Survey of Potentially Inappropriate Prescription Using STOPP/START Criteria in Inha University Hospital

Original
Article

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Background: Prescribing potentially harmful drugs and omitting essential drugs to older patients is a common problem because they take so many medications. In this study, our goal was to identify potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) using Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to the Right Treatment (START) criteria to improve proper prescription and reduce improper prescription.

Methods: Enrolled in this study were 117 patients older than 65 years old who were hospitalized at Inha University Hospital in Incheon due to pneumonia from January 2012 to March 2012. Patient data, including medical histories, current diagnoses, current medications, and biochemical data were recorded from electronic records. STOPP and START were applied to their clinical datasheets.

Results: STOPP criteria identified 24 patients who had 29 PIMs. Most potential inappropriate prescribing was of cardiovascular medications, followed by drugs whose primary effect is on the urogenital system and gastrointestinal system. START criteria identified 31 patients who had 46 PPOs. The cardiovascular system drugs comprised most of the PPOs. No PPOs were identified under the central nervous system criteria.

Conclusion: Given the current Korean medical system conditions and considering the many clinically important situations when prescribing drugs, STOPP/START criteria are not absolute criteria to prevent improper prescription, but sagacious usage of these standards can help physicians to prescribe properly in clinical practice.

Keywords: Aged Patients; STOPP/START Criteria; Potentially Inappropriate Medications; Potential Prescribing Omissions

INTRODUCTION

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Aged patients have multiple diseases and so take many medications. There are many side effects of medication itself and drug-drug interactions, so physicians should consider these when they prescribe for elderly patients. Improved prescribing in the elderly tool (IPET) and Beers' criteria have been widely used as screening tools of inappropriate prescription to elderly patients,¹⁾ but IPET does not contain many drugs frequently used for elderly patients, and Beers' criteria contains drugs not used in Korea.

Some researchers found these tools were limited in discovering inappropriate prescription.^{2,3)}

O'Mahony and Gallagher⁴⁾ suggested the need for new criteria. A panel composed of 18 Irish and British experts of geriatrics, clinical pharmacology, geriatric psychology, and primary medicine made a list of 65 medications that should not be prescribed for specific diseases and 22 medications that should be prescribed for specific conditions. These are the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)/Screening Tool to Alert doctors to the Right Treatment (START) criteria, developed to overcome the limitations of previous IPET and Beers' criteria (Appendix 1).³⁾ In this study, we reviewed the diseases and medications of the elderly patients admitted to Inha University Hospital, and analyzed the prescriptions by applying the STOPP/START criteria.

METHODS

1. Study Population

Enrolled in this study were 117 patients 65 years or older admitted to any department in Inha University Hospital in Incheon due to pneumonia from the 1st of January 2012 to 31 March 2012. Patients with cancer stage 4, severely ill, cardiopulmonary resuscitation (CPR) prohibition request patients, and patients who had received CPR were excluded. We excluded patients who had received or refused CPR and terminal stage cancer patients because in those cases physicians may have knowingly used inappropriate medication necessarily or may not use needed long-term medication due to short life expectancy.

2. Research Methods

We reviewed patients' sex, age, height, weight, past medical history, recent diagnosis, and medications they took before and after administration based on medical records. Regardless of formula, we reviewed all oral, intravenous and inhaled medications, and checked dosage and mode of use. We checked serum creatinine levels and calculated glomerular filtration rate.

Based on the information collected, we checked potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) by applying each item of the STOPP/START criteria to the patients. This report is a retrospective study based on

medical records, and was approved by institutional review board of Inha University Hospital, and informed consent was waived.

