Strategies to reduce the risk of iatrogenic illness in complex older adults

Graziando Onder, Tischa J. M. van der Cammen, Mirko Petrovic, Annemie Somers, Chakravarti Rajkumar

Abstract

Older patients are particularly vulnerable to adverse drug reactions (ADRs) because age is associated with changes in pharmacokinetics and pharmacodynamics that may alter drug metabolism. In addition, other conditions, commonly observed in older adults, may increase the risk of ADRs in the older population (including polypharmacy, comorbidity, cognitive and functional limitations). ADRs in older adults are frequently preventable, suggesting that screening and prevention programmes aimed at reducing the rate of iatrogenic illness are necessary in this population. The present study reviews available approaches that may be used to screen and prevent the occurrence of ADRs in older adults, including medication review, avoiding the use of potentially inappropriate medications, computer-based prescribing systems and comprehensive geriatric assessment. Available evidence on these approaches is mixed and controversial, and none of them showed a clear beneficial effect on patients' health outcomes. Limitation of these interventions is the lack of standardisation, and these differences may give reason for the variability of the results documented in randomised clinical studies. Interestingly, most of the available research is focused on a single intervention targeting either clinical or pharmacological factors causing ADRs. When these approaches are combined, positive effects on patients' health outcomes can be shown, suggesting that integration of skills from different health care professionals is needed to address medical complexity of the older adults. The challenge for future research is to integrate valuable information obtained by existing instruments and methodologies in a complete and global approach targeting all potential factors involved in the onset of ADRs.

Keywords: older adults, adverse drug reactions, prevention, older people

Introduction

Adverse drug reactions (ADRs) represent a major burden on health care. In Western countries, ADRs cause 3–5% of all hospital admissions and are responsible for 5–10% of in-hospital costs [1, 2]. Older patients are particularly vulnerable to ADRs because age is associated with changes in pharmacokinetics and pharmacodynamics that may alter drug metabolism [3].

In addition, conditions commonly observed in complex older adults may increase the risk of ADRs in the older population. Firstly, older adults have a genuine need for more drugs, and co-administration of multiple drugs (polypharmacy) can lead to drug–drug interactions, contributing to an increased rate of ADRs [4]. Noticeably, few older patients with polypharmacy are included in pharmacological trials, and therefore, the safety profile of many drugs in an older frail population, especially when used in combination, is still debated. Secondly, comorbidity may lead to risk of drug–disease interaction [5], e.g. some beta-blockers taken for heart disease or high blood pressure can worsen asthma and mask hypoglycaemia in diabetic patients, metoclopramide for
gastrectomy may increase dopamine receptor blockade and worsen motor symptoms in a patient with Parkinson's disease. In addition, some specific conditions may alter drug metabolism. Typical examples of this phenomenon are kidney and liver diseases that lead to a reduced drug clearance and therefore to a higher risk of ADRs, or heart failure, which may cause changes in pharmacokinetics, including diminished renal and hepatic blood flow, reduced splanchnic blood flow and liver metabolic capacity and hepatic venous congestion and a reduction in the volume of distribution [6]. Thirdly, the presence of cognitive impairment can alter benefits and burdens, impact on treatment adherence and may cause communication difficulties including decreased ability to report adverse effects [7]. Fourthly, the presence of functional deficits and disability may limit the ability of patients to take medicines accurately. Functional deficits are related to a reduced ability to manage pill containers and therefore to reduced compliance with medication [8].

ADRs in older adults are mostly preventable as the majority of ADRs are type A (due to an exaggerated response to the expected action of the drug) and dose related [9]. This type of ADRs may be induced by several factors and issues, such as patient characteristics, disease, medications or medication classes were associated with the outcome. However, the study was done retrospectively and relied on voluntarily reported ADRs that may result in underreporting.

