Adverse drug reactions in older people: detection and prevention

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Running title: ADR detection and prevention in older people

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Abstract

Adverse drug reactions (ADRs) in older adults are an important healthcare problem since they are frequently a cause of hospitalisation, occur commonly during admission, and are an important cause of morbidity and mortality. Older adults are particularly susceptible to ADRs because they are usually on multiple drug regimens and because age is associated with changes in pharmacokinetics and pharmacodynamics.

The presentation of an ADR in older adults is often atypical, which further complicates its recognition. One potential strategy for improving recognition of ADRs is to identify those patients who are at risk of an ADR. The recently developed GerontoNet ADR Risk Score is a practical tool for identification of older patients who are at increased risk for an ADR and who may represent a target for interventions aimed at reducing ADRs.

Provision of adequate education in the domain of clinical geriatric pharmacology can improve recognition of the ADR. Besides formal surveillance systems, built-in computer programmes with electronic prescribing databases and clinical pharmacist involvement in patient care within multidisciplinary geriatric teams might help to minimise the occurrence of ADRs. In addition, a number of actions can be taken in hospitals to stimulate appropriate prescribing and to assure adequate communication between primary and hospital care. In older adults with complex medical problems and needs, a global evaluation obtained by comprehensive geriatric assessment may be helpful in simplifying drug prescription and prioritizing pharmacological and health care needs, resulting in an improvement in quality of prescribing.

Introduction

An adverse drug reaction (ADR) may be defined as any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and drug abuse.[1]

ADRs, including drug interactions, in older adults are a very important healthcare problem since they are frequently a cause of admission to hospital, occur commonly during hospitalisation, and are an important cause of morbidity and mortality.[2-5] Older adults are particularly susceptible to ADRs not only due to age-associated changes in pharmacokinetics and pharmacodynamics but also because of higher prevalence of co-morbidity, disability, and multiple drug regimens.[6-8]

The average rate of ADR–related hospital admissions is 16.6% in older patients compared to 4.1% in younger patients with 88% considered preventable.[9,10] Studies specifically undertaken in older adults have found that 24 % of patients are admitted due to ADR[2] and 14% experience an ADR as an inpatient.[11, 12] Moreover, ADRs in older adults can have severe medical and economic consequences. These consequences include an increased risk of serious disease, with potential long-term disability, institutionalization, and even death, which in turn increase expenditures for medical care.[13]

Classification

ADRs can be classified into two main types: type A or B.[14] Type A refers to ADRs that are associated with the pharmacological action of a drug and are dose-related. In addition, type A ADRs are common, predictable, and have a low mortality (e.g., digoxin toxicity, serotonin syndrome with selective serotonin receptor inhibitors, or anti-cholinergic effects of tricyclic antidepressants). In contrast, type B adverse drug reactions are unrelated to the pharmacological action of a drug. They are often immunologically mediated (for example

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penicillin hypersensitivity), are relatively uncommon, and are more serious in nature than type A reactions. Type C adverse reactions are associated with long-term therapy and are related to cumulative dose (e.g., hypothalamic-pituitary-adrenal axis suppression). While Type D adverse reactions occur some time after the use of the drug and are usually dose-related and uncommon (e.g., tardive dyskinesia after use of antipsychotics), Type E adverse reactions occur soon after withdrawal of the drug (e.g., myocardial ischemia after a beta-blocker withdrawal) although they are also uncommon. In contrast, Type F ADRs are often caused by a drug-drug interaction, are dose-related, and common.[15]

More than 80% of ADRs leading to hospital admission or accruing during hospitalisation are type A. Major drug groups that cause type A adverse drug reactions are antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic drugs, and non-steroidal anti-inflammatory drugs.[16, 17]

Risk factors for ADRs in older adults

Several factors that alter drug distribution or metabolism can make an ADR more likely. These include renal or hepatic function impairment and patient characteristics, such as age, number of drugs that the patient is receiving, and co-morbidity.[18] Changes in pharmacokinetics and pharmacodynamics also play an important role in the increased risk of ADRs in older adults, the most important of which is reduced renal clearance. In addition, age-related changes in renal structure may lead to altered drug excretion. Therefore, the dosage of a drug eliminated through the kidneys should be adjusted for decreased renal function.[19]