3. Statistical Analysis

PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

RESULTS

1. Characteristics of Study Population

Of the 117 research subjects, 65 people were male (55%) and 52 were female (45%), with a mean age of 77.4 years. The most common age group was from 75 to 84, 58 persons (56%),

Table 1. Characteristics of the study population

Characteristic	Value
Total patients	117
Male	65 (55)
Female	52 (45)
Age distribution (y)	
Mean age	77.4 ± 6.5
65–74	42 (34)
75–84	58 (56)
≥85	17 (10)
Morbidities	
Hypertension	71 (60.7)
Diabetes	34 (29.0)
Ischemic heart disease	24 (20.5)
Stroke	19 (16.2)
Chronic obstructive pulmonary disease	19 (16.2)
Osteoporosis	13 (11.1)
Atrial fibrillation	9 (7.7)
Congestive heart failure	7 (5.9)
Dementia	6 (5.1)
Depression	6 (5.1)
Falls	3 (2.6)
Average of drug prescriptions per patient	14
Range of drug prescriptions per patient	6–25

Values are presented as number, number (%), or mean ± SD.

followed by age group from 65 to 74, 42 persons (34%). There were 17 people over age 85 (10%). The oldest age was 95 years old; there were two such people. Hypertension was the most common disease, and 71 patients suffered from it (60.7% of the patients). Diabetes (29.0%) and ischemic heart disease (20.5%) followed hypertension. The average number of drugs per patient was 14, with a range from 6 to 25 (Table 1).

2. Application of Screening Tool of Older Persons' Potentially Inappropriate Prescriptions Criteria

Twenty-four patients who had 29 PIMs were identified by using the STOPP criteria. Males had PIMs (21.5%) slightly more often than females (19.2%). Twenty people had one inappropriate prescription (23.0%), and four people had two or more inappropriate prescriptions (3.3%) (Table 2). Inappropriate prescriptions were found in 12 lists by 65 criteria.

The most frequent inappropriate prescription was for cardiovascular system medications (11 PIMs, 37.9%), followed by drugs whose primary effect is on the urogenital (10 PIMs, 34.5%) and gastrointestinal system (5 PIMs, 17.2%). Among the cardiovascular drugs, calcium channel blockers given to patients with chronic constipation was the most common PIMs (5 PIMs, 17.2%), and among genitourinary system drugs, antimuscarinic agents given to chronic constipation patients was the most common (5 PIMs, 17.2%). One inappropriate prescription was

Table 2. Number of patients with potentially inappropriate medications identified by Screening Tool of Older Persons' potentially inappropriate Prescriptions

Variable	Value
No. of potentially inappropriate medications	
1	20 (17.1)
2	3 (2.6)
3	1 (0.9)
4	0 (0)
Total potentially inappropriate prescriptions	29
Patients who has taken potentially inappropriate medications	24 (20.5)
Male (n = 65)	14 (21.5)
Female (n = 52)	10 (19.2)

Values are presented as number (%) or number.

found each for central nervous system drugs, musculoskeletal system drugs, and medications that can be harmful to patients hurt from a fall (Table 3).

3. Application of Screening Tool to Alert Doctors to the Right Treatment Criteria

PPOs, which are absolutely necessary but not given to the patients, included 46 cases in 31 patients found by the START criteria. PPOs were more common in men (29.2%) than in women (23.0%). Twenty patients had one drug prescription omission, and one patient had four drug omissions (Table 4). PPOs were found in 12 lists between 22 criteria.

Cardiovascular drugs accounted for most of the PPOs (17 PPOs, 37.0%), and of those, aspirin (5 PPOs, 10.9%) and statins

Table 3. PIMs identified by Screening Tool of Older Persons' potentially inappropriate Prescriptions

Criteria	No (%)
Cardiovascular system	11 (37.9)
Calcium channel blockers and constipation	5 (17.2)
Noncardioselective beta-blocker and COPD	3 (10.3)
Beta-blocker in combination with verapamil	2 (6.9)
Aspirin and warfarin without H ₂ antagonist/PPI	1 (3.4)
Urogenital system	10 (34.5)
Antimuscarinic drugs with chronic constipation	5 (17.2)
Antimuscarinic drugs with chronic prostatism	3 (10.3)
Beta-blockers with long-term urinary catheter in situ	1 (3.4)
Bladder antimuscarinic drugs with dementia	1 (3.4)
Gastrointestinal system	
Anticholinergic with chronic constipation	5 (17.2)
Central nervous system	
TCA and calcium channel blockers	1 (3.4)
Musculoskeletal system	
Warfarin and NSAID together	1 (3.4)
Drugs that adversely affect fallers	
First-generation antihistamines	1 (3.4)
Total PIMs	29

PIMs: potentially inappropriate medications, COPD: chronic obstructive pulmonary disease, PPI: proton pump inhibitor, TCA: tricyclic antidepressants, NSAID: non-steroidal anti-inflammatory drug.