More recently, authors of the present study proposed a risk score, named the GerontoNET ADR risk score, as 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 [6]. This score was developed based on (i) data from the medical literature and (ii) secondary analysis of the Gruppo Italiano di Farmacoepidemiologia nell’Anziano (GIFA) (Italian Group of Pharmacoepidemiology in the Elderly) database. Thereafter, this score was validated in a population of 483 older adults consecutively admitted to four university hospitals in Europe. Results of the study showed that number of drugs and history of a previous ADR were the strongest predictors of ADRs, followed by heart failure, liver disease, the presence of ≥4 conditions and renal failure (Table 1). Based on this study, a score of 4 out of 10 or higher seemed to have the best balance between sensitivity and specificity and may be used to identify patients at high risk for ADRs.

The GerontoNET ADR risk score has the advantage to represent a practical and simple method of identifying patients at an increased risk of an ADR, which may represent a target for interventions aimed at reducing drug-related illness. All the variables included in the risk score address conditions or problems usually evaluated during a standard geriatric assessment, and no specific test or complex biological parameter is required. However, it still should be validated in different settings and studies. Indeed, a recent observational study showed that in a sample of 513 acutely ill patients aged ≥65 years, the GerontoNET ADR risk score missed almost 40% of those at risk of ADRs, underlining the need for identification of new risk factors to be added to

### The case of Mrs. M

Mrs. M is an 81 years old widow, living alone in her own house. She suffers from diabetes mellitus, hypertension, ischemic heart disease, glaucoma, osteoarthritis and osteoporosis. Her weight is 46 kg and she is 160 cm tall. Because of osteoarthritis she reports slowness and reduced level of physical activity. She is currently on the following drugs: Atenolol 50 mg/day, Perindopril 5 mg/day, Rabeprazole 20 mg/day, Metformin 1000 mg/day, Hydrochlorothiazide 12.5 mg/day, Timolol eye drops (0.5%, twice daily in both eyes), ASA 100 mg/day, Diazepam 5 mg/day. Her blood pressure is 152/88 mmHg and her last HbA1c was 8.2%.

### Table 1. The GerontoNet ADR risk score

<table>
<thead>
<tr>
<th>Points</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Four or more co-morbid conditions</td>
</tr>
<tr>
<td>1</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>1</td>
<td>Liver diseasea</td>
</tr>
<tr>
<td>0</td>
<td>No of drugs ≤5</td>
</tr>
<tr>
<td>1</td>
<td>≥5–7</td>
</tr>
<tr>
<td>4</td>
<td>≥8</td>
</tr>
<tr>
<td>2</td>
<td>Previous ADR</td>
</tr>
<tr>
<td>1</td>
<td>Renal failureab</td>
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</table>

aDefined as transaminases greater than twice normal limit.
bDefined as creatinine clearance <60 ml/min.

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**Strategies to reduce the risk of iatrogenic illness**

Identification of the population at risk of ADRs represents the first step to target additional resources towards this group and to put in place strategies of prevention. Despite the fact that identification and quantification of risk factors for iatrogenic illness is judged to be a public health priority, few data exist that allow stratification of patients according to likelihood of an ADR.

Bates et al. [10] tried to develop a risk stratification model for patients likely to experience an adverse drug event, using two approaches: a cohort analysis using limited information readily available electronically and a case–control study. In this study, the authors identified few independent predictors of adverse drug events, which had relatively little power, making unsuccessful their attempt to develop a risk score. Johnston and colleagues tried to identify specific patient characteristics associated with an increased risk of experiencing an ADRs or medication error, showing that age, clinical diagnoses, admission sources, types of insurance and the use of specific medications or medication classes were associated with the outcome. However, the study was done retrospectively and relied on voluntarily reported ADRs that may result in underreporting.

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the score [11]. Despite these concerns, the GerontoNET ADR risk score represents the only tool available so far to identify patients at risk of ADRs, which may be target of interventions aimed at reducing their risk of ADRs.

Mrs. M presents with multiple risk factors for ADR, including comorbidity and polypharmacy. She screened positive on the risk of ADR based on the GerontoNET ADR risk score (score = 5; ≥ 4 comorbid conditions: 1 point and ≥ 8 drugs: 4 points), suggesting a high risk for ADR and the need for an intervention to prevent the risk of ADR.

Approaches to prevent ADRs

Medication review

Medication review is a patient-care service that seeks to enhance a patient’s understanding of, and improve health outcomes with, their medication regimen. Medication review is provided by a pharmacist through an individualised assessment during which the medication scheme is analysed in a structured manner, with full access to the medical file (including, e.g. laboratory data), in order to identify drug-related problems (DRPs). A first step thus consists of the identification of all the medications that the patient is taking. Secondly, the drug scheme is screened for DRPs, i.e. any misuse, underuse or overuse of drugs. Possible solutions to the DRPs are then discussed with the treating physician and, if possible, with the patient him/herself; a medication management plan is created to address any issues, and the pharmacist discusses with the patient how the medications are best taken.

A recent review suggests that when pharmacists play a proactive role in performing medication reviews, pharmacotherapy for older patients is improved, but the evidence of the impact of pharmacists’ interventions on health outcomes, quality of life or cost-effectiveness of care is mixed and not conclusive [12]. Interestingly, in a recent randomised clinical trial (RCT) performed in 851 adults hospitalised with acute coronary syndromes or acute decompensated heart failure, an approach based on pharmacist-assisted medication reconciliation, inpatient pharmacist counselling, low-literacy adherence aids and individualised telephone follow-up after discharge did not significantly alter the per-patient number of clinically important medication errors [incidence rate ratio, 0.92 (95% CI: 0.77–1.10)] or adverse drug events [incidence rate ratio, 1.09 (CI: 0.86–1.39)] [13].

Better results have been reported when pharmacists are skilled and work in the context of a multidisciplinary team. Spinewine et al. [14] showed that in an RCT performed among 203 in-hospital patients aged 70 or older, pharmaceutical care provided by a specialist clinical pharmacist who had direct contacts with the Geriatric Evaluation and Management team resulted in an appropriate use of medicines during the hospital stay and after discharge. In addition, a recent meta-analysis showed that a team-based care including pharmacists resulted in a 47% reduction in adverse drug events [15]. These findings indicate that interventions focused selectively on a pharmaceutical approach are not successful in reducing iatrogenic illness in older adults, but that safe drug use goes along with global assessment of patients’ clinical and functional parameters. Indeed, a potential limitation of research assessing the role of pharmacists in preventing ADRs is that many studies may have provided the pharmacists with minimal education.

Table 2. Results of clinical studies assessing the effect on ADRs of an intervention based on pharmacists working in the context of a multidisciplinary team

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klopotowska et al. [16]</td>
<td>115 patients in ICU (mean age 63 years)</td>
<td>RCT</td>
<td>Hospital pharmacist reviewed medication orders for patients admitted to the ICU and discussed those during patient review meetings with the attending ICU physicians</td>
<td>Preventable adverse drug events were reduced from 4.0 per 1,000 monitored patient-days during the baseline period to 1.0 per 1,000 monitored patient-days during the intervention period (P = 0.25).</td>
</tr>
<tr>
<td>Schnipper et al. [17]</td>
<td>322 in-hospital patients (62% age &gt;60 years)</td>
<td>RCT</td>
<td>Computerised medication reconciliation tool and process redesign involving physicians, nurses and pharmacists</td>
<td>Adverse drug events rate was 1.44 per patient among control patients and 1.05 per patient among intervention patients (adjusted relative risk, 0.72; 95% CI: 0.52–0.99)</td>
</tr>
<tr>
<td>Kucukarslan et al. [18]</td>
<td>165 in-hospital patients (mean age 55 years)</td>
<td>RCT</td>
<td>Rounding team including a pharmacist</td>
<td>Rate of preventable adverse drug events was reduced by 78%, from 26.5 per 1000 hospital days to 5.7 per 1,000 hospital days during the intervention period (P &lt; 0.001) after the intervention. The rate of preventable adverse drug events decreased by 66%, from 10.4 per 1,000 patient-days (95% confidence interval CI: 7–14) before the intervention to 3.5 (95% CI: 1–5; P &lt; 0.001) after the intervention. In the control unit, the rate was essentially unchanged during the same time periods: 10.9 (95% CI: 6–16) and 12.4 (95% CI: 8–17) per 1,000 patient-days</td>
</tr>
<tr>
<td>Leape et al. [19]</td>
<td>75 patients in ICU</td>
<td>RCT</td>
<td>A senior pharmacist made rounds with the ICU team and remained in the ICU for consultation in the morning and was available on call throughout the day</td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomised clinical trial.
and training updates on geriatric pharmacotherapy, and this might be grossly insufficient, given the complexity of optimising pharmacotherapy in older frail adults suffering from multiple conditions and receiving multiple medications. In addition, available RCT assessing the effect of an approach based on pharmacists working in a multidisciplinary team on ADRs (Table 2) was mainly performed among hospitalised patients (either in acute care unit or ICU), and sample sizes of these studies were limited, indicating the need of large-scale multicentre trials performed in different settings (i.e. nursing home, community) [16–19].

