

INVITED REVIEW

Pharmacotherapy and the Role of Pharmacists in Rehabilitation Medicine

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Pharmacotherapy is important in older patients undergoing rehabilitation because such patients, especially those with frailty and physical disabilities, are susceptible to drug-related functional impairment. Drug-related problems include polypharmacy, potentially inappropriate medications (PIMs), and potential prescription omissions. These problems are associated with adverse drug events such as dysphagia, depression, drowsiness, falls and fractures, incontinence, decreased appetite, and Parkinson's syndrome, leading to impaired improvement in activities of daily living (ADL), quality of life (QOL), and nutritional status. Moreover, the anticholinergic burden is associated with impaired physical and cognitive functions. Therefore, pharmacist-centered multidisciplinary pharmacotherapy should be performed to maximize rehabilitation outcