Avoiding Inappropriate Medication Prescription in Older Intensive Care Survivors

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ABSTRACT

- *Objective:* To present an overview of the phenomenon of inappropriate medication prescription in older critically ill patients and examine possible strategies of intervention.
- *Methods:* Review of the literature.
- *Results:* Polypharmacy and inappropriate prescribing of medications in older persons may lead to a significant risk of adverse drug-related events and mortality. The intensive care unit (ICU) is often the place where potentially inappropriate medications (PIMs) are first prescribed. Common PIMs at ICU discharge are antipsychotics, benzodiazepines, opioids, anticholinergic medications, antidepressants, and drugs causing orthostatic hypotension. Different classes of medications, typically intended for short-term use, are sometimes inappropriately continued after discharge from the hospital. At admission, potential risk factors for PIM are multiple morbidities, polypharmacy, frailty and cognitive decline; at discharge, a high number of pre-admission PIMs, discharge to a location other than home, discharge from a surgical service, longer length of ICU and hospital stay, and mechanical ventilation. Inappropriate prescribing in older patients can be detected through either the use of explicit criteria, drug utilization reviews, and multidisciplinary teams, including a geriatrician and/or the involvement of a clinical pharmacist.
- *Conclusion:* Use of PIMs may be common in critical patients, both on admission and at discharge from ICU. Therapeutic reconciliation is recommended at every transition of care (eg, at hospital or ICU admission and discharge) in order to improve appropriateness of prescription.

Key words: *elderly; intensive care unit; inappropriate medications; antipsychotics.*

Since older persons are often affected by multiple chronic diseases and are prescribed several medications, the quality and safety of prescribing these medications has become a global health care issue [1–4]. Polypharmacy and inappropriate prescribing of medications among the elderly is receiving significant attention in the medical literature [5,6]. Inappropriate medications in the elderly can lead to falls, cognitive impairment and delirium, poorer health status, and higher mortality [7–10]. Medications are considered potentially inappropriate when (a) the risks of treatment outweigh the benefits [11], (b) they are prescribed for periods longer than clinically indicated or without any clear indication, (c) they are not prescribed when indicated [12], and (d) they are likely to interact with other drugs and diseases. Medications included in this category are often referred to as potentially inappropriate medications (PIMs), as in some situations their use is justified; however, if the risk of harm from the drug is judged to outweigh the potential clinical benefit after an individual patient's clinical circumstances are considered, these drugs are considered "actually inappropriate medications" (AIMs) [6].

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Advancing age is associated with substantial pharmacokinetic and pharmacodynamics changes, such as altered distribution volumes and altered permeability of the blood-brain barrier, impaired liver metabolism and renal capacity, up- and down-regulation of target receptors, transmitters, and signaling pathways changes, impaired homeostasis, and increased risk of adverse drug reactions (ADRs) that lead to increased mortality and morbidity and higher health care costs [2,11,13–19]. Studies show that ADRs cause approximately 5% of hospital admissions in the general population, but the percentage rises to 10% in older persons [20].

Avoiding PIMs represents a strategy aimed at reducing drug-related mortality and morbidity. This article provides an overview of the phenomenon of inappropriate medication prescription in older critically ill patients and examines available strategies of intervention.

Inappropriate Medications at ICU Discharge

Though PIMs and AIMs may be identified at the time of hospital discharge, the intensive care unit (ICU) is often the place where these medications are first prescribed [21]. Acute hospitalization may increase PIM prescribing because of newly prescribed medications, the presence of multiple prescribers, inadequate medication reconciliation, and a lack of care coordination among inpatient providers or in the transition back to outpatient care [22)].

A known complication of critical illness and ICU stay is a significant increase in psychological symptoms, sleep cycle alterations, delirium, and cognitive impairment, which may be associated with increased prescription of specific PIMs, such as antipsychotics or benzodiazepines [6,23,24]. Despite the lack of reliable evidence supporting their use in the ICU, antipsychotic agents are used routinely in ICU patients [25] to treat a variety of conditions, such as substance withdrawal, agitation not responding to other therapies, or delirium. Results from a multicenter study of 164,996 hospitalizations across 71 academic medical centers in the US showed that 1 out of 10 ICU patients received an antipsychotic during their hospital stay [25]. Jasiak et al estimated that one-third of patients initiated on an atypical antipsychotic therapy for ICU delirium received a hospital discharge prescription for these medications, with a potential annual outpatient medication cost of approximately $2255 per patient [26].

One potential consequence of antipsychotic use in the ICU is their continuation after the transition to other clinical settings, including discharge from the hospital [27] (**Table 1**). A study of 120 elderly ICU survivors found that 12% (14/120) of patients were discharged with a prescription for antipsychotics and for 11 of 14 patients, these drugs were initiated during the ICU admission [21]. Another single-center retrospective study of 59 medical ICU patients showed that antipsychotics were continued in 47% of patients at ICU discharge and in 32% of patients at hospital discharge [26]. Kram et al conducted a retrospective cohort study of 156 patients admitted to an ICU who received at least two doses of an antipsychotic for delirium [28]. Of the 133 survivors, antipsychotic therapy was continued for 84.2% patients upon ICU transfer and for 28.6% patients upon hospital discharge, despite the majority of these patients having evidence of delirium resolution or no indication for continuation of these medications [28]. Similar results were shown by Flurie et al, who found that 26% of patients (23/87) were continued on antipsychotic therapy after their discharge from the medical ICU to the medical ward. Of the 23 patients continued on antipsychotic therapy, 39% (9/23) were discharged from the hospital with an antipsychotic [29]. In a recent study, Tomichek et al showed that 1 out of every 4 antipsychotic-treated patients was discharged on an antipsychotic even though the majority was no longer delirious [27].