Mrs. M ...

The medication review process is based on the following steps:

1) Structured pharmaceutical anamnesis: Mrs. M is interviewed and information of the GP and the community pharmacist is gathered as well. Specific questions on use of drugs easily forgotten (such as sleeping pills, inhaled drugs, over-the-counter drugs and supplements and drugs on an ‘as needed’ basis) and on time and mode of administration are asked.

2) Structured screening for drug related problems (DRPs): drugs are assessed for indication, correct dose, choice of the appropriate treatment, frequency and time of intake. Drug-drug interactions, presence of ADRs and underprescribing are also assessed. Potential DRPs related to the case of Mrs M are the following:
   - Pirindopril, hydrochlorothiazide, and metformin: are doses adjusted for renal function?
   - Metformine use: the HBA1C-level is not satisfactory and attempts should be made to improve glucose control, but with due regard to avoiding hypoglycaemic episodes.
   - Diazepam use: inappropriate in older adults because of increased risk of falls
   - Calcium/vitamin D and bisphosphonate may be necessary given the diagnosis of osteoporosis
   - Rabeprazole: no clear indication
   - Atenolol: not the best choice for the treatment of hypertension
   - Timolol: combined use of timolol and atenolol can increase the risk of symptomatic bradycardia and falls

3) This list is then discussed with the treating physician and a plan for implementation and evaluation is created.

Avoid use of inappropriate medications

The issue of appropriate prescribing has invoked a wide interest in the medical literature, and different criteria were developed in the last decades [20]. Since 1991, Beers and colleagues developed a set of criteria with the intent to provide a tool for assessing the quality of prescribing in older persons [20]. In their latest version updated by the American Geriatrics Society in 2012, Beers criteria identify a list of 53 inappropriate drugs or drug classes divided into three categories: potentially inappropriate drugs to avoid independence of comorbidities, potentially inappropriate drugs to avoid in older adults with certain diseases and syndromes, and medications to be used with caution [21]. Limitation of the Beers criteria includes the fact that they were developed to be applied to the older adults living in the USA and do not account for differences in drug policy and pharmaceutical marketing in other countries.

More recently, a tool for screening potentially inappropriate drugs called STOPP (Screening Tool of Older Persons’ Prescriptions) and one for detection of potential prescribing omissions of indicated, potentially beneficial drugs called START (Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatment) were developed [22]. These criteria are organised according to physiological systems and encompass both potentially inappropriate prescribing and omission of potentially beneficial pharmacotherapy. Recent data showed that the use of STOPP/START criteria to screen hospitalised older patients’ medications leads to significant and sustained improvements in the appropriateness of prescribing at discharge and for up to 6 months after discharge, suggesting that this tool represents a simple and easily applied method of optimising prescribing appropriateness in older hospitalised patients [23]. In addition, in a study performed among 600 patients aged 65 or older admitted to hospital, STOPP criteria were significantly associated with avoidable adverse drug events that cause or contribute to urgent hospitalisation [24].

Finally, the medication appropriateness index (MAI) represents a judgment-based process measure [25]. The MAI is a measure of prescribing appropriateness that assesses 10 elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, drug–drug interactions, drug–disease interactions, duplication, duration and cost. These elements are assessed based on clinical judgment, rather than objective measures and the ratings generate a weighted score that serves as a summary measure of prescribing appropriateness. Limitations of the index are related to the fact that it is time-consuming and does not assess underprescribing.

Mrs. M ...

Beers and START and STOPP criteria identified the following concerns about Mrs. M treatment:

Beers 2012 criteria
   - Diazepam: increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents

STOPP
   - Diazepam: risk of prolonged sedation, confusion, impaired balance, falls.
   - Atenolol: risk of masking hypoglycaemic symptoms
   - Rabeprazole: if full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated)

START
   - Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient’s functional status remains independent for activities of daily living and life expectancy is greater than 5 years
   - Calcium and vitamin D supplement in patients with known osteoporosis
Computer-based prescribing systems

Clinical Decisions Support Systems (CDSS) and Computerized Prescription Support System (CPSS) are interactive softwares, designed to assist physicians to correct prescribing, with the aim of reducing prescribing errors, improving prescribing appropriateness and ultimately lead to a reduction in iatrogenic illness. These softwares provide support at the time of prescription by implementing different algorithms and tools to identify potentially inappropriate prescribing, drug interactions, risk of iatrogenic illness, appropriate drug dosage and contraindicated treatments. Computerized Provider Order Entry Systems (CPOE), which are based on these softwares, enable providers to enter medical orders into a computer system that is located within an inpatient or ambulatory setting. CPOE introduces automation at the time of ordering and can occur instantly, accurately, reliably and more legibly than handwritten orders.

These computer-based prescribing systems were promoted as having great potential for reducing medication errors and ADRs. So far they have shown the potential to change healthcare provider behaviour, but very few studies demonstrated an improvement in patient outcomes. A systematic review evaluating the effects of CPOE based on CDSS on the development of adverse drug events showed that only 5 out of 10 eligible studies reported a statistically significant reduction in the number of adverse drug events. Interestingly, no RCT was included in this systematic review [26]. Interestingly, in an RCT conducted in two academic centres in the USA, CDSS intervention was shown to be markedly effective in reducing the prescribing of an undesired drug–drug combination, but it caused clinically important treatment delays in patients who needed immediate drug therapy [27]. These adverse consequences were deemed sufficiently serious to warrant discontinuation of the intervention and early termination of the study.

Limitation of computer-based prescribing systems relates to the fact that they are home-grown and not standardised, with different types of tool or algorithms implemented depending on study or population considered. In addition, they often do not assess the complexity of older adults related to comorbidity, geriatric syndromes and impairments in multiple systems (i.e. cognitive and functional impairments), being mainly focused on pharmacological issues.

In conclusion, clear evidence suggesting an effect of computer-based prescribing systems is lacking. Efforts are required to further integrate additional clinical and laboratory information into these systems, including specific symptoms, geriatric conditions and functional status to the use of specific medications.

Mrs. M...

Computer-based prescribing systems may raise various concerns related to Mrs. M therapy. The following warning messages are taken from the CPSS developed by the Istituto di Ricerche Farmacologiche Mario Negri

Drug interactions
- Rabeprazole- Hydrochlorothiazide (moderate risk): increased risk of hypomagnasemia in case of prolonged use of PPI
- Perindopril- Hydrochlorothiazide (moderate risk): increased risk of hypotension at the first dose
- Metformin- Atenolol (moderate): risk of masking hypoglycemic symptoms

Inappropriate drug use:
- Diazepam (Beers 2003, Beers 2012, STOPP): risk of prolonged sedation, confusion, impaired balance, falls
- Atenolol (STOPP): risk of masking hypoglycemic symptoms
- Rabeprazol (STOPP): if full therapeutic dosage for >8 weeks (dose reduction or earlier discontinuation indicated)

Underuse of drugs:
- Statin (START): statin therapy is indicated with a documented history of coronary, cerebral or peripheral vascular disease, where the patient’s functional status remains independent for activities of daily living and life expectancy is greater than 5 years
- Calcium and vitamin D (START): Calcium and vitamin D supplement in patients with known osteoporosis

Anticholinergic Cognitive Burden (ACB scale)
- Atenolol = 1; Diazepam = 1
- Total score = 2 - moderate anticholinergic effect

Dose
The following drugs need dose adjustment based on creatinine clearance:
- Perindopril, Atenolol, Metformin, Hydrochlorothiazide

GerontoNET
GerontoNET ADR risk score ≥4, suggesting a high risk for ADR.

Comprehensive geriatric assessment and management

Medical complexity of older adults may have a great role in the onset of ADRs and should always be considered before prescribing a pharmacological treatment in the elderly. Also drugs that have proved in clinical trials clear beneficial effects to treat a chronic condition and whose use is
Mrs. M...

… the CGA identifies several problematic areas of Mrs. M which may limit the use of drugs:

1) Malnutrition - The use of multiple drugs may impair appetite and reduce food intake. In particular, metformin may cause anorexia and weight loss. Mrs. M is underweight (BMI < 18 kg/m²) and for this reason treatment with metformin should be reconsidered and opportunity to reduce the overall number of drugs should be evaluated.

2) Social problems and frailty - Lack of social support and frailty may suggest potential difficulties in managing complex drug regimens and possible problems in drug adherence. In particular, applying a tight blood pressure and glycaemic control to Mrs. M may be problematic because of potential medication errors and severity and consequences of ADR may be accentuated by these factors.

3) Falls - Mrs. M presents several risk factors for falls, including polypharmacy, use of benzodiazepines and diuretics and functional limitations (slowness). Therefore the CGA identifies her as a person at high risk for fall. This suggests the need to reduce the number of used drugs and withdrawal from the use of benzodiazepines and diuretics. Vitamin D supplementation may be considered given its positive effects on osteoporosis and falls and its safe profile.

4) Limited life expectancy - given the presence of the malnutrition, frailty, comorbidities and advanced age, life expectancy of Mrs. M might not be long enough to get benefit from intensive drug treatment. For example, tight glycaemic control may be unrewarding if life expectancy < 3 years.

Conclusions

In conclusion, several approaches have been proposed in the last few decades to reduce the risk of ADRs in older adults. These interventions were focused on factors influencing the risk of iatrogenic illness, including quality of drug prescribing, polypharmacy, comorbidities, medication errors, factors influencing drug metabolism and patients’ individual characteristics. However, none of them did show a clear beneficial effect on patients’ health outcomes: available evidence on the impact of medication review, avoidance of inappropriate medications, CGA and computer-based prescribing systems is mixed and controversial.

A limitation of all the described approaches is the lack of standardisation. Computer-based prescribing systems are often home-grown, and they implement different types of information, tools and algorithms. Criteria to assess the quality of prescribing vary across countries and no widely accepted gold standard exists, yet. Geriatric assessment and
management programmes are extremely heterogeneous in terms of structural components and care processes. Similarly, large differences were described in the delivery of the pharmacist-led medication review. These differences may give reason for the variability of the results documented when these interventions were implemented.

Interestingly, most of the available research is focused on a single intervention targeting either clinical or pharmacological factors causing ADRs. When these approaches were combined, as for studies assessing the efficacy of an intervention based on experienced pharmacists performing medication review in the context of a multidisciplinary team, positive effects on patients’ health outcomes were shown. This finding indicates that safe drug use goes along with global assessment of patients clinical and functional parameters and that integration of skills from different healthcare professionals is needed to address medical complexity of older adults. The challenge for future research is to integrate valuable information obtained by existing instruments and methodologies in a complete and global approach targeting all potential factors involved in the onset of ADRs.

**Key points**

- Several interventions have been proposed to reduce the risk of ADRs in older adults, including medication review; avoiding the use of potentially inappropriate medications, computer-based prescribing systems and CGA.
- These interventions are poorly standardised, and evidence on their benefits is mixed and controversial.
- Few studies demonstrated that when these approaches are combined, positive effects on patients’ health outcomes can be shown, suggesting that integration of skills from different health care professionals is needed to address medical complexity of older adults.
- Future research should integrate valuable information obtained by existing instruments and methodologies in a complete and global approach targeting all potential factors involved in the onset of ADRs.

**Acknowledgement**

Thanks to Prof. Marc Bogaert from the Heymans Institute of Pharmacology, Ghent University for his contribution to the manuscript.

**Conflicts of interest**

None declared.

**Funding**

This project was not supported by external funding. The work of Dr Onder is supported by a grant from the Italian Ministry of Health (Giovani Ricercatori 2007, n. 4).

**References**


Received 21 September 2012; accepted in revised form 17 January 2013