Table 4. Number of patients with potential prescribing omissions by Screening Tool to Alert doctors to the Right Treatment

Variable	Value
No. of potentially prescribing omission	
1	20 (17.1)
2	8 (6.8)
3	2 (1.7)
4	1 (0.9)
Total potentially prescribing omission	46
Patients who had potentially prescribing omission	31 (26.5)
Male (n = 65)	19 (29.2)
Female (n = 52)	12 (23.1)

Values are presented as number (%) or number.

(5 PPOs, 10.9%) are the most commonly omitted drugs. In the field of the musculoskeletal system, bisphosphonates are the most commonly omitted drugs (6 PPOs, 13.0%). Statins were one of the most commonly omitted drugs in the cardiovascular and endocrinology system (10 PPOs, 22.2%). There were no omitted central nervous system medications (Table 5).

DISCUSSION

According to the National Health and Nutrition Examination Survey III, over half of patients between 65 to 74 years old take more than two medications, and 12% take over five. Over 75 years of age, more than 60% take two or more medications, and 16% take more than five medications.⁵⁾ A study conducted on 20,575 outpatients and 4,519 inpatients at one university hospital in Korea reported that outpatients were prescribed an average of six medications, and inpatients received 18.⁶⁾

Generally, elderly patients have multiple chronic diseases requiring a number of medications, and hospital admission will often more than double their usual amount. Therefore, physicians should pay close attention to medical history and current medication when adding a new medication for elderly patients.

In our study PIMs were found in 20.5% of patients according to the STOPP criteria. This is similar to the 21.4% in 1,329 elderly people who visited three general practices in Ireland.²⁾ The fact that about one fifth of patients admitted to a university

Table 5. PPOs identified by Screening Tool to Alert doctors to the Right Treatment tool

Criteria	No (%)
Cardiovascular system	17 (37.0)
Aspirin	5 (10.9)
Statin	5 (10.9)
ACE inhibitor and congestive heart failure	4 (8.7)
Warfarin and atrial fibrillation	2 (4.3)
Beta-blocker	1 (2.2)
Musculoskeletal system	11 (23.9)
Bisphosphonate	6 (13.0)
Ca ²⁺ and vitamin D ₂ supplement in osteoporosis	5 (10.9)
Endocrine system	11 (23.9)
Statin	5 (10.9)
Aspirin	4 (8.7)
ACE inhibitor	2 (4.3)
Respiratory system	
Beta-2 agonist for chronic obstructive pulmonary disease	4 (8.7)
Gastrointestinal system	
Gastroesophageal reflux disease and proton pump inhibitor	3 (6.5)
Total PPOs	46

PPOs: potentially prescribing omissions, ACE: angiotensin converting enzyme.

hospital where they are cared for by so many doctors and nurses have more than one inappropriate prescription is an important message to physicians.

Prescription for patients who had chronic constipation was the most common inappropriately prescribed medication, with 15 instances found in the current study. Possible explanations include that the physician ignored conditions such as constipation that could disturb the patient's quality of life, or the physician did not know that calcium channel blocker (CCB) could aggravate constipation, or that the patient has constipation. Another possible explanation is that though the physician knew it is possible that CCBs worsen constipation, important heart drugs could not be withheld.

One study that analyzed inappropriate drug prescriptions in elderly patients, using Beers' criteria intended for outpatients, found that of 20,575 people and the elderly of the 4,519 people admitted to a university hospital in 2004, 27.8% of patients

received inappropriate medications.⁶⁾ That is higher than the percentage of 20.5 of this study, but lower than other studies²⁾ using the STOPP criteria. Perhaps because only hospitalized pneumonia patients are considered in this study, the percentage of inappropriate prescription may be lower than in other studies.