When examining the specific factors that may contribute to a patient being discharged on an antipsychotic, authors found that the specific antipsychotic used correlated with risk of continuation [27,30], with atypical antipsychotics having a greater likelihood of being continued than haloperidol [27,30]. Possible explanation for these results could be that physicians perceive less long-term risk from atypical agents, so may be more likely to continue them on discharge [30]. However, such an approach is not always safe. Indeed, although atypical antipsychotic agents tend to cause less tardive dyskinesia, they are known to be associated with similar rates of other adverse events compared with typical agents and have been linked to an increased risk of sudden cardiac death and pneumonia in the elderly [31,32].

Other factors independently associated with being discharged on a new antipsychotic medication were the severity of the acute illness as measured with the Acute Physiology and Chronic Health Evaluation II score at

Table 1. Studies Assessing Antipsychotics Prescription at Intensive Care Unit Discharge

Study	Design	Setting/Participants	Results
Morandi et al 2011 [21]	Prospective cohort study	Tertiary care, academic medical center ICU/ 120 elderly ICU survivors	• 12% (14/120) of patients were discharged with a prescription for antipsychotics; for 11 of 14 patients, these drugs were initiated during the ICU admission
Jasiak et al 2013 [26]	Retrospective study	MICU/ 59 patients	• 47% (28/59) continued on the atypical antipsychotic upon discharge from the medical ICU • 71.4% patients (20/28) were prescribed continued therapy as an outpatient
Kram et al 2015 [28]	Retrospective cohort study	ICU/ 156 patients	• AAP therapy was continued for 84.2% (112/133 survivors) of patients upon ICU transfer and for 28.6% (38/133) patients upon hospital discharge
Flurie et al 2015 [29]	Retrospective chart review	MICU/ 87 patients	• 26% (23/87) were continued on antipsychotic therapy after their transfer from the MICU to the medical ward • 39% (9/23) were discharged from the hospital with an antipsychotic.
Rowe et al 2015 [30]	Retrospective cohort study	Trauma-surgical ICU or neurocritical care unit/341 records	• 24% (82/341) were discharged on a new antipsychotic • 67% without documented indication
Marshall et al 2016 [33]	Retrospective cohort study	Academic medical center ICU/39,248 ICU admissions	• 21% (642/3119 newly-initiated) were continued on therapy on discharge from the hospital
Tomichek et al 2016 [27]	Prospective cohort	MICU and SICU/ 500 patients	• 42%(208/500) treated with an antipsychotic • 24% (42/172) prescribed an antipsychotic at discharge

AAP = atypical antipsychotic prescribing; MICU = medical intensive care unit; SICU = surgical intensive care unit.

ICU admission (odds ratio [OR] 1 [95% confidence interval {CI}, 1.0–1.1]) and days treated with benzodiazepines (OR 1.1 [95% CI, 1.0–1.14]) [30]. Conversely, perhaps due to different practice patterns, Tomichek et al did not find an association between benzodiazepines administration and antipsychotic prescription at discharge in post hoc analyses [27].

Another possible reason for antipsychotic continuation may reside in the indication chosen [33]. Antipsychotic agents have sedative properties and they might be used to optimize sleep during hospitalization, despite the lack of evidence to support this indication [34]. Other factors potentially contributing to continuation of antipsychotics may include persistent delirium and agitation, newly diagnosed psychiatric illness, and difficulties experienced by physicians in deprescribing [35] with improper/incomplete medication reconciliation [33].

The continuation of antipsychotic therapy increased 30-day readmission rates in patients compared to those who had therapy stopped before discharge [33]. In addition to the well-described cardiac effects (prolonged QT interval), neuroleptic malignant syndrome and extrapyramidal symptoms may also occur, and longer-term use can predispose patients to metabolic disturbances, falls, and increase the risk of death in elderly patients with dementia [31].

Benzodiazepines and sedative hypnotics are commonly used to treat insomnia and agitation in older adults despite significant risk. Benzodiazepine administration was found to be an independent risk factor for a daily transition to delirium [36,37]. Pandharipande et al reported that every unit dose of lorazepam was associated with a higher risk for daily transition to delirium (OR 1.2, 95% CI 1.1–1.4, $P = 0.003$) [36] in critically ill patients. A more recent analysis found for every 5 mg of midazolam administered to a patient who is awake and without delirium, there is a 4% chance that this patient will develop delirium the next ICU day [37].

Given that the risk for benzodiazepine-associated delirium is dose-dependent, clinicians should use strategies known to reduce the daily number of benzodiazepines administered that often includes the use of a

sedative associated with less delirium occurrence, such as dexmedetomidine or propofol [38]. Evidence has shown that long-term use of benzodiazepines has little benefit with many risks, including an increased susceptibility to spontaneous bacterial infection [39,40] and mortality in the setting of infection [41]. Nakafero et al showed that exposure to benzodiazepines was associated with increased occurrence of both influenza-like-illness–related pneumonia and mortality. Benzodiazepine use was associated also with increased occurrence of asthma exacerbation and with increased all-cause mortality during a median follow-up of 2 years in a cohort of asthmatic patients [42] as well with an increased risk of pneumonia and long-term mortality in patients with a prior diagnosis of community- acquired pneumonia [40]. Long-term use of benzodiazepines is also associated with increased risk of falls [43–45], cognitive impairment [46–48] and disability [49,50].

