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Development of a Risk Assessment Tool for Falls Prevention in Hospital Inpatients Based on the Medication Appropriateness Index (MAI) and Modified Beer's Criteria

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Abstract
Medication review is an essential component of comprehensive falls assessment. A medication review by pharmacists can assist to identify and notify prescribers of medications that require adjustment or discontinuation. Beers Criteria and the Medication Assessment Index (MAI) are explicit and implicit inappropriate prescribing (IP) tools, respectively. While the Beers Criteria has been applied to falls prevention, the MAI has not. Developing alternative falls prevention tools has been spurned by both the desire to overcome limitations of the Beers Criteria, coupled with the need for implicit criteria which includes consideration for patient – specific clinical judgement. A literature search and review of the Beers Criteria and MAI tools revealed advantages and disadvantages of each. Using combined explicit/implicit falls assessment criteria using both the Beers Criteria and MAI as a framework, a falls specific inappropriate prescribing (FASPIP) tool for use in elderly hospitalized patients was developed. Validation of the FASPIP in the clinical setting is needed.

Falls and recurrent falls are the leading cause of injury–related death and the most common cause of nonfatal injuries and hospital trauma admissions among older adults [1]. Approximately 10% of fatal falls for older adults occur in the hospital setting [2]. From 2001 to 2008, the estimated number of fall-related hospitalizations in older adults increased 50% [3]. However, there is better evidence for falls prevention in the community versus hospital setting. The Joint Commission specifically requires that patients in hospitals and long term care facilities be assessed for fall risk..."including the potential risk associated with the patient's medication regime [4]." A National Patient Safety Goal to reduce the risk of patient harm resulting from falls has been established [4]. Further, the Centers for Medicare & Medicaid Services will no longer reimburse for preventable injuries from falls sustained by Medicare beneficiaries during their hospital stay.

Inappropriate prescribing and polypharmacy are among the strongest risk factors for falls in the elderly [5]. Moreover, they are *modifiable* risk factors. Yet we lack an appropriate, specifically designed assessment tool to screen and detect inappropriate prescribing (IP). While several tools have been described for the purposes of assessing IP in general (Inappropriate Prescribing in the Elderly Tool (IPET) [6], the Beers Criteria [7], the Medication Appropriateness Index (MAI) [8], the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) [9], and Screening Tool to Alert Doctors to the Right Treatment (START)[10]), their validity is controversial, their adoption in clinical practice and health services research is heterogeneous and their applicability and benefit to falls prevention is uncertain. When used individually, these tools fail to provide an integrative framework for fall prevention which considers patient's active complaints, other conditions and medications, and adverse drug effects [11]. In fact, no medication screening tools that have good diagnostic properties have been reported in the literature for fall risk in hospital patients [12]. Further efforts are warranted to improve existing tools and facilitate their usage in hospitalized patients.

In this paper, we aim to critically review the two most frequently used tools to assess IP, the Beers criteria and the Medication Appropriateness Index (MAI), and using a structured framework develop a falls specific IP assessment tool (FASPIP).

Beers Criteria

The Beers Criteria are the most commonly and internationally used criteria to assess IP; having been adopted by various healthcare settings and incorporated into federal quality regulations and measures for managed care plans. The most recent Beers criteria list consists of 48 medications and medication classes (78 medications altogether) some of which contribute to the risk of falls through various

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pharmacologic mechanisms, such as orthostasis, dizziness, decreased postural reflexes, extrapyramidal symptoms, drugging, myorelaxant effects, visual impairment, impaired cognition and sedation[7]. The Criteria also lists medications to be avoided in the presence of 20 conditions or diseases, not necessarily pertaining to falls. Also included in the Beers Criteria is a dose-related list, i.e., drugs that should not exceed a maximum dose. So the criteria include three categories: a general list, dose-related list and comorbidity list.

Beers Criteria Advantages

The Beers listing provides simple, easy to follow, reproducible, inexpensive to assess and explicit criteria for identifying IP. Explicit measures are designed to be a standard that can be applied to all patients, computerized and easily assessed in large patient samples [13]. The criteria are adaptable to administrative datasets using computerized algorithms. The criteria were developed with consensus methodology using the Delphi method and are based on literature reviews. Additionally, use of the criteria does not require information about the indication for the drug.

Explicit "drugs to avoid" criteria have been applied to falls prevention, in part due to their easy applicability whereas tools such as the MAI are rarely applied due to their need for comprehensive clinical information interpreted by a skilled individual. Thus, the Beers Criteria are the most widely used falls-assessment tool and have been adopted for use in Long Term Care facilities in the U.S [13].