PPOs reviewed using the START criteria was 26.5%, slightly higher than the 22.7% in the Ireland study.²⁾ Statins were the most commonly omitted drugs. In the START criteria, statins are recommended for patients who have coronary artery, cerebrovascular, and peripheral vascular disease if they can do normal activities of daily life and their life expectancy is more than five years. Diabetes patients are also recommended to use statins if they have major risk factors for cardiovascular disease. However, the insurance guidelines of Korea allow the prescription only if the total blood cholesterol is more than 220 mg/dL, or triglycerides are 200 mg/dL or more, even with a cardiovascular risk factor, so it seems that there are many prescription omissions of statins. There is a need to develop new guidelines about inappropriate prescription for elderly patients in Korea.

This study has some limitations. First, it is impossible to generalize to the entire elderly population since this study was restricted to pneumonia patients admitted to a university hospital. Second, it is possible that there are omissions of patients' past medical history and medications, because we checked the patients' history and drugs only through the medical records created by the doctors or nurses.

However, this study is significant in that it is the first to describe the prescription of inappropriate drugs in elderly patients by using the STOPP/START criteria in Korea. In addition, while the role of previous tools was just to find inappropriate prescriptions, this study attempted to find potential prescription omissions using a new tool called START.

Analytic tools such as STOPP/START criteria are not the best way to find inappropriate prescription and potential omission for elderly patients. There might be many cases when a physician needs to use medication that nevertheless will be flagged as inappropriate. Prescription that meets each clinical situation is important, but if the physician understands these criteria and uses them properly, it should help minimize inappropriate prescriptions and reduce the side effects.

Hereafter, conducting a long term study using STOPP/START criteria including not only the patients of a university

hospital but also of a convalescent hospital and primary clinic is needed. We think there is a need to develop appropriate criteria to match the actual conditions in Korea.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix 1. Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)/Screening Tool to Alert Doctors to the Right Treatment (START) criteria

1. STOPP

The following prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

1) Cardiovascular system

- (1) Digoxin at a long-term dose $> 125 \mu\text{g/d}$ with impaired renal function (estimated glomerular filtration rate [GFR] $< 50 \text{ mL/min}$) (increased risk of toxicity)
- (2) Loop diuretic for dependent ankle edema only, i.e., no clinical signs of heart failure (no evidence of efficacy, compression hosiery usually more appropriate)
- (3) Loop diuretic as first-line monotherapy for hypertension (safer, more effective alternatives available)
- (4) Thiazide diuretic with a history of gout (may exacerbate gout)
- (5) Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (COPD) (risk of bronchospasm)
- (6) Beta-blocker in combination with verapamil (risk of symptomatic heart block)
- (7) Use of diltiazem or verapamil with New York Heart Association class III or IV heart failure (may worsen heart failure)
- (8) Calcium channel blockers with chronic constipation (may exacerbate constipation)
- (9) Use of aspirin and warfarin in combination without histamine H_2 receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (PPI, high risk of gastro-intestinal bleeding)
- (10) Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for efficacy)
- (11) Aspirin with a past history of peptic ulcer disease without histamine H_2 receptor antagonist or PPI (risk of bleeding)
- (12) Aspirin at dose $> 150 \text{ mg/d}$ (increased bleeding risk, no evidence for increased efficacy)
- (13) Aspirin with no history of coronary, cerebral, or peripheral arterial symptoms or occlusive arterial event (not indicated)
- (14) Aspirin to treat dizziness not clearly attributable to cerebrovascular disease (not indicated)
- (15) Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (no proven added benefit)
- (16) Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit)
- (17) Aspirin, clopidogrel, dipyridamole, or warfarin with concurrent bleeding disorder (high risk of bleeding)