Other common types of PIMs at ICU discharge were opioids, anticholinergic medications, antidepressants, and drugs causing orthostatic hypotension [6]. Of the anticholinergic AIMs, H2 blockers (61%) and promethazine (15%) were the most common [6]. Only 16% of opioids, 23% of antidepressants, and 10% of drugs causing orthostatic hypotension were found to be actually inappropriate after the patient's circumstances were considered (eg, postoperative pain control, a new diagnosis of major depressive disorder) [6].

Inappropriate Medications at Hospital Discharge

Medications typically intended for short-term use during acute illness are sometimes continued after discharge without documented indication [51]. Poudel et al found that in 206 patients 70 years of age and older discharged to residential aged care facilities from acute care, at least 1 PIM was identified in 112 (54.4%) patients on admission and 102 (49.5%) patients on discharge [11]. Commonly prescribed PIM categories, at both admission and discharge, were central nervous system, cardiovascular, gastrointestinal, and respiratory drugs and analgesics [6,11,52,53]. Of all medications prescribed at admission (1728), 10.8% were PIMs, and at discharge, of 1759 medications, 9.6% were PIMs. Of the total 187 PIMs on admission, 56 (30%) were stopped, and 131 (70%) were continued; 32 new PIMs were introduced [11].

Morandi et al in 2011 conducted a prospective cohort study including 120 patients age ≥ 60 who were discharged after receiving care in a medical, surgical, or cardiovascular ICU for shock or respiratory failure. The percentage of patients prescribed at least 1 PIM increased from 66% at pre-admission to 85% at discharge. The number of patients with 0 PIMs dropped from 34% at preadmission to 14% at discharge, and the number of patients with 3 or more PIMS increased from 16% at preadmission to 37% at discharge. While it is possible that these drugs may be appropriate when started during an acute illness in the ICU (eg, stress ulcer prophylaxis with H2-antagonists in mechanically ventilated patients), most should have been discontinued at ICU and/or hospital discharge [21].

Inappropriate prescriptions of proton pump inhibitors (PPIs) in hospital and primary care have been widely reported [54,55]. In a study conducted by Ahrens et al in 31 primary care practices, for 58% (263/506) of patients discharged from 35 hospitals with a PPI recommendation in hospital discharge letters, an appropriate indication was missing. In 57% of these cases general practitioners followed this recommendation and continued the prescription for more than 1 month [54]. The strongest factor associated with appropriate and inappropriate continuation of PPI after discharge was PPI prescription prior to hospitalization [54]. Although PPIs are safe, they can cause adverse effects. PPI intake has been found to have a significant association with risk of community-acquired pneumonia [56,57], hip fractures [58], *Clostridium difficile*-associated diarrhea [55,61,62], and to reduce the therapeutic effects of bisphosphonates [59] and low-dose aspirin [60].

Unintentional medication continuation is not a problem isolated to a single drug class or disease [63]. Scales et al evaluated rates of and risk factors for potentially unintentional medication continuation following hospitalization in a population of elderly patients (≥ 66 years) [51]. They created distinct cohorts by identifying seniors not previously receiving four classes of medications typically used to treat or prevent complications of acute illness: antipsychotic medications; gastric acid suppressants (ie, histamine-2 blockers and proton pump inhibitors); benzodiazepines; and inhaled bronchodilators and steroids [51]. Prescription without documented indication occurred across all medication classes, from 12,209 patients (1.4 %) for antipsychotic medications to 34,140 patients (6.1 %) for gastric acid suppressants [51].

Several potential risk factors were considered. The relationship between multimorbidity and polypharma-