Beers Criteria Limitations

Beers Criteria was developed to detect IP; it was not designed as a fall-specific tool. Further, it was developed for a different health care system than hospitals, i.e., nursing homes. Medications are included on the list with little falls potential (e.g. ticlopidine, nitrofurantoin) and in some cases medications are inappropriately listed. Although it provides an excellent foundation, there is a growing body of evidence regarding the limitations of the Beers Criteria, including limited reliability in the hospital setting. Several studies observed that the use of Beers Criteria alone misses a significant amount of IP [14]. Concerns have been raised about the generalizability of Beers criteria to falls prevention in the hospital setting. Ackroyd-Stolanz noted that use of Beers Criteria alone for identifying older hospitalized patients at risk of falls failed to identify the vast majority of falls [15]. The difference in potential IP between patients who fell and those who did not was nonsignificant (10.9% vs. 9.3%, p = 0.27) [12]. Holguin-Hernandez noted the need to adapt and complement the Beers Criteria and that 25.1% of hospitalized patients received medications that can cause falls, not included in the Beers Criteria [16]. Others have observed a correlation between IP and falls [17].

Beers Criteria, originally developed in 1991 [18], and updated in 1997 [19] and 2002 [7], has not been updated in over 10 years. The criteria are not an exhaustive list of all medications known to be associated with increased risk of falls (e.g. loop diuretics). A drug on the list may represent IP, not because of its risk for falls but because of its risk of ADR in general. In some cases, drugs on the list should be avoided generically (e.g. digoxin in doses > 125 mcg/day). In most cases no threshold (e.g. creatinine clearance or GFR) is provided to identify high risk patients. In other cases, IP depends on the dosage or duration of treatment. Many drugs not listed in the criteria have subsequently been associated with a high incidence of falls in older patients. Some of these medications represent classes of medications not known at the time the criteria were developed. As new drugs were approved, the list was not updated. For example, evidence is building that SSRIs increase fall risk as much as the older tricyclic antidepressants [20]. Other agents have been removed from the U.S. market (e.g. guanidine, propoxyphene) or are older, outdated and not commonly used. Some of the drugs on the criteria are used more commonly outside the U.S.

The criteria also omit other prescribing considerations such as dosing, duration of therapy, polypharmacy, drug interactions, or under use. For example, use of four or more medications has been linked with an increased risk of falls for older patients [21]. Beers Criteria does not consider the effect of combinations of medication classes, nor does the list include over-the-counter medications or herbal products. Since the listing is based on a literature review and consensus, not all the criteria are evidence-based or based on strong-empirical data linking them to falls. Additionally, being an explicit approach, Beers criteria does not account for a risk/benefit analysis based on patient-specific clinical judgments, thus determinations refer to "potentially" IP [12].

Medication Appropriateness Index (MAI)

MAI is an implicit measure of medication appropriateness and the most comprehensive one to date. MAI has been developed and tested in studies of elderly male patients (> 65 yrs old). Like the Beers Criteria, the MAI was developed to detect IP; it was not designed as a falls-specific tool. MAI uses 10 criteria for each medication a patient is taking, assessing medication indication, effectiveness, dosage, directions, drug-drug interactions, drug-disease interactions, expense, practicality, duplication, and treatment duration (Table 1) . Each criterion is rated as "appropriate", "marginally appropriate", or "inappropriate" [8][22].

Table 1. MAI criteria (items) [adapted from Reference 8]

Questions to be rated for each medication
Are there significant drug-drug interactions?
Are there significant drug-disease interactions?
Is there an indication for the drug?
Is the drug effective for the indication?
Is there unnecessary duplication with other drugs?
Is the duration of therapy acceptable?
Is the dosage correct?
Are the directions correct?**
Are the directions practical?**
Is this drug the least expensive alternative compared with others of equal utility?**

**The three questions to be deleted for our FASPIP. Also, questions regarding drug-drug and drug –disease interactions could be consolidated.

Initially, the MAI was developed as an item-level analysis tool (i.e. for each of the ten criteria/items). Recognizing the need to assess IP more globally, a summated MAI score per medication was later developed using a weighting scheme [22]. The ratings generate a weighted score that serves as a summary measure of prescribing appropriateness ranging from 0 to 18 (0 = no item inappropriate; 18 = all items inappropriate). Given its versatility, MAI could be developed in the future, into a person-level summary, to reflect the total burden of inappropriate medication [22]. The critical elements of any assessment tools are validity, reliability and prediction of clinical outcomes.

a. Validity: Is MAI measuring what it is intended to measure?