2) Central nervous system and psychotropic drugs

- (1) Tricyclic antidepressants (TCAs) with dementia (risk of worsening cognitive impairment)
- (2) TCAs with glaucoma (likely to exacerbate glaucoma)
- (3) TCAs with cardiac conductive abnormalities (pro-arrhythmic effects)
- (4) TCAs with constipation (likely to worsen constipation)
- (5) TCAs with an opiate or calcium channel blocker (risk of severe constipation)
- (6) TCAs with prostatism or prior history of urinary retention (risk of urinary retention)
- (7) Long-term (i.e., $> 1 \text{ mo}$), long-acting benzodiazepines, e.g., chlordiazepoxide, fluzepam, nitrazepam, chlorazepate, and benzodiazepines with long-acting metabolites, e.g., diazepam (risk of prolonged sedation, confusion, impaired balance, falls)
- (8) Long-term (i.e., $> 1 \text{ mo}$) neuroleptics as long-term hypnotics (risk of confusion, hypotension, extrapyramidal side effects, falls)
- (9) Long-term neuroleptics ($> 1 \text{ mo}$) in those with parkinsonism (likely to worsen extrapyramidal symptoms)
- (10) Phenothiazines in patients with epilepsy (may lower seizure threshold)
- (11) Anticholinergics to treat extrapyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity)
- (12) Selective serotonin re-uptake inhibitors (SSRI's) with a history of clinically significant hyponatraemia (non-iatrogenic hyponatraemia $< 130 \text{ mmol/L}$ within the previous 2 months)
- (13) Prolonged use ($> 1 \text{ wk}$) of first generation antihistamines, i.e., diphenhydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anticholinergic side effects)

3) Gastro-intestinal system

- (1) Diphenoxylate, loperamide, or codeine phosphate for treatment of diarrhoea of unknown cause (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis)
- (2) Diphenoxylate, loperamide, or codeine phosphate for treatment of severe infective gastroenteritis, i.e., bloody diarrhoea, high fever or severe systemic toxicity (risk of exacerbation or protraction of infection)
- (3) Prochlorperazine (Stemetil) or metoclopramide with parkinsonism (risk of exacerbating parkinsonism)
- (4) PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (earlier discontinuation or dose reduction for maintenance/prophylactic treatment of peptic ulcer disease, esophagitis or gastroesophageal reflux disease indicated)
- (5) Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation)

Appendix 1. Continued

4) Respiratory system

- (1) Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)
- (2) Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic steroids)
- (3) Nebulised ipratropium with glaucoma (may exacerbate glaucoma)

5) Musculoskeletal system

- (1) Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastro-intestinal bleeding, unless with concurrent histamine H₂ receptor antagonist, PPI or misoprostol (risk of peptic ulcer relapse)
- (2) NSAID with moderate-severe hypertension (moderate, 160/100 mm Hg–179/109 mm Hg; severe, $\geq$ 180/110 mm Hg) (risk of exacerbation of hypertension)
- (3) NSAID with heart failure (risk of exacerbation of heart failure)
- (4) Long-term use of NSAID (>3 mo) for relief of mild joint pain in osteoarthritis (simple analgesics preferable and usually as effective for pain relief)
- (5) Warfarin and NSAID together (risk of gastro-intestinal bleeding)
- (6) NSAID with chronic renal failure (estimated GFR 20–50 mL/min) (risk of deterioration in renal function)
- (7) Long-term corticosteroids (>3 mo) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects)
- (8) Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol (allopurinol first choice prophylactic drug in gout)

6) Urogenital system

- (1) Bladder antimuscarinic drugs with dementia (risk of increased confusion, agitation)
- (2) Bladder antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma)
- (3) Bladder antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation)
- (4) Bladder antimuscarinic drugs with chronic prostatism (risk of urinary retention)
- (5) Alpha-blockers in males with frequent incontinence, i.e., one or more episodes of incontinence daily (risk of urinary frequency and worsening of incontinence)
- (6) Alpha-blockers with long-term urinary catheter *in situ*, i.e., more than 2 months (drug not indicated)