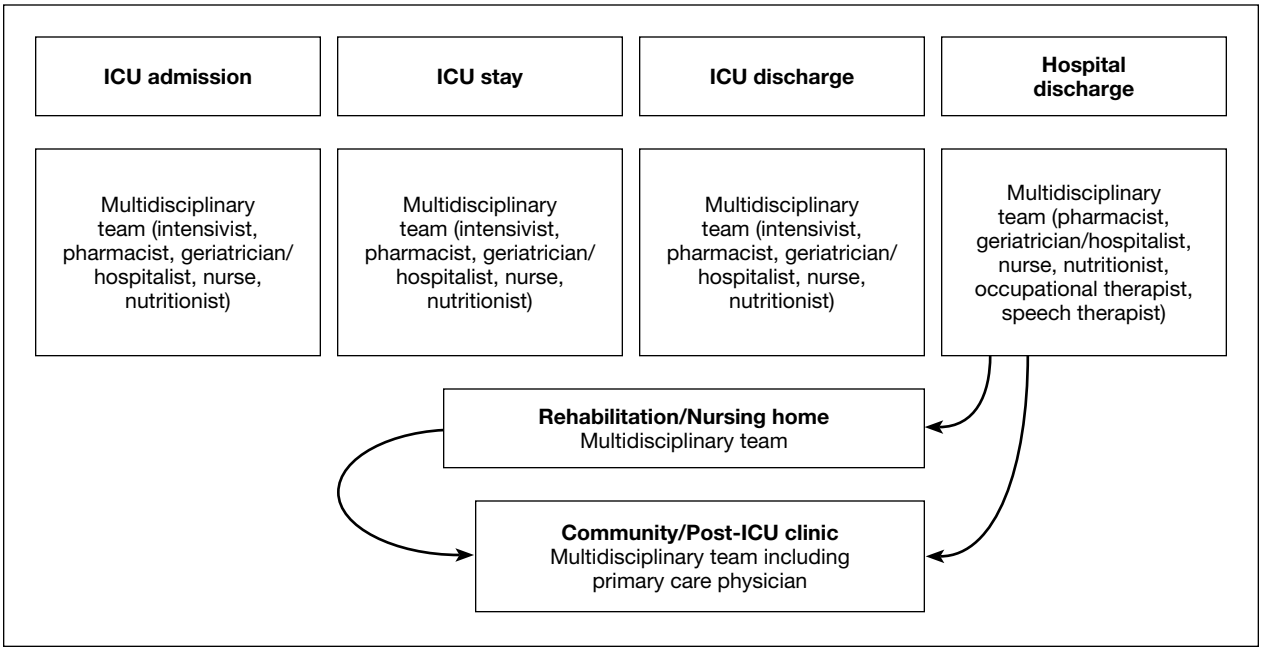

Figure. A multidisciplinary team should be involved in the medication reconciliation at each care transition.

cy is well described in the literature, and several studies have identified a positive association between the number of drugs and the use of PIMs [64–66]. Conversely, Poudel et al did not find any association between polypharmacy and PIM use [11]. Associations were found between the use of PIMs, frailty status, and cognitive decline of patients at admission and at discharge [11], while no association was observed with age, gender, in-hospital falls, delirium, and functional decline [11,67]. Other potential risk factors of a high number of PIMs at discharge were a high number of pre-admission PIMs, discharge to a location other than home, and discharge from a surgical service [1,6,68,69]. Length of ICU stay and mechanical ventilation had a positive influence on the number of PIMs used by acutely ill older patients [11,63,69]. In the study of Scales et al, the greatest absolute risk factor across all medication groups was longer hospitalization. The increased OR for medication continuation after a hospitalization lasting more than 7 days ranged from 2.03 (95% CI 1.94–2.11) for respiratory inhalers to 6.35 (95% CI 5.91–6.82) for antipsychotic medications [51].

Inappropriate Medications: Where and How to Intervene?

Early detection of PIMs may prevent adverse drug events and improve geriatric care in older adults [13,70]. PIM prevalence can often be a useful indicator of prescribing quality [2]. Appropriate interventions and an improved quality of prescribed medications require appropriate assessment tools to decrease the number of patients discharged on these medications [71,72]. Medication reconciliation is the process of avoiding inadvertent inconsistencies within a patient's drug regimen, which can occur during transitions in different setting of care [73]. A multidisciplinary team should be involved in the medication reconciliation at each care transition to reevaluate medications use according to the clinical conditions, cognitive/functional status and the coexistence of geriatric syndromes (eg, dementia, malnutrition, delirium, urinary incontinence, frailty) (**Figure**). Medication reconciliation should be performed at ICU admission, ICU discharge, and hospital discharge. At discharge, effective communication between the hospital team and the outpatient provider should include timely, accurate, and complete documentation of indication, dosage, frequency, route of administration, and planned duration of use of all medications. This approach would allow the primary care practitioners and the caregivers to understand the reason why the patient is on a given medication, and thus providing them with the necessary information to discontinue or continue the therapy. Patients might then be discharged home or to rehabilitation or nurs-

ing home settings. A post discharge follow-up should then be performed in each setting to reevaluate the appropriateness of medications prescribed in the previous settings or to evaluate the necessity to initiate necessary drugs according to the patients' conditions.

Criteria for the Evaluation of Inappropriate Medications Prescription

Explicit criteria derived from expert reports or published reviews are available (**Table 2**). These have high reliability and reproducibility but focus mainly on specific drugs and disease states. Although these criteria address some aspects of prescribing in older patients, they seldom consider the frailty of such patients. The omission of health status from established prescribing tools may help explain the lack of clinical benefit from algorithm-based medication reviews [74]. The American Geriatrics Society (AGS) Beers criteria for potentially inappropriate medications use in older adults is an explicit list of PIMs best avoided in older adults in general and in those with certain diseases or syndromes, prescribed at reduced dosage, with caution or carefully monitored [75]. The Beers criteria are commonly used, and they do measure some surrogates of frailty. They were originally developed in 1991 [76] for use in the older nursing home population and have been subsequently updated to apply to all persons older than 65 years, regardless of their place of residence [18]. The recently updated Beers criteria divides medications into 3 main categories according to major therapeutic classes and organ systems: 34 medications are considered potentially inappropriate, independent of diagnosis; 14 are to be avoided in older adults with certain diseases and syndromes that can be exacerbated by the listed drug, and 14 others are to be used with caution in older adults [18]. In 2015 two major components were added: (1) drugs for which dose adjustment is required based on kidney function and (2) drug-drug interactions [18,77].

Beers criteria PIMs have been found to be associated with poor health outcomes, including confusion, falls, and mortality [7,75,78]. The STOPP (Screening Tool of Older Person's potentially inappropriate Prescriptions) and START (Screening Tool to Alert doctors to the Right Treatment) are evidence-based sets of criteria that were developed in Ireland and updated in October 2014, including some of the new criteria for direct oral anticoagulants, drugs affecting or affected by renal system and anti-muscarinic/anticholinergic agents [79]. The updated STOPP/START criteria are considered more sensitive and specific for the detection of inappropriate prescription than the previous version [80,81]. The criteria are organized according to the physiological systems to which each relates, thereby enhancing their usability and refer to classes of medications [80,81]. The STOPP and START tools are scored by the summary of the number of medications that meet certain criteria, with each potentially inappropriate medication and potential prescribing omission generating 1 point [82]. Previous research indicates that a 0.5–decrease in STOPP score yielded a 17% risk reduction in medication-related hospital admissions [83]. Some studies that compared STOPP and Beers criteria revealed a greater correlation between drug-related adverse events and PIMS defined with the former, suggesting that the STOPP criteria may be more helpful clinically [84,85].

