jarernsiripornkul N, Krska J, Capps PA, Richards RM, Lee A. Patient reporting of potential adverse drug reactions: a methodological study. *Br J Clin Pharmacol.* 2002;53(3):318-325.
16. Corso DM, Pucino F, DeLeo JM, Calis KA, Gallelli JF. Development of a questionnaire for detecting potential adverse drug reactions. *Ann Pharmacother.* 1992;26(7-8):890-896.
17. de Vries ST, Mol PG, de Zeeuw D, Haaijer-Ruskamp FM, Denig P. Development and initial validation of a patient-reported adverse drug event questionnaire. *Drug Saf.* 2013;36(9):765-777.
18. Foster JM, van Sonderen E, Lee AJ, et al. A self-rating scale for patient-perceived side effects of inhaled corticosteroids. *Respir Res.* 2006;7(1):131.
19. Bytzer P, Talley NJ, Jones MP, Horowitz M. Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther.* 2001;15(1):137-142.
20. Lindström E, Lewander T, Malm U, Malt UF, Lublin H, Ahlfors UG. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia: clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nord J Psychiatry.* 2001; 55(Supp 44):5-69.
21. Cahir C, Bennett K, Teljeur C, Fahey T. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. *Br J Clin Pharmacol.* 2014;77(1):201-210.
22. Parry G, Cline A, Goldmann D. Deciphering harm measurement. *JAMA.* 2012;307(20):2155-2156.
23. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med.* 2004;140(10):795-801.
24. Chrischilles EA, VanGilder R, Wright K, Kelly M, Wallace RB. Inappropriate medication use as a risk factor for self-reported adverse drug effects in older adults. *J Am Geriatr Soc.* 2009;57(6):1000-1006.
25. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Ann Intern Med.* 1992;117(8): 634-640.
26. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother.* 2010;44(6):957-963.
27. Avorn J, Shrank WH. Adverse drug reactions in elderly people: a substantial cause of preventable illness. *BMJ.* 2008;336(7650): 956-957.
28. Kim S, Bennett K, Wallace E, Fahey T, Cahir C. Measuring medication adherence in older community-dwelling patients with multimorbidity. *Eur J Clin Pharmacol.* 2018;74(3):357-364.

29. Williams JWSD Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Making the diagnosis by history and physical examination. *Ann Intern Med.* 1992;117(9):705-710.

30. Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Do older hospital patients recognize adverse drug reactions? *Age Ageing.* 2000;29(1):79-81.

31. Sinnott C, Hugh SM, Boyce MB, Bradley CP. What to give the patient who has everything? A qualitative study of prescribing for multimorbidity in primary care. *Br J Gen Pract.* 2015;65(632): e184-e191.

32. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA.* 2006;296(15): 1858-1866.

33. Gandhi TK, Burstin HR, Cook EF, et al. Drug complications in outpatients. *J Gen Intern Med.* 2000;15(3):149-154.

34. Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. *Drug Saf.* 2007;30(8):669-675.

35. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am.* 2005;25(1):107-130.

36. De Smedt RH, Denig P, Haaijer-Ruskamp FM, Jaarsma T. Perceived medication adverse effects and coping strategies reported by chronic heart failure patients. *Int J Clin Pract.* 2009;63(2):233-242.

37. Pound P, Britten N, Morgan M, et al. Resisting medicines: a synthesis of qualitative studies of medicine taking. *Soc Sci Med.* 2005; 61(1):133-155.

38. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med.* 2005;165(2): 234-240.

39. Pham D, Grodin JL. Dilemmas in the dosing of heart failure drugs: titrating diuretics in chronic heart failure. *Card Fail Rev.* 2017;3(2): 108-112.

40. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med.* 2011;171(11):1013-1019.

41. McMahon CG, Cahir CA, Kenny RA, Bennett K. Inappropriate prescribing in older fallers presenting to an Irish emergency department. *Age Ageing.* 2014;43(1):44-50.

42. O'Kelly M, Teljeur C, O'Kelly F. Ni Shúilleabháin A, O'Dowd T. Structure of general practice in Ireland 1982-2015. *Irish College of General Practitioners.* February 2016.

43. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence-based, patient-centred deprescribing process. *Br J Clin Pharmacol.* 2014; 78(4):738-747.

44. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015; 175(5):827-834.

45. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. *BMJ.* 2016;353:i2893.

46. Tierney WM. Adverse outpatient drug events—a problem and an opportunity. *N Engl J Med.* 2003;348(16):1587-1589.

47. Schnipper JL, Kirwin JL, Cotugno MC, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization. *Arch Intern Med.* 2006;166(5):565-571.