The validity of an instrument is of decisive importance for any tool used in clinical practice and research. MAI is a comprehensive instrument and formally testing its validity may represent a complex task. Most papers discussing the validity of MAI invoke face validity and content validity. While these elements are valuable, it is important to keep in mind their definition. Face validity refers to expert opinions, supporting the value of a test. Content validity (rational validity) still refers to expert opinions, except that the opinions are analyzed statistically. Both terms refer to the degree to which the content of the items reflects the content domain of interest. In addition, concurrent validity (ability to distinguish between meaningful groups, tested versus a gold standard) and predictive validity (ability to predict health outcomes) are in general, important types of validity required for the scientific acceptance of a measurement tool.

b. Reliability: If MAI is administered repeatedly, will it produce similar results?

The reliability of MAI was tested in several studies. When tested by the originators of the MAI index, the inter-rater percent agreement was 93% with an overall all items Kappa statistic of 0.83. The intra-rater agreement at 2-4 months for drugs overall was 97% and the overall all items Kappa statistic was 0.92 [8]. Similar results were reported for the reliability of the summated MAI: inter-rater agreement as assessed by the intraclass correlation coefficient was 0.74; percent agreement was 59%, and intra-rater reliability at 2-4 months was 71% [22].

It has to be noted that these MAI reliability studies had been performed by the originators of the index, in a single setting, with groups of elderly veterans from the Veterans Affairs General Internal Medicine Clinic in Durham, North Carolina. However, a measurement tool needs to be tested in various populations and settings, and generate consistent results, before being used universally. In a VA hospital setting, with investigators other than the originators, the inter-rater agreement on MAI for all drugs overall was 89%, and the kappa statistic was 0.59 [8]. In two European settings, with evaluators other than the scale's developers, inter- rater reliability was modest and intra-rater reliability was good [23][24]. These results support the use of MAI as a reasonably reliable, precise instrument.

c. Does MAI have the ability to detect change over time in response to a pharmacist intervention?

Several studies suggest that MAI is responsive to change over time in health services interventions. The MAI was the primary outcome in a randomized clinical trial evaluating the effect of pharmaceutical care from admission to discharge in geriatric patients. Patients in the intervention group were significantly more likely than control patients to have an improvement in the MAI score from admission to discharge (OR= 9,1; 95% confidence interval 4.2 -21.6), but notably, not in the Beers Criteria [25]. MAI was responsive to change in another randomized clinical trial, where inappropriate prescribing scores declined significantly more in the pharmaceutical care group than in the control group at 3 months (decrease 24% versus 6%, respectively) and the effect was sustained at 12 months (decrease 28% versus 5%). This MAI change translated into changes in adverse drug events rates [26]. Consistent results have been reported in studies conducted with various types of interventions, such as inpatient and outpatient geriatric clinic care programs [27], multidisciplinary team interventions [28] or in different settings, such as older adults undergoing first-time transfer from a hospital to a long-term care facility [29].

d. Does MAI have predictive ability? Can MAI scores predict clinically significant health outcomes, such as adverse drug reactions, falls, fall–related injuries?

To the authors' knowledge no study to date has addressed the predictive ability of MAI for falls and very few studies have examined the association between MAI and other health outcomes. Indeed at least two questions contained in the MAI tool have little relevance to falls. A study conducted in a VA hospital setting, found that the original MAI scoring was not associated with adverse drug reactions (ADR), after controlling for age, number of drugs and comorbidities; however, a modified MAI score (weighing more heavily the MAI criteria for which the clinical outcome is likely an ADR, significantly predicted the ADR risk (OR 1.13, 95% CI 1.02-1.26). The Beers Criteria were not associated with ADR in this study [13]. In other studies, an unfavorable MAI score was indirectly associated with ADR [26] and with inadequate blood pressure control and increased usage of emergency room visits [30].

MAI Advantages

The MAI has several advantages for IP assessment: it focuses on the patient, rather than on the drug (as opposed to the Beers Criteria); it is comprehensive and therefore potentially sensitive to detect meaningful IP, or disease; it addresses multiple components of prescribing appropriateness, and can be applied to every medication in the context of patient-specific characteristics [31]. Moreover, MAI has been tested in both inpatient and ambulatory settings. While it is a judgment–based scale, MAI has a good to very good intra-rater and inter-rater reliability performance, most likely supported by explicit definitions and instructions which allow for a standardization of the rating process [8]. Further improvements in its validity and reliability, by more in-depth instructions, have been suggested [32]. The MAI was last updated in 2010.