Several other sets of criteria have been published to identify PIMs, such as the FORTA (Fit for the Aged) and the PRISCUS [86] criteria. FORTA allows a disease-related evaluation revealing over-treatment and under-treatment, and medications are graded as follows: **A**, indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication; **B**, drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns; **C,** drugs with questionable efficacy/safety profiles in the elderly which should be avoided or omitted in the presence of too many drugs or side effects; **D,** avoid in the elderly, omit first, refer also to negative listings. Negative lists such as PRISCUS, which provide an explicit listing of drugs, independent of the diagnosis, are easy to use. On the other hand, constant updates are needed, and such lists carry the risk of an assumption that drugs not listed would be appropriate in every case [87]. Both sets of criteria have in common that they refer to long-term medication and drugs frequently used during the inpatient stay, such as antibiotics, are hardly taken into account [87].

The Medication Appropriateness Index measures overall prescribing quality through 10 separate but interrelated domains [8]. Three components are used to detect PIMs: indication, effectiveness, and duplication. However, it does not give any precise guidance in relation to specific medicines and therefore has limited application for objectively defining PIMs.

Table 2. Criteria for the Evaluation of Inappropriate Medications Prescription

Criteria	Description	Disadvantages	Advantages
Beers [75,112]	53 medications/drug classes • Potentially inappropriate in all older people • Potentially inappropriate in older people with certain diseases • Drugs to be used with caution in older people • Drugs for which dose adjustment is required based on kidney function • Drug–drug interactions	• Include several medications that are not available in European formularies or are rarely prescribed in Europe • Several of the medications listed are rarely used in everyday clinical practice, in particular, in the older patient • Certain drugs listed in the Beers criteria as being absolutely contraindicated in older people, irrespective of diagnosis	• Comprehensive list of PIMs and are well organized and accessible • Easy to use, both in clinical and r esearch settings • Easily incorporated into computerized decision support systems to prevent inappropriate use and in reviews of administrative claims databases to determine the prevalence and predictors of use • Specific recommendations and quality of evidence are provided
STOPP/START [79,82,83,112]	STOPP: 65 criteria according to the physiological systems to which each relates. They include drug-drug and drug-disease interactions with specific sections for analgesic drugs, drugs that adversely affect older patients at risk of falls and duplicate drug class prescriptions. START: 22 criteria address commonly encountered instances of potentially inappropriate underprescribing, where no contraindication to prescription exists and where life expectancy and functional status justifies the prescription Are scored by totaling the number of medications that meet certain criteria, with each potentially inappropriate medication and potential prescribing omission generating 1 point	• Does not evaluate medication underuse • Need continuous updating	• Good inter-rater reliability between physicians and pharmacists • Inclusion of medications used both in the United States and in Europe • Logical organization and structure with easy-to-use explicit lists of medication criteria • Short time to complete, usually about 3 minutes
FORTA [87]	Disease-related evaluation revealing over- and under-treatment. Medications are graded as follows: **A:** Indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication; **B:** Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns; **C: Drugs with questionable efficacy/safety profiles in the elderly which should be avoided or omitted in the presence of too many drugs or side effects;** **D:** Avoid in the elderly, omit first, refer also to negative listings	• Further validation in controlled studies is needed before widespread use • Drugs frequently used during the inpatient stay are hardly taken into account	

(continued on page 74)

Table 2. Criteria for the Evaluation of Inappropriate Medications Prescription (*continued*)

Criteria	Description	Disadvantages	Advantages
PRISCUS [86]	83 drugs in a total of 18 drug classes were rated as potentially inappropriate for elderly patients	• Drugs frequently used during the inpatient stay are hardly taken into account	
MAI [8,22,112]	Assesses prescribing appropriateness using 10 criteria: • Indication • Effectiveness • Dose • Correct direction • Practical directions • Drug-drug interactions • Drug-disease interactions • Duplication • Duration • Cost Each medication is rated as *appropriate*, *marginally appropriate*, or *inappropriate* according to each of the criteria, with each individual rating receiving a weighted score. Indication, effectiveness, and duplication can be used without the other 7 components to detect polypharmacy and inappropriate prescribing. The scores are then summed to provide a summary measure of appropriateness for each medication, ranging from 0 (completely appropriate prescription) to 18 (completely inappropriate prescription)	• At least 10 minutes to complete the entire tool • Does not address the underuse of appropriate prescribing • Despite good intra-rater and inter-rater reliability, clinical judgment can be subjective and result in inconsistent application	• Can be used in inpatient and ambulatory settings • Good intra-rater and inter-rater reliability among hospital pharmacists and hospital physician
IPET [88,89,112]	• 45 different medications in 14 classes of drugs considered inappropriate identified from an extensive list of inappropriate prescription instances drawn up by an expert • Strong emphasis on cardiovascular and psychotropic drugs as well as NSAIDs	• Three of the 14 categories in the tool relate to the use of tricyclic antidepressants, now infrequently prescribed in older people • Does not evaluate drug-disease or drug-drug interactions • Insufficient convincing evidence regarding the use of IPET to reduce the incidence of adverse drug events, health resource utilization, or mortality adverse effects	• Quick reference for clinicians

Table 2. Criteria for the Evaluation of Inappropriate Medications Prescription (*continued*)

Criteria	Description	Disadvantages	Advantages
Drug utilization reviews [16]	Consensus opinion by drug therapy experts to define standards or explicit criteria for a single drug, class of drugs, or group of drugs. Identify problems such as dosage range, duration, therapeutic duplication, excessive dosage, drug-drug interactions and therapeutic duplication 3 categories: • Prospective: evaluation of a patient's drug therapy before medication is dispensed • Concurrent: ongoing monitoring of drug therapy during the course of treatment • Retrospective: review of drug therapy after the patient has received the medication		

FORTA = Fit for the Aged; IPET = Inappropriate Prescribing in the Elderly Tool; MAI = Medication Appropriateness Index; START = Screening Tool to Alert doctors to the Right Treatment; STOPP = Screening Tool of Older Person's potentially inappropriate Prescriptions.

Another prescribing quality assessment tool is the Inappropriate Prescribing in the Elderly Tool (IPET), which consists of a list of the 14 most prevalent prescription errors identified from an extensive list of inappropriate prescription instances drawn up by an expert Canadian Consensus Panel [88,89].

Another approach to assess the appropriateness of drugs prescribed for older people is the use of Drug Utilization Reviews (DURs) [16]. DURs use consensus opinion by drug therapy experts to define standards or explicit criteria for a single drug, class of drugs, or group of drugs [16]. DURs typically use retrospective information from large, nonclinical administrative databases to identify problems such as dosage range, duration, therapeutic duplication, and drug interactions [90, 91]. Monane et al [92] evaluated a program designed to decrease the use of PIMs among the elderly through a computerized online DUR database. Computer alerts triggered telephone calls to physicians by pharmacists to discuss a potential problem and any therapeutic substitution options. From a total of 43,007 telepharmacy calls generated by the alerts, they were able to reach 19,368 physicians regarding 24,266 alerts (56%). The rate of change to a more appropriate therapeutic agent was 24% (5860), but ranged from 40% for long half-life benzodiazepines to 2% to 7% for drugs that theoretically were contraindicated by patients' self-reported history [92].

Computerized Support Systems to Reduce Inappropriate Prescribing in the Elderly

Other potential solutions for reducing inappropriate medications may include continuing medical education, electronic medical records surveillance, routine clinical evaluation, and/or improved hand-off communication between discharging and accepting providers. Incorporating this assessment of medication appropriateness into the medication reconciliation process when patients are discharged or transferred out of the ICU has the potential to enhance patient safety [21,93]. A randomized controlled trial conducted by Raebel et al [94] reported the effectiveness of a computerized pharmacy alert system plus collaboration between health care professionals for decreasing potentially inappropriate medication dispensing in elderly patients. Another study showed that computer-based access to complete drug profiles and alerts about potential prescribing problems reduced the occurrence of potentially inap-

Table 3. Studies Assessing the Effects of Computerized Support Systems on Reducing Inappropriate Prescribing in the Elderly

Study	Design	Participants	Intervention Type	Outcome Measures	Results
Monane et al 1998 [92]	Cohort study	23,269	Computerized alerts triggered telephone call to physician by pharmacist	Contact rate with physician and change rate to suggested drug regimen over 1-year period	• Contact rate for reaching the physician was 56% • Rate of change to a more appropriate therapeutic agent was 24% ($P < 0.001$).
Raebel et al 2007 [94]	Randomized controlled trial	29,840 Intervention 29,840 Usual care	Medication alert to pharmacist regarding inappropriate prescription	Number of inappropriate medications dispensed to elderly during intervention period of 1 year	• Newly dispensed prescriptions for inappropriate medications were 1.8% for intervention group and 2.2% in usual care group ($P = 0.002$)
Tamblyn et al 2003 [95]	Cluster randomized control design	6284 Intervention 6276 Control	Physician provided with computerized decision support system	Initiation and discontinuation rates of inappropriate prescriptions	• Number of new inappropriate prescriptions was significantly lower compared with control group (relative rate, 0.82 [95% confidence interval, 0.69–0.98])

propriate prescriptions [95]. A summary of these studies is shown in **Table 3**.

Interdisciplinary Teams to Reduce Inappropriate Prescribing in the Elderly

Some studies evaluated the effect of multidisciplinary teamwork in improving inappropriate medication prescribing in the elderly (**Table 4**). An interdisciplinary team, involving a geriatrician, together with nurses, dietician, occupational therapist, physiotherapist, speech therapist, psychologist, and psychiatrists, reduced the total number of PIMs prescribed at discharge and serious adverse drug reactions [3,93,96–101]. Conversely, another study showed that patients treated in a geriatrics evaluation and management unit (GEMU) had a statistically significant difference in appropriateness of drug profiles compared with patients in general wards, in terms of prescription of fewer drugs with anticholinergic effects, psychotropic drugs, and cardiovascular drugs [102]. The important role of comprehensive geriatric evaluation to reduce the risk of serious adverse drug reactions and suboptimal prescribing in elderly patients was confirmed by Schmader et al who evaluated the effect of inpatient and outpatient geriatric evaluation and management, as compared with usual care, in reducing adverse drug reactions and suboptimal prescribing in frail elderly patients. Between discharge and 12 months, patients receiving care from geriatric evaluation and management clinics had a 35% reduction in the risk of serious adverse drug reactions compared with usual outpatient care [97].

Pharmacists in hospitals can play a significant role in the initiation of changes to patient's therapy and management [11] (**Table 5**). Medication review by the pharmacist in an acute care or primary care setting and at discharge from the ICU and the hospital can reduce inappropriate prescribing and possibly avoid adverse drug effects without adversely affecting health-related quality of life [103–107]. Moreover, a pharmacist transition coordinator was shown to improve aspects of inappropriate use of medicines across health sectors [108]. Different results were showed by Lau et al in a national survey between nursing homes and residents, who found that the presence of a consultant pharmacist had no effect on potentially inappropriate prescriptions [9]. However, they did not specify the extent of the pharmacists' involvement and it is, therefore, uncertain whether this finding adequately reflects the effectiveness of a consultant pharmacist on the quality of prescribing in nursing homes [93].

Mattison et al recently emphasized that studies of PIMs should determine scenarios in which it is appropriate to prescribe PIMs, moving beyond simply labeling some medications as "potentially inappropriate," since some PIMs are appropriately prescribed in

Table 4. Studies Assessing the Effects of Interdisciplinary Team on Reducing Inappropriate Prescribing in the Elderly

Study	Design	Participants	Intervention Type	Outcome Measures	Results
Allard et al 2001 [99]	Randomized controlled trial	136 Intervention 130 Control	Pharmacist, 2 physicians, 1 nurse	Number of PIPs (Quebec Committee on Drug Use in the Elderly)	• Mean number of PIPs per patient declined by 0.24 in the experimental group (n = 127) and by 0.15 in the control group (n = 116) • Decline in PIPs was even larger in the experimental group that had case conferences (n = 80), in which the mean number of PIPs per patient declined by 0.31 • Difference between the experimental group and the control group was not statistically significant in the intent-to-treat analysis • Number of drugs prescribed was not modified by the intervention, nor were the results of the global assessment of the patients' drug profiles
Elliott et al 2001 [101]	Cross-sectional study	1301 patients	Intervention based on audit and multidisciplinary staff feedback	Prevalence and appropriateness of benzodiazepine prescribing (evidence-based prescribing indicator)	• At baseline, benzodiazepines were prescribed for 36% of patients, and 20% of prescriptions were appropriate • 4 to 6 weeks after feedback, more prescriptions were appropriate (44%, $P < 0.001$). • For patients who were using a benzodiazepine prior to admission and had a contraindication, there were more attempts to withdraw or reduce the dose (47% vs 21%, $P = 0.002$) and more prescriptions were for acceptable indications (7.4% vs 2.6%, $P = 0.024$). • 6 months after feedback, appropriateness of prescribing remained improved compared with baseline (50%, $P = 0.002$)
Schmader et al 2004 [97]	Randomized controlled trial	430 Intervention 404 Control	Multidisciplinary geriatric team (geriatrician, social worker, nurse)	ADRs and inappropriate drug use (MAI and Beers' criteria)	• GEMU was associated with significant reductions ($P < 0.05$) in the number of unnecessary drugs, MAI score, and number of inappropriate drugs
Crotty et al 2004 [98]	Randomized controlled trial	154 residents	2 multidisciplinary case conferences (including a geriatrician, GP, pharmacist, and residential care staff)	Appropriateness of medications (MAI)	• Medication appropriateness improved in the intervention group (MAI mean change 4.1 [95% CI 2.1—6.1]) compared with control group (MAI mean change 0.4 [95% CI –0.4 to 1.2]; $P < 0.001$)
Saltvedt et al 2005 [102]	Randomized trial	254 patients	Multidisciplinary geriatric team care including a geriatrician	Inappropriate drug prescribing (Beers' Criteria)	• 13 (10%) GEMU patients and 12 (9%) medical ward patients prescribed inappropriate medications at inclusion compared with (4%) GEMU patients and 7 (6%) medical ward patients at discharge (statistically insignificant differences)

(continued on page 78)

Table 4. Studies Assessing the Effects of Interdisciplinary Team on Reducing Inappropriate Prescribing in the Elderly (*continued*)

Study	Design	Participants	Intervention Type	Outcome Measures	Results
Spinewine et al 2007 [100]	Randomized controlled trial	203 patients	GEM care (control group) or pharmaceutical care in addition to GEM care (intervention group)	Appropriateness of prescribing on admission, at discharge, and 3 months after discharge (MAI, Beers and ACOVE criteria)	• Intervention patients, compared to controls, have an improvement in the MAI and in the ACOVE underuse criteria from admission to discharge [OR 9.1 [95% CI 4.2–21.6] and OR 6.1 [95% CI 2.2–17.0], respectively).
Lang et al 2012 [3]	Prospective and interventional study	150 acutely ill elderly patients	Interdisciplinary geriatric and psychiatric care	Appropriateness of prescribing at admission and discharge (STOPP/START criteria)	• Compared with admission, the intervention reduced the total number of medications prescribed at discharge from 1347 to 790 ($P < 0.001$) • Incidence rates for PIMs and prescribing omissions reduced from 77% to 19% ($P < 0.001$) and from 65% to 11% ($P < 0.001$), respectively
Dalleur et al 2014 [96]	Randomized controlled study	46 frail patients (ISAR score ≥ 2/6)	Multidisciplinary team (nurses, geriatricians, dietician, occupational therapist, physiotherapist, speech therapist, psychologist)	Appropriateness of prescribing (STOPP criteria)	• Discontinuation at discharge of PIMs present on admission was twice as high in the intervention group as in the control group (39.7 vs. 19.3 %; OR 2.75 [CI, 1.22–6.24]; $P = 0.013$)