The possibility of reduced hepatic metabolism in older age should also be anticipated. Consequently, drugs that normally show significant, hepatic, first-pass metabolism may instead have a higher bioavailability and faster onset, which will require initiation at lower

doses with possible extended administration intervals. Cytochrome P450 oxidation declines too, increasing the risk for toxicity and possible drug-drug interactions for drugs that are substrates of these enzymes.[20, 21] A rapid decline in serum albumin during acute illness may additionally result in altered free-drug kinetics.

Cardiac output is another system function that can decline substantially with age, the chief results of which are lowered blood flow to the kidneys and liver. For high extraction drugs this could alter the overall elimination of the drug because the elimination of such compounds depends upon blood flow. Moreover, the reduced clearance of such compounds will produce an increase in half-life as a result of decreased blood flow. [22]

In older adults, lean body mass and total body water decrease, with a relative increase in total body fat. These changes cause a decreased volume of distribution for hydrophilic drugs. The reverse situation occurs with lipid-soluble drugs, which exhibit an increased volume of distribution that can lead to altered elimination half-life, although not necessarily an altered rate of clearance. [23]

Pharmacodynamic changes in the end-organ responsiveness to drugs at receptor or post-receptor levels result in altered, usually increased, sensitivity to several classes of drugs such as anticoagulants, and cardiovascular and psychotropic drugs.[16] Moreover, reduced homeostatic mechanisms make older people more prone to adverse effects (e.g., orthostatic hypotension is more likely to occur at a 'normal dose' of a vasodilator drug in an old person, based on sluggish baroreceptor response).[24]

The role of age as a cause of increased risk of ADRs should be preferably seen in the context of accumulated, patient-specific physiological and functional changes, which are probably more important than chronological age per se in predicting adverse drug reactions.[25]

Older adults tend to use multiple drugs as a consequence of several chronic clinical conditions. It has been found in the literature that the number of drugs taken among older patients is up to 6 prescribed medications and up to 3 non-prescribed medications.[26] In particular, frail older adults residing in nursing homes are prone to polypharmacy and resultant ADRs. However, when addressing polypharmacy we should take into account that several chronic conditions frequently require more then one drug in order to be adequately treated (i.e., 'rational polypharmacy' resulting from treatment via different mechanisms). Nevertheless, it has been shown that polypharmacy positively correlates with an increased risk for ADRs, as well as drug-drug and drug-disease interactions.[27] As an illustration, patients taking two drugs face a 13% risk of adverse drug-drug interactions, which rises to 38% for four drugs, and to 82% if seven or more drugs are given simultaneously.[28] On the other hand, polypharmacy can increase the risk for medication non-adherence, which consecutively can cause suboptimal therapeutic effectiveness and poor clinical response. If not recognized, the non-adherence can lead to a dose augmentation of the initial medication or the addition of a second drug, thereby increasing the risk for an ADR.[29] In addition, living alone, receiving drugs from different prescribers, and having cognitive problems and/or poor knowledge of the drugs prescribed have all been suggested to lead to higher risk of non-adherence and consecutive adverse drug reactions.[30]

The use of potentially inappropriate medications in older adults has also been described as one of the causes of ADRs.[31] Inappropriate prescribing, a potentially preventable risk factor for ADRs, occurs frequently and deserves nowadays much more attention than in the past due to the explosion in the sheer number of drugs available, less overall knowledge in their use by providers, and most importantly, less time for consideration in regard to the patient. This is exemplified by a Swedish study of patients 75 years or older in which 18% of prescribed medications were found to be inappropriate.[32]

Several methods and instruments have been developed for the purpose of medication appropriateness assessment, and are categorized as implicit (judgment-based) or explicit (criteria-based) approaches, or using a combination of both. Using an implicit approach means that clinical information of the individual patient is taken into account to judge appropriateness. In contrast, explicit criteria tend to be founded on lists of drugs to avoid, or indicators for appropriate prescribing for several drugs or diseases. Explicit criteria used with prescription data alone or with clinical data are commonly used to detect inappropriate prescribing.