MAI Limitations

The MAI, while rather comprehensive, is burdensome, as it can take up to 10 minutes per drug to apply the instrument and it requires a well-trained health professional [8]. This may considerably limit the use of MAI in clinical and health care services research. For instance, in studies drawing their samples from the EPOC study population [33], only half of the 532 patients were feasibly evaluated with the MAI instrument [13][34]; in consequence this contributed to the lack of statistical power to assess the association between MAI and adverse drug events.

In spite of its depth of investigation, MAI is not fully comprehensive, critics noting that although ADR due to drug-drug or drug-disease interactions are considered, MAI does not assess the full range of ADR, nor does it addresses their causality. Neither patient compliance nor underprescribing are assessed [22]. Whether these limitations are having an impact on falls prevention, remains a subject of discussion.

Moreover, due to time constraints, MAI is difficult to adopt in routine universal clinical practice, and due to its complexity, MAI is difficult to apply on large prescribing databases. These, in turn, may considerably limit the MAI's potential to improve the quality of prescribing on a large scale in the face of an ever growing population of elderly patients experiencing falls and falls-related injuries. The advantages and disadvantages of Beer's Criteria and MAI described in detail above are summarized in Table 2.

The dilemma of diagnosing and preventing IP with tools such as implicit MAI, or explicit Beers Criteria, raises the question whether we should approach the problem with a different perspective. The question is not whether to use an explicit or an implicit medication appropriateness tool. The two types of tools serve different purposes. Explicit and drug-oriented criteria or indicators which are independent of patient characteristics, have good reliability, are easy to use, and are easily coded in large administrative databases. Yet, it is questionable whether prescribing quality can be improved based on such limited prescription data alone [35][36][37]. Implicit and patient-oriented criteria are more comprehensive, allowing medication evaluations in the

context of patient characteristics (diagnosis, comorbidity, etc) and while extremely time consuming, they have the highest likelihood to optimize the therapeutic management of the patients.

Methodology

A search for English-language articles was conducted in PubMed, Ovid, Scopus, Google Scholar and the Cochrane Central Register of Controlled Trials (2000-2011) using a combination of keywords: elderly, falls, inappropriate medications, hospital, Beers Criteria, Medication Appropriateness Index, MAI, aged, for literature identifying medications implicated in falls for older patients, free text, and links to related articles. A manual search of the reference lists of retrieved articles and reviews was conducted to identify additional publications. Secondary references from all authoritative reviews were identified. Using the Beers Criteria as a framework for development of a FASPIP, modifications were made to include medications if they appeared in peer-reviewed articles as implicated in falls for older patients. Papers were not limited to those pertaining to falls in hospitalized patients.

Our critical review of the MAI tool revealed its utility in identification of not merely unnecessary drugs (polypharmacy) but rather inappropriate medication usage based on indication, efficacy, drug-drug or drug-disease interaction, dosage, duration or therapeutic duplication. We then undertook revision of the MAI tool, omitting questions which had no relevance to fall assessment.

Results

The systematic literature review revealed a small number of primary research studies that have investigated the use of Beers Criteria for fall-related injury prevention. No studies have evaluated the MAI tool for falls. Various classes of medications have been examined in the literature.

Based on the literature, we developed a comprehensive list of medications associated with falls. This list is intended to be updated as new medications are either approved by FDA or identified in the literature as causing falls (Table 3). The list was alphabetized for ease of use. Omitted were drugs which do not necessarily increase the potential for falls but rather may increase harm from falls (e.g. bleeds from anticoagulants). Drugs that are currently rarely used clinically were omitted. Several drugs which have been removed from the U.S. market were also omitted. The list has been designed to be used in tandem with the revised MAI tool. Unlike previous tools, our tool includes OTC and herbal products reported in the literature. The list is not designed to include all drugs which can cause falls. Rather, it includes the more common medications implicated in falls in day to day clinical practice. The comorbidity list of Beer's criteria and portion of the Beer's criteria list pertaining to "drugs that should generally be avoided in the elderly" were considered too restrictive and cumbersome to use and not reflective of "real world" prescribing practices. Some drugs, while inappropriate overall, might be necessary in given clinical situation. Our list does not contain these sections at all. Our list is simply an alphabetized list of medications which have been associated with falls in the literature or prescribing information.