ACOVE = Assessing Care of Vulnerable Elders; ADRs = adverse drug reactions; CI = confidence interval; GEMU = geriatric evaluation and management unit; GP = general practitioner; ISAR = Identification of Seniors At Risk; MAI = Medication Appropriateness Index; OR = odds ratio; PIMs = potentially inappropriate medications; PIPs = potentially inappropriate prescriptions.

specific clinical situations [109]. Morandi et al showed that the positive predictive value (PPV) depends on the drug type. Thus, when developing a screening system, one cannot be concerned only with high negative predictive value (NPV), one must consider PPV as well [6]. Screening tools that include medication classes with low PPV will generate false positive "flags" or warnings, which could lead to misguided clinical decisions [6]. The fact that many PIMs are not AIMs also reveals the value of using a multidisciplinary team to identify AIMs from lists of PIMs generated when discharge medication lists are screened [6,110]. Thus, a multidisciplinary team is needed to consider the clinical context to distinguish PIMs from AIMs [6]. Of course, such a team is not available in some settings; when resources are limited, knowledge of which PIMs are most likely AIMs (ie, have high PPVs) could guide the development of computer-based decision support systems or other surveillance approaches that are efficient in that particular setting [6].

Approaches for optimizing prescribing in this population mainly depend on patient needs and comorbidities and most available data are derived from randomized controlled trials involving a single drug. Such trials do not take into account the confounding effects of multiple comorbidities and patient preferences. Therefore, approaches for optimizing prescription management that are available for and validated in younger patients are not applicable to elderly subjects [3,111].

Conclusion

Clinicians should seek to identify and discontinue AIMs at 3 important transitions during a critically ill elderly patient's hospital course: at the time of hospital or ICU admission; at ICU discharge; and at hospital discharge. The patient's clinical situation should be reviewed at every transition points, ideally by a multidisciplinary team of clinicians, to judge the appropriateness of each PIM [6]. After the hospital discharge, patient's medications should be then reviewed by a multidisciplinary team and/or by the primary care physician according to the

Table 5. Studies Assessing the Effects of Interventions by Pharmacists on Reducing Inappropriate Prescribing in the Elderly

Study	Study Design	Participants	Intervention	Outcome Measures	Results
Lipton et al 1992 [104]	Randomized controlled trial	123 Intervention 113 Control	Medication review at hospital discharge and at periodic intervals for 3 months post discharge	Scheduling, appropriateness, dosage and omitted but necessary therapy	• Overall appropriateness of prescribing score differed significantly between experimental (mean –SE 0.59–0.05) and control (0.76–0.05) groups ($P = 0.01$).
Hanlon et al 1996 [103]	Randomized controlled trial	88 Intervention 80 Control	Medication review and written recommendations to physician	Prescribing appropriateness (MAI)	• MAI declined significantly in interventions vs control group at 3 months (24% vs 6%; $P = 0.0006$) and 12 months (28% vs 5%; $P = 0.0002$).
Krska et al 2001 [105]	Randomized controlled trial	168 Intervention 164 Control	Medication review	Resolution of pharmaceutical care issues, use of health and social services and health-related quality of life	• In intervention group inappropriate dosage regimen was found in 5.7% of and was resolved in 78.3% cases • In the control group, inappropriate dosage regimen was found in 6.5% and was resolved in only 17.9% cases ($P < 0.001$)
Brown and Earnhart 2004 [106]	Retrospective case series	99	ACE team pharmacist consulted all patients care including a geriatrician	Prevalence of PIMs (Beers' criteria)	• Upon admission, 10.1% were PIMs compared with 2.02% on discharge ($P < 0.02$).
Lau et al 2004 [9]	Survey	1588 Intervention 1814 Control	Weekly onsite availability of consultant pharmacist	PIMs	• No significant relationship between PIMs and weekly onsite availability of consultant pharmacist. For intervention group, OR 0.96 (95% CI 0.81–1.14) and for control group, OR 1.00 (95% CI 1.00–1.00)
Crotty et al 2004 [108]	Randomized controlled trial	56 Intervention 54 Control	Medication management transfer summary and medication review by community pharmacist followed by case conference	PIMs (MAI)	• At 8-week follow-up, the mean MAI was significantly lower in the intervention group than in the control group (2.5 [95% CI 1.4–3.7] vs 6.5 [95% CI 3.9–9.1]; $P = 0.007$)
Belfield et al 2017 [107]	Retrospective interventional study	61 Historical group 81 Intervention group	Intervention by clinical pharmacists	Proportion of inpatient days with inappropriate AST	• Intervention resulted in a 31% absolute reduction in inappropriate patient days of AST and a 24% absolute reduction in patients discharged on inappropriate AST

ACE = Acute Care for Elders; AST = acid suppressive therapy; CI = confidence interval; MAI = Medication Appropriateness Index; OR = odds ratio; PIMs = potentially inappropriate medications. SE = standard error.

final discharge destination (ie, home, nursing home, rehabilitation) by using any of the validated tools. Regardless of the approach, it is clear that standardized care processes, including enhanced clinical decision support, are necessary to ensure that physicians do not continue exposing our patients to unnecessary medications and harm after discharge.

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