7) Endocrine system

- (1) Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)
- (2) Beta-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes, i.e., $\geq$ 1 episode per month (risk of masking hypoglycaemic symptoms)
- (3) Estrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
- (4) Estrogens without progestogen in patients with intact uterus (risk of endometrial cancer)

8) Drugs that adversely affect those prone to falls ($\geq$ 1 fall in past 3 months)

- (1) Benzodiazepines (sedative, may cause reduced sensorium, impair balance)
- (2) Neuroleptic drugs (may cause gait dyspraxia, parkinsonism)
- (3) First generation antihistamines (sedative, may impair sensorium)
- (4) Vasodilator drugs known to cause hypotension in those with persistent postural hypotension, i.e., recurrent > 20 mm Hg drop in systolic blood pressure (risk of syncope, falls)
- (5) Long-term opiates in those with recurrent falls (risk of drowsiness, postural hypotension, vertigo)

9) Analgesic drugs

- (1) Use of long-term powerful opiates, e.g., morphine or fentanyl as first line therapy for mild-moderate pain (World Health Organization analgesic ladder not observed)
- (2) Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation)
- (3) Long-term opiates in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome (risk of exacerbation of cognitive impairment)

Appendix 1. Continued

10) Duplicate drug classes

Any regular duplicate drug class prescription e.g. two concurrent opiates, NSAID's, SSRI's, loop diuretics, angiotensin converting enzyme (ACE) inhibitors (optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug). This excludes duplicate prescribing of drugs that may be required on a PRN (when necessary, from the Latin "pro re nata") basis, e.g., inhaled beta-2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain

2. START, i.e., Appropriate, Indicated but Often Omitted Treatments

These medications should be considered for people ≥ 65 years of age with the following conditions, where no contra-indication to prescription exists

1) Cardiovascular system

- (1) Warfarin in the presence of chronic atrial fibrillation
- (2) Aspirin in the presence of chronic atrial fibrillation, where warfarin is contra-indicated, but not aspirin
- (3) Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm
- (4) Antihypertensive therapy where systolic blood pressure consistently > 160 mm Hg
- (5) 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 > 5 years
- (6) ACE inhibitor with chronic heart failure
- (7) ACE inhibitor following acute myocardial infarction
- (8) Beta-blocker with chronic stable angina

2) Respiratory system

- (1) Regular inhaled beta-2 agonist or anticholinergic agent for mild to moderate asthma or COPD
- (2) Regular inhaled corticosteroid for moderate-severe asthma or COPD, where predicted forced expired volume in one second $< 50\%$
- (3) Home continuous oxygen with documented chronic type 1 respiratory failure ($PO_2 < 8.0$ kPa, $PCO_2 < 6.5$ kPa) or type 2 respiratory failure ($PO_2 < 8.0$ kPa, $PCO_2 > 6.5$ kPa)

3) Central nervous system

- (1) L-dopa in idiopathic Parkinson's disease with definite functional impairment and resultant disability
- (2) Antidepressant drug in the presence of moderate-severe depressive symptoms lasting at least 3 months

4) Gastro-intestinal system

- (1) PPI with severe gastro-esophageal acid reflux disease or peptic stricture requiring dilatation
- (2) Fiber supplement for chronic, symptomatic diverticular disease with constipation

5) Musculoskeletal system

- (1) Disease-modifying antirheumatic drug with active moderate-severe rheumatoid disease lasting > 12 weeks
- (2) Bisphosphonates in patients taking maintenance oral corticosteroid therapy
- (3) Calcium and vitamin D supplement in patients with known osteoporosis (radiological evidence or previous fragility fracture or acquired dorsal kyphosis)

6) Endocrine system

- (1) Metformin with type 2 diabetes $\pm$ metabolic syndrome in the absence of renal impairment (estimated GFR < 50 mL/min)
- (2) ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy, i.e., overt urinalysis proteinuria or microralbuminuria (> 30 mg/24 hours) $\pm$ serum biochemical renal impairment (estimated GFR < 50 mL/min)
- (3) Antiplatelet therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present (hypertension, hypercholesterolaemia, smoking history)
- (4) Statin therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present