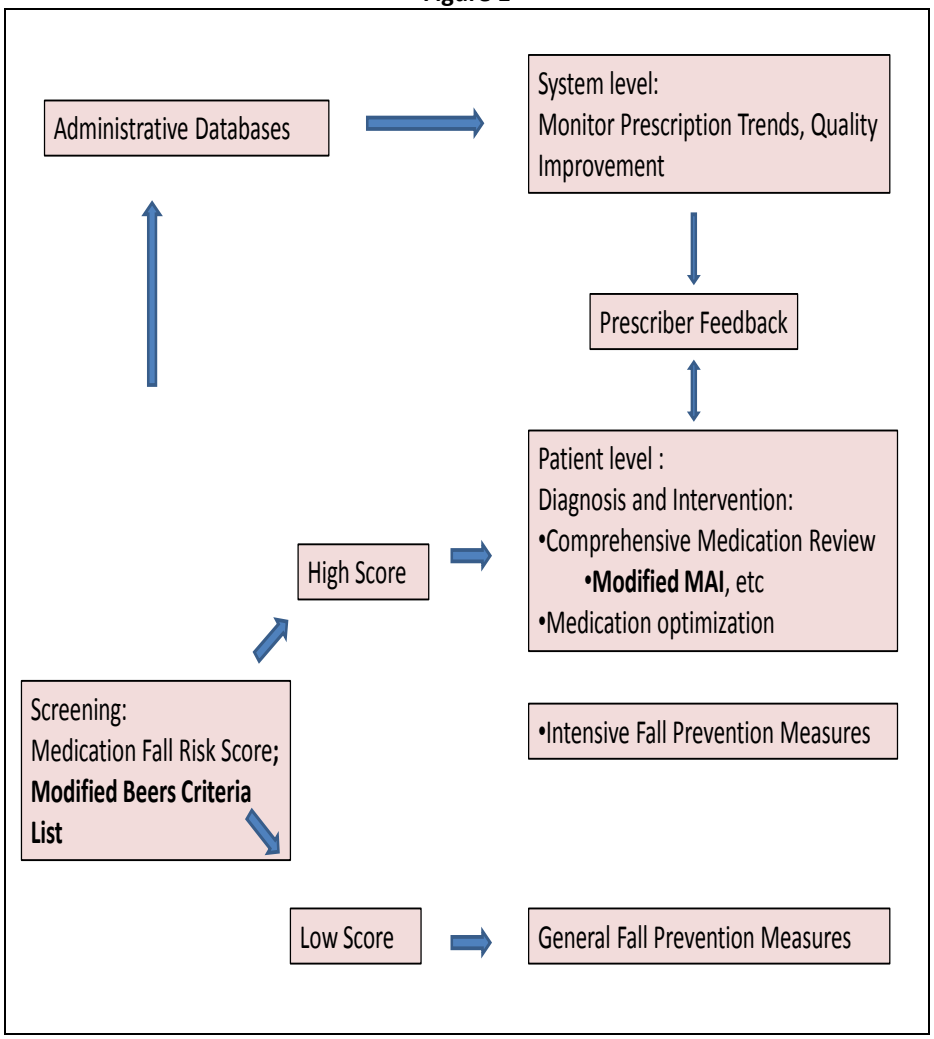
For the MAI, we attempted to simplify the tool to reduce the time involved to complete per patient. Three questions pertaining to cost of medication, and correctness or practicality of directions were omitted. Thus, the MAI was shortened to 7 questions only.

Discussion

Inappropriate prescribing is a complex problem, requiring complex solutions. Addressing its causes is important. Patients, prescribers and the environment in which prescribers operate constitute the main targets of action [38]. While the optimization of the training of the prescribers and of the communication between prescribers and pharmacists are both essential, in an environment with an ever increasing information base , dealing with an ever increasing complexity, quality checks and improvements will only grow in their importance. Information technology holds a great promise. It has been suggested that prescribing in the future will use three interacting databases- the patient's drug history, an evidence- based drug information and guidelines databases, and clinical information repositories [38] [39] [40].

However, for the time being, we need immediate tools to deal with IP among elderly patients at increased risk for falls. Given the magnitude of falls events in the geriatric population, we need an effective and feasible screening tool and a comprehensive remediation approach. The sequential integration of implicit criteria (such as MAI) with explicit criteria (such as updated Beers criteria) may be one of the options. Such an approach would entail development and validation of a FASPIP, which should be user friendly and time efficient; this tool would identify patients in which a more in-depth, comprehensive medication assessment is needed, and for which higher intensity fall prevention measures are required (**Figure 1**). In spite of its advantages, as outlined above, MAI is not a screening tool, per se; MAI or similar comprehensive indices for medication review may serve however, as a gold standard, against which to test other screening tools.