Since no ideal measure exists, the combination of a structured approach and clinical judgment is recommended. Currently, the following tools exist to evaluate potentially inappropriate prescribing in older adults: the Beers' Criteria,[33] Improved Prescribing in the Elderly Tool (IPET),[34] and Screening Tool of Older Persons (STOPP)[35] are explicit approaches, while the Medication Appropriateness Index (MAI)[36] is an implicit model.

Recognition and reporting of ADRs – a novel risk score

Not all clinicians, pharmacists, nurses, or patients are able to recognize ADR. This is due to various reasons including education and previous experience. The presentation of an ADR in older adults is often atypical and non-specific, which further complicates its recognition. The ADR may therefore mistakenly be ascribed to the onset of a new medical problem or an already existing diagnosis. In that sense, various clinical symptoms such as delirium, drowsiness, light-headedness, apathy, dyspepsia, anorexia, chronic constipation, urinary incontinence or retention, and falls are often accepted as a primary diagnosis rather than secondary to medication.[37] With respect to falls, the use of sedatives and hypnotics, antidepressants, and benzodiazepines has shown significant association in the older population.[38]

The difficulty in distinguishing drug-induced symptoms from a definitive medical diagnosis often results in the addition of yet another drug to treat the symptoms, which increases the risk of drug-drug interactions and ADR- a phenomenon known as 'the prescribing cascade'.[37] Therefore, in an attempt to improve ADR recognition in older adults, its diagnosis should routinely be a part of the broader diagnostic approach. In older patients taking drugs, the differential diagnosis should always include the possibility of adverse drug effects. However, if the patient is taking several drugs it is not always easy to distinguish which drug, if any, is causative. When a drug is suspected as the cause of an acute change in a patient's clinical condition, the clinician should initially consider the known adverse effects of the particular drug. This is limited by the knowledge that not all adverse affects are reported or documented, particularly for recently marketed drugs. If the suspected reactions involve a known toxicity of a particular drug, then the link between the onset of the reaction and drug administration should be established. Other conditions that may predispose patients to such reactions should also be considered.

Several criteria have been proposed as a structured causality assessment of ADRs.[39] One of the often-used criteria in addition to the Naranjo algorithm[40] is the WHO–UMC (World Health Organization–Uppsala Monitoring Centre) system of causality categories (Table 1).[41] The WHO-UMC has been developed as a practical tool for the assessment of case reports in daily clinical practice.

Another important risk factor for developing an ADR is previous occurrence. Re-exposure to offending drugs due to poor documentation can cause the patient to experience the same ADR again. Therefore, it is important to stress the need for accurate documentation of ADR at the time of the event and to provide relevant information to the patient about ADR in order to prevent further occurrence.[42]

There is increasing interest among clinicians and researchers to find ways to reduce ADR occurrences. Prevention of ADR by identifying individuals at high risk is central to improving patient care and outcomes. One potential strategy for prevention is to identify those patients who are at risk of an ADR and to target additional resources toward this group. An example of this approach might be that when a patient is identified as being at risk, the physician and/or the pharmacist pay extra attention to all the medications that he or she receives.

In addition to numerous scales that are used in geriatric medicine to identify risks (e.g., cardiovascular), disorders (e.g., depression), and dysfunctions (e.g., cognitive problems and disability in activities of daily living or instrumental activities of daily living), there has been a need to develop a practical score to detect older patients who are at risk for an ADR. Hospitalized older adults are usually 'frail' and present with acute diseases, which may increase their susceptibility to ADRs and intensify the severity of drug-related illnesses.[43] Moreover, in-hospital patients, who often have a genuine need for many drugs, are usually the victims of a 'prescribing cascade' that leads to an increased likelihood of ADRs.[37] Also, because of these complexities in prescribing, older adults often receive inappropriate drugs whose risks outweigh the benefits.[44] Therefore, the hospital is an ideal setting to study ADRs because pharmacological non-compliance is reduced and the daily evaluation of patients, as well as the constant review of charts and medical records, provides an opportunity for careful reporting of all suspected ADRs. This opportunity makes the in-hospital population an ideal group to study ADRs and to develop a score to assess the risk of drug-related illness.