Figure 1

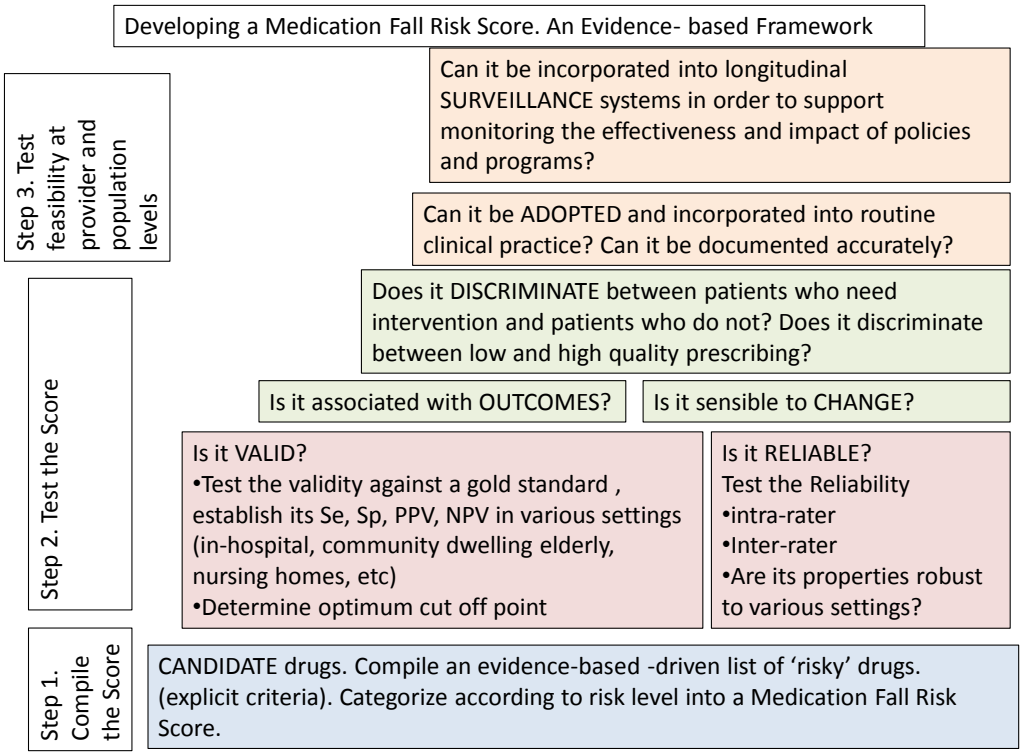


This two-stage model for a Fall Specific Inappropriate Prescribing Assessment Tool (FASPIP) would have the advantage of using a screening tool which is user friendly and time-efficient, followed by a more complex and laborious tool. This approach would yield a risk stratification of patients according to their level of risk of falling, which could further be integrated with existing risk assessment tools involving other falls related risk factors.

This model would capitalize on the advantages of both types of criteria. Additionally, in contrast with a static approach using lists such as the Beers Criteria, prescriber involvement (with a target MAI-based assessment) in real time is important, as most culprit drugs are "potentially inappropriate" and individual patients may legitimately necessitate a particular drug [41]. Additionally, prescriber feedback is crucially important, as the ultimate goal of a quality development initiative, is improving prescribing appropriateness. Active multifaceted strategies, feedback from peers and "real-time" reminders are recognized as among the few strategies which are potentially effective in influencing prescriber behavior [42]. Not only is feedback an effective behavioral tool, but a comprehensive medication review and reconciliation would also offer prescribers the much needed "real time" rational alternatives, which, in turn, will support the adoption of the screening tool [36] [41].

The development of a Screening Tool would require an extensive (re)consideration of its evidence–based support (**Figure 2**). Such a tool could be developed and then dynamically updated as evidence cumulates. Even with current IT advances this task may be within reach.

Figure 2. An evidence-based framework for developing a falls specific medication IP tool



We have completed the first step in this approach, i.e. the evidence based selection of candidate drug. This listing would need to be dynamically updated. Additionally, the candidate drugs may need to be assessed for their risk level determined by available evidence. Sources of information would be systematic reviews, rating the available evidence using a standardized taxonomy, rather than expert opinions and integrating meta-analyses, such as the ones on drugs in older people conducted for psychotropic [21] and cardiac and analgesic drugs [43].

The determination of risk level is important, as not all drugs have the same risk profile in increasing the risk for falls. Drugs such as antidepressants, antipsychotics, sedatives/hypnotics, and opiate analgesics have the highest risk; medication such as digoxin, diuretics, class 1A antiarrhythmics, sedating antihistamines, anticonvulsants (not including benzodiazepines and barbiturates), may be associated with a moderate risk of falling. Efforts have already being taken in this direction, yet their further development, dissemination and adoption seem to be lagging. For example, a medication classification based on their level of increasing the falls risk has been proposed by Beasley and Patatanian in 2009 [44]. These authors suggest that a score greater than 6 may warrant further in depth- medication review. Yet, in order for such an instrument to be widely adopted as a screening tool, it needs to be tested for its validity and reliability, optimum cut off points need to be determined, and the association with clinical outcomes needs to be determined, as outlined in Figure 2. Use of the literature alone for validation of a FASPIP is inadequate. Steps 2 and 3 of Figure 2 require further research. While the FASPIP was developed for hospitalized patients, the authors anticipate that the tool could be useful in other settings, including nursing homes.

Summary and conclusion

Patient falls are a high risk, high cost challenge for hospitals. The equilibrium between efficiently treating patients and avoiding falls is particularly elusive in older patients with multiple chronic diseases. Medication assessment includes recommendations to discontinue medications, decrease the dosage, use other treatments with reduced falls risk, monitor laboratory values and educate patients on how to minimize the risk of falls. Risk reduction strategies should include involvement of pharmacists in falls risk medication assessment on admission, for any newly ordered medications, and at discharge with appropriate follow-up as above.

Our study focused on improving the most commonly used IP tools for use as FASPIP. Based on the literature, we have added many additional high-risk medications and drug classes

to the criteria and simplified the MAI for use as a FASPIP. Combining a revised listing of medications which can cause falls with a revised MAI, we developed a FASPIP based on both explicit and implicit criteria for use in hospitalized elderly patients.

Further research is needed to measure the impact of this FASPIP tool on physician prescribing habits and ultimately, fall reduction. Application in clinical practice is still to be extensively studied. Comparing outcomes using the FASPIP vs. other tools could give us a rough idea to what extent the FASPIP is relevant in clinical practice to influence fall prevention. A continuous approach to falls prevention is ideal, and the goal is to update the FASPIP tool annually. Implications for hospital geriatric practice are vast.

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Table 2
Summary of Advantages and Disadvantages of Beer's Criteria and MAI

BEER'S CRITERIA	MAI
ADVANTAGES • Greatest experience and usage • Adopted by Federal quality regulators • Simple • Inexpensive • Applicable to all patients • Adaptable to computerized algorithms • Does not require information about indication for drug • May be assessed in large patient samples	**ADVANTAGES** • Last updated in 2010 • Applicable to every medication • Comprehensive • Focuses on the patient, not the drug • Good inter- and intra-rater reliability • Tested in both inpatient and ambulatory settings • Able to detect changes over time • Addresses multiple components of prescribing appropriateness • Applicable to every medication in the context of patient specific appropriateness
DISADVANTAGES • Not updated for > 10 years • Not designed as a falls assessment tool • Limited reliability in a hospital setting • Incomplete • Not evidence-based • Usage of 3 lists can be confusing (conflicts with above) • Some drugs on list not even used in U.S. • Inaccurate- misses significant amount of inappropriate prescribing resulting in falls • Omits dosing, duration of therapy, drug interactions, polypharmacy considerations	**DISADVANTAGES** • Complex • Not designed as a falls assessment tool • Requires comprehensive clinical data • Difficult to apply to large prescribing databases • Requires well trained health professional and interpretation by a skilled individual • Incomplete (e.g. does not assess causality) • No data available regarding predictive ability for falls • Burdensome- may take 10 minutes/drug to apply • Requires comprehensive clinical patient-specific information • Limited formal validity

Table 3. Medications Associated With Falls in the Literature*

**This list should be used in the context of a comprehensive clinical patient assessment and in consideration of the patient's history and physical examination, laboratory assessment, and gait and balance assessment.*