Based on these considerations, a group of researchers from four European universities, all belonging to the GerontoNet group, a network of academic departments of geriatric medicine in the European Union, recently developed and validated a practical, efficient, and simple method of identifying patients who are at increased risk of an ADR in a population of

in-hospital older adults.[45] This score was developed based on (a) data from the medical literature and (b) secondary analysis of the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA) (Italian Group of Pharmacoepidemiology in the Elderly) database, a study that was specifically designed to collect data about ADRs among in-hospital patients in Italy. Thereafter, this score was validated in a population of older adults consecutively admitted to 4 university hospitals in Europe.

The mean age of the 5936 participants in the GIFA study was 78.0 years (SD [standard deviation] 7.2), and the mean number of drugs used during the hospital stay was 6.3 (SD 3.6). Overall, the occurrence rate of ADRs was 6.5%. The number of drugs and a history of a previous ADR were the strongest predictors of ADRs, followed by heart failure, liver disease, presence of four or more co-morbidities, and renal failure. The ability of the risk score to predict ADRs was 0.71. The variables mentioned were retained in a stepwise regression model and used to compute the ADR risk score.

The mean age of the 483 patients in the validation study was 80.3 years (SD 7.6) and the mean number of drugs used during the hospitalisation was 11.0 (SD 7.0). Overall, the occurrence rate of ADRs was 11.6%. The variables associated with ADRs and included in the risk score were four or more co-morbid conditions (1 point), heart failure (1 point), liver disease i.e. liver function tests more than 2 times the Upper Limit of Normal (1 point), number of daily drugs (maximum 4 points for $\geq$ 8 drugs, 1 point for 5-8 drugs, 0 points $\leq$ 5 drugs), previous ADR (2 points) and renal failure i.e. estimated GFR < 60 ml/min (1 point). The range of the score was 0 to 10 points. A cut point between 3 and 4 seemed to provide a good balance between sensitivity (68%) and specificity (65%) and may be used to identify patients at high risk for ADR. The ability of the risk score to predict ADRs in the validation study was 0.7.

The findings of this study are concordant with previous findings, which demonstrated that the number of concomitantly used drugs is the most important risk factor for the occurrence of ADRs.[3, 6, 18, 43, 46-50] Also, a history of an ADR was confirmed to be a strong risk factor for a subsequent ADR, suggesting that a certain group of patients might be more susceptible to the negative effects of drugs because of ethnic, genetic, or cultural factors.[51] Finally, the authors confirmed the finding that certain co-morbidities, in particular heart failure, hepatic disease, and impaired renal function, may change drug kinetics, leading to an increased risk of ADRs.[52, 53] This study proposes the GerontoNet ADR Risk Score as a practical and simple tool for identification of older patients who are at increased risk for an ADR and who may represent a target for interventions aimed at reducing ADRs (Table 2). The ADR Risk Score allows stratification of patients according to the likelihood of developing an ADR and is hoped to significantly improve prescribing practice and reduce the occurrence of ADR amongst older patients.

However, this tool still has to be validated in different settings and countries as the findings cannot be extrapolated to older persons who are living in the community or in nursing homes. Also, the prescribing patterns are different in various countries, as is the epidemiology of disease burden. Moreover, in this study, the authors did not assess the risk for ADRs in regard to individual drug classes and the preventability of ADRs.