Acarbose	Clomipramine	Furosemide
Acebutolol	Clonazepam	Gabapentin
Acetazolamide	Clozapine	Glimepiride
Alprazolam	Codeine	Glpizide
Amiloride	Cyclizine	Glyburide
Amitriptyline	Cyclobenzaprine	Glycopyrrolate
Amlodipine	Cyproheptadine	Gotu Kola
Amobarbital	Dandelion	Guanabenz
Amoxapine	Desipramine	Guanethidine
Aripiprazole	Desloratidine	Guanfacine
Asenapine	Dexbrompheniramine	Haloperidol
Atenolol	Dexchlorpheniramine	Hydrochlorthiazide
Atropine	Dexmedetomidine	Hydrocodone
Azilisartan	Dimenhydrate	Hydromorphone
Baclofen	Diazepam	Hydroxyzine
Belladonna alkaloids	Diclofenac	Hyoscyamine
Benzapril	Dicyclomine	Ibuprofen
Benztropine	Digoxin	Imipramine
Betaxolol	Diltiazem	Indapamide
Buspirone	Diphenhydramine	Indomethacin
Bisprolol	Diphenoxylate	Insulin
Bromcriptine	Disopyramide	Irbesartan
Buchu	Divalproex sodium	Isocarboxazid
Buprenorphine	Doxazosin	Isosorbide (mononitrate &
Butabarbital	Doxepin	dinitrate)
Butorphanol	Doxylamine	Isradipine
Bupropion	Duloxetine	Ketamine
Bumetanide	Enalapril	Ketotifen
Candesartan	Eprosartan	Labetolol
Captopril	Escitalopram	Lacosamimde
Carbamazepine	Esmolol	Lamotrigine
Carisoprodol	Estazolam	Levetiracetam
Cat's claw	Ethacrynic acid	Levocetirizine
Celecoxib	Etomidate	Levodopa/Carbidopa
Cetirizine	Ethosuximide	Levorphanol
Chloral hydrate	Exenatide	Licorice
Chlorazepate	Eye drops	Linagliptin
Chlordiazepoxide	Famotidine	Liraglutide
Chlorpheniramine	Felbamate	Lisinopril
Chlorpromazine	Felodipine	Lithium
Chlorpropamide	Fentanyl	Loratadine
Chlorothiazide	Fexofenadine	Lorazepam
Chlorthalidone	Fluoxetine	Loxapine
Cimetidine	Fluphenazine	Maprotiline
Citalopram	Fluvoxamine	Meclizine
Clemastine	Flurazepam	Meperidine
Clevidipine	Fosinopril	Methocarbamol
Clonidine	Fosphenytoin	Mesoridazine

Metalaxone
Methyldopa
Metoclopramide
Metoprolol
Methyldopa
Methazolamide
Metformin
Methadone
Methscopolamine
Methsuximide
Metolazone
Miqlitol
Minoxidil
Mirtazapine
Moexipril
Molindone
Morphine
Nadolol
Nalbuphine
Naproxen
Nateglinide
Nebivolol
Nefazodone
Nicardipine
Nifedipine
Nimodipine
Nitrates
Nitrous Oxide
Nitroglycerin
Nizatidine
Nortriptylline
Olanzapine
Olmesartan
Opium tincture
Orphenadrine
Oxazepam
Oxcarbazepine
Oxybutynin
Oxycodone
Oxymorphone
Pamabrom
Paraldehyde
Paroxetine
Penbutolol
Pennywort
Pentazocine
Pentobarbital
Perphenazine
Phenobarbital
Phenyltoloxamine
Phenytoin
Pimozide
Pindolol
Pioglitazone
Piroxicam
Prazosin
Pregabalin
Primadone
Procainamide
Promethazine
Propantheline
Propofol
Propranolol
Protriptylline
Quarazepam
Quetiapine
Quinapril
Quinidine
Ramapril
Ranitidine
Repaglinide
Reserpine
Risperidone
Rosiglitazone
Rufinamide
Saxagliptin
Scopolamine (systemic & ophthalmic)
Secobarbital
Selegline
Sertraline
Sevoflurane
Sitagliptin
Sotalol
Spironolactone
Stinging Nettle
St. John's Wart
Sufentanil
Telmisartan
Temazepam
Terazosin
Thioridazine
Thiopental
Thiothixene
Tiagabine
Timolol (systemic & ophthalmic)
Tizanidine
Tolazamide
Tolbutamide
Tolerodine
Topiramate
Torsemide
Trandolapril
Tranylcypromine
Trandolapril
Trazodone
Triamterene
Trihexyphenidyl
Trimipramine
Tramadol
Trifluperazine
Tripelennamine
Triprolidine
Valproic acid
Valsartan
Venlafaxine
Verapamil
Yarrow
Ziconotide
Ziprasidone
Zolpidem
Zonisamide