Prevention

ADRs in older adults are mostly preventable as the majority of ADRs are type A and dose-related. Provision of adequate education in the domain of clinical geriatric pharmacology with regard to the most common ADRs and the most frequently responsible agents together with the relationship of medication and symptoms can improve recognition of the ADR. Moreover, knowledge of pharmacological principles and changed pharmacokinetics

and drug response is indispensable in promotion of appropriate prescribing.[54] Therefore, prescribers have to judiciously judge the need for a particular drug in a patient and to use this drug at the lowest dose necessary to achieve benefit. In addition, different strategies can be proposed, addressing both patients and treatments: minor co-morbid conditions should be left out of consideration, whereas frailty, renal insufficiency, and alteration in cognitive function should be taken into account. Treatments should be periodically reconsidered and adapted depending on renal function,[55, 56] while poor compliance should be examined and self-administration of over-the-counter drugs discouraged. Most importantly, occurrence of some symptoms should be identified as the adverse consequence of drug administration, the first treatment of which is drug withdrawal and not the addition of a new medication.[57]

Appropriate prescribing is not only about drug choice, but careful evaluation of doses, duration of therapy, monitoring for adverse reactions, and drug-drug interactions. As older adults are often treated by several physicians, there is a risk for polypharmacy and therefore the occurrence of adverse drug reactions.

Currently, the main mechanism for identifying drug or population factors associated with ADRs is that of national pharmacovigilance systems.[15] Besides formal surveillance systems, all health-care professionals have a responsibility to report adverse drug reactions that they detect even if causal links are not certain. Built-in computer programmes or software with electronic prescribing databases and greater clinical pharmacist involvement in patient care within multidisciplinary geriatric teams might help to highlight inappropriate prescribing and minimise the occurrence of ADR.[5, 58]

In addition, a number of actions can be taken in hospitals to stimulate appropriate prescribing and to assure adequate communication between primary and hospital care: education of caregivers; accurate recording of drugs used; more accurate recording of adverse effect history; better instructions to patients about changes in drug regimens and about newly

started drugs; and information to first-line professionals (general practitioners, care workers, community pharmacists) and the patient's caregivers where appropriate about changes in drug regimens and advice for follow-up.

The interplay of the above-mentioned strategies may lead not only to a better understanding of changes in pharmacokinetics and pharmacodynamics in older age and a better communication between patients and physicians but also to an improved quality of drug use and prevention of ADRs. [59] However, evidence concerning beneficial effects on hard endpoints is still scarce probably due to methodological limitations of existing studies.[44]

A key point in preventing ADR relates to the fact that medical complexity of older adults should always be considered before prescribing a pharmacological treatment in order to minimize the risk of drug-related illness. Also, drugs that have proven clear beneficial effects in clinical trials to treat a chronic condition and whose use is indicated in clinical guidelines (CGL) should be used carefully in complex older adults. This is because they may interact with co-existing diseases or geriatric syndromes, may not be taken correctly because of the presence of cognitive deficits or disability, or may be useless because the health expectancy of the patient is too short to determine a beneficial effect of the drug.[60, 61] In these situations the risk of iatrogenic illness is elevated and may exceed the potential benefit observed from a given pharmacological treatment. In this context, it seems clear that a global assessment of patients' characteristics, including factors mentioned above, is necessary to have a full assessment of iatrogenic illness and to improve the quality of prescribing. The traditional approach to patients, diseases, and needs does not provide information on these problematic areas. In the past decades the comprehensive geriatric assessment (CGA) has been proposed as a methodology to provide a more global approach and assessment of older adults and their problems, allowing a more specific and sensible care plan for each single patient.[62] CGA is a simultaneous, multilevel assessment of various domains by a multidisciplinary team to ensure

that problems are identified, quantified, and managed appropriately. This includes assessment of medical, psychiatric, functional, and social domains followed by development of a management plan, including rehabilitation. Usually the multidisciplinary team will include as a minimum experienced medical, nursing, and therapy staff. CGA is considered the "technology" of geriatrics and its application results in a clear and significant improvement in the chances of a patient being alive and in their own home at up to a year after a hospital admission as a result of the evaluation of various problematic areas.[63] In addition, it allows a complete and global assessment and management of health care problems, including evaluation of drugs with the goal of recognizing and prevention of potential drug-related problems and improvement in the quality of prescribing. Several studies so far have assessed the effect of CGA and management on drug prescribing and drug-related illness, showing a substantial improvement in quality of prescription.[64, 65]

A large study of 834 frail older adults admitted to Veterans Hospitals in the US, which compared the CGA approach with usual care, showed a 35% reduction in the risk of a serious adverse drug reaction, and a substantial reduction in unnecessary and inappropriate drug use and in the number of conditions with omitted drugs significantly associated with the intervention.[66] However, one needs to be careful in interpreting the generalization and the clinical relevance of CGA in less expert settings.

Results of these studies confirm that in complex older adults, a full and global evaluation of the problems and needs obtained by CGA may be extremely helpful in simplifying drug prescription and prioritizing pharmacological and health care needs, resulting in an improvement in quality of prescribing and in a reduction in the risk of drug related illness. For this reason, so far, CGA is the only intervention that has demonstrated a reduction in risk of ADR in older adults.

In conclusion, detection and prevention of ADR in older adults remains an important part of good clinical practice and a challenge for even the most experienced clinician. The basic rule in the process of detection an ADR is a simple question: 'Could this patient's condition be due to one or more of the drugs he/she has taken?' Particular attention towards patients who are at high risk could reduce the impact of ADR both in terms of cost and quality of care.

References

1. World Health Organization. International drug monitoring: the role of the hospital. *World Health Organ Tech Rep*. 1969; 425:5-24.

2. Mannesse C, Derkx F, de Ridder M, Man in 't Veld A, van der Cammen T. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing*. 2000; 29:35-39.

3. Lazarou J, Pomeranz B, Corey P. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998; 279:1200-5.

4. Cresswell K, Fernando B, McKinstry B, Sheikh A. Adverse drug events in the elderly. *Br Med Bull*. 2007; 83:259-274.

5. Somers A, Petrovic M, Robays H, Bogaert M. Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur J Clin Pharmacol*. 2003; 58:707-714.

6. Routledge P, O'Mahony M, Woodhouse K. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol*. 2003; 57: 121-126.

7. O'Mahony MS, Woodhouse KW. Age, environmental factors and drug metabolism. *Pharmacol Ther*. 1994; 61:279-287.

8. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol*. 2003; 38:843-853.

9. Leendertse A, Egberts A, Stoker L, van den Bemt P; HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med*. 2008; 168:1890-1896.

10. Beijer H, de Blaey C. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci*. 2002; 24: 46–54.

11. Gray S, Sager M, Lestico M, Jalaluddin M. Adverse drug events in hospitalized elderly. *J Gerontol A Biol Sci Med Sci*. 1998; 53: M59–63.

12. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park B, Breckenridge A. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004; 329: 15-19.

13. Ray W, Griffin M, Shorr R. Adverse drug reactions and the elderly. *Health Affairs* 1990; 9: 114-122.

14. Rawlins M, Thompson J. Pathogenesis of adverse drug reactions. In: Davies D, ed. Textbook of adverse drug reactions, 2nd ed. Oxford: Oxford University Press, 1981: 11.

15. Edwards R, Aronson J. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*.2000; 356: 1255-1259.

16. Wang L. Epidemiology and prevention of adverse drug reactions in the elderly. *J Geriatr Cardiol*. 2005; 2: 248-253.

17. Rawlins M, Thompson J. Pathogenesis of adverse drug reactions. In: Davies D, ed. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977: 44.

18. Aronson J. Adverse drug reactions—no farewell to harms. *Br J Clin Pharmacol*. 2007; 63:131-135.

19. Laroche ML, Charmes JP, Marcheix A, Bouthier A, Merle L. Problems encountered with the evaluation of renal function in the elderly in order to adjust drug administration. *Pharmacotherapy*. 2006; 26:1041–1046.

20. Page R, Linnebur S, Bryant L, Ruscin J. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging*. 2010; 5:75-87.

21. Kinirons MT, Crome P. Clinical pharmacokinetic considerations in the elderly. An update. *Clin Pharmacokinet*. 1997; 33:302–312.

22. Mayersohn M. Pharmacokinetics in the Elderly. *Environ Health Perspect* 1994; 102 (Suppl 11):119-124.

23. Klotz U, Avant G, Hoyumpa A, Schenker S, Wilkinson G. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest* 1975; 55: 347-359.

24. Swift C. Pharmacodynamics: Changes in homeostatic mechanisms, receptor and target organ sensitivity in the elderly. *Br Med Bull*. 1990; 40: 36-52.

25. Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. *Ann Intern Med*. 1991; 114:956-966.

26. Stewart R, Cooper J. Polypharmacy in the aged. Practical solutions. *Drugs Aging*. 1994; 4:449-461.

27. Hajjar E, Cafiero A, Hanlon J. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007; 5:314–316.

28. Goldberg R, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *Am J Emerg Med*. 1996; 14: 447–450.

29. Col N, Fanale JE, Kronholm P. The role of medication non-compliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med*. 1990; 150: 841–845.

30. Barat I, Andreasen F, Damsgaard EM. Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol*. 2001; 51:615-622.

31. Lindley C, Tully M, Paramsothy V, Tallis R. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing*. 1992; 21:294-300.

32. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. *Drugs Aging*. 2005; 22:69-82.

33. BeersMH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med* 1991; 151: 1825–32.

34. Naugler CT, Brymer C, Stolee P, Arcese ZA. Development and validation of an improving prescribing in the elderly tool. *Can J Clin Pharmacol* 2000; 7:103–107.

35. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons'potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008; 37:673–679.

36. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992; 45:1045–1051.

37. Rochon P, Gurwitz J. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997; 315: 1096–1099.

38. Woolcott J, Richardson K, Wiens M, Patel B, Marin J, Khan K, Marra C. Meta-analysis of the Impact of 9 Medication Classes on Falls in Elderly Persons. *Arch Intern Med*. 2009; 169:1952-1960.

39. Agbabiaka TB, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf*. 2008; 31: 21–37.

40. Naranjo CA, Busto U, Sellers EM *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30: 239–245.

41. http://who-umc.org/Graphics/24734.pdf

42. Shenfield G, Robb T, Duguid M. Recording previous adverse drug reactions—a gap in the system *Br J Clin Pharmacol* 2001; 5: 623–626.

43. Onder G, Pedone C, Landi F, Cesari M, Della Vedova C, Bernabei R, Gambassi G. Adverse drug reactions as cause of hospital admissions: results from the Italian Group

of Pharmacoepidemiology in the Elderly (GIFA). *J Am Geriatr Soc*. 2002; 50:1962-1968.

44. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet*. 2007; 370: 173-184.

45. Onder G, Petrovic M, Tangiisuran B, Meinardi MC, Markito-Notenboom WP, Somers A, Rajkumar C, Bernabei R, van der Cammen TJ. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. *Arch Intern Med*. 2010; 170:1142-1148.

46. Gurwitz J, Field T, Harrold L, Rothschild J, Debellis K, Seger A, Cadoret C, Fish L, Garber L, Kelleher M, Bates D. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003; 289:1107-1116.

47. Field T, Gurwitz J, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Bates D. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med*. 2001; 161:1629-1634.

48. Onder G, Landi F, Della Vedova C, Atkinson H, Pedone C, Cesari M, Bernabei R, Gambassi G; GIFA Study. Moderate alcohol consumption and adverse drug reactions among older adults. *Pharmacoepidemiol Drug Saf*. 2002; 1:385-392.

49. Bates D, Miller E, Cullen D, Burdick L, Williams L, Laird N, Petersen LA, Small S, Sweitzer B, Vander Vliet M, Leape L. ADE Prevention Study Group. Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med*. 1999; 159:2553-2560.

50. Gurwitz JH, Rochon P. Improving the quality of medication use in elderly patients: a not-so-simple prescription. *Arch Intern Med*. 2002; 162:1670-1672.

51. McDowell S, Coleman J, Ferner R. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ*. 2006; 332:1177-1181.

52. Zeeh J, Platt D. The aging liver: structural and functional changes and their consequences for drug treatment in old age. *Gerontology*. 2002; 48:121-127.

53. Catananti C, Liperoti R, Settanni S, Lattanzio F, Bernabei R, Fialova D, Landi F, Onder G. Heart failure and adverse drug reactions among hospitalized older adults. *Clin Pharmacol Ther*. 2009; 86:307-310.

54. Routledge P, O'Mahony M, Woodhouse K. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol* 2004; 57: 121–126.

55. Laroche M, Charmes J, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J Clin Pharmacol*. 2006; 63: 177-186.

56. Laroche M, Charmes J, Marcheix A, Bouthier F, Merle L. Estimation of glomerular filtration rate in the elderly: Cockcroft-Gault formula versus modification of diet in renal disease formula. *Pharmacotherapy*. 2006; 26:1041-1046.

57. Merle L, Laroche M, Dantoine T, Charmes J. Predicting and preventing adverse drug reactions in the very old. *Drugs Aging*. 2005; 22:375-392.

58. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, Kettis-Lindblad A, Melhus H, Mörlin C.A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med*. 2009; 169:894-900.

59. Somers A, Robays H, Vander Stichele R, Van Maele G, Bogaert M, Petrovic M. Contribution of drug related problems to hospital admission in the elderly. *J Nutr Health Aging*. 2010; 14:477-482.

60. Fusco D, Lattanzio F, Tosato M, Corsonello A, Cherubini A, Volpato S, Maraldi C, Ruggiero C, Onder G. Development of CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) project: rationale and methodology. *Drugs Aging*. 2009; 26 Suppl 1:3-13.

61. Boyd CM, Darer J, Boult C, Fried L, Boult L, Wu A. Clinical practice guidelines and quality of care for older patients with multiple co-morbid diseases: implications for pay for performance. *JAMA*. 2005; 294:716-724.

62. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med* 2010;26:275-286.

63. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2011; 7: CD006211.

64. Onder G, Lattanzio F, Battaglia M, Cerullo F, Sportiello R, Bernabei R, Landi F. The Risk of Adverse Drug Reactions in Older Patients: Beyond Drug Metabolism. *Curr Drug Metab*. 2011; 12: 647-651.

65. Lampela P, Hartikainen S, Lavikainen P, Sulkava R, Huupponen R. Effects of medication assessment as part of a comprehensive geriatric assessment on drug use over a 1-year period: a population-based intervention study. *Drugs Aging*. 2010; 27:507-521.

66. Schmader KE, Hanlon JT, Pieper CF, Sloane R, Ruby CM, Twersky J, Francis SD, Branch LG, Lindblad CI, Artz M, Weinberger M, Feussner JR, Cohen HJ. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med*. 2004; 116:394-401.

Table 1. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	- Event or laboratory test abnormality, with plausible time relationship to drug intake - Cannot be explained by disease or other drug - Response to withdrawal plausible (pharmacologically, pathologically) - Event definitive pharmacologically or phenomenologically (i.e. an - objective and specific medical disorder or a recognised - pharmacological phenomenon) - Rechallenge satisfactory, if necessary
Probable/ Likely	- Event or laboratory test abnormality, with reasonable time - relationship to drug intake - Unlikely to be attributed to disease or other drugs - Response to withdrawal clinically reasonable - Rechallenge not required
Possible	- Event or laboratory test abnormality, with reasonable time relationship to drug intake - Could also be explained by disease or other drugs - Information on drug withdrawal may be lacking or unclear
Unlikely	- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) - Disease or other drugs provide plausible explanations
Conditional/ Unclassified	- Event or laboratory test abnormality - More data for proper assessment needed, or - Additional data under examination
Unassessable/ Unclassifiable	- Report suggesting an adverse reaction - Cannot be judged because information is insufficient or contradictory - Data cannot be supplemented or verified

*All points should be reasonably complied with

Table 2. The GerontoNet ADR Risk Score

	Points
4 or more co-morbid conditions	1
Congestive heart failure	1
Liver disease*	1
No of drugs:	
< 5	0
5-7	1
≥ 8	4
Previous ADR	2
Renal failure**	1

*defined as liver function tests >2x Upper Limit of Normal

* *defined as creatinine clearance < 40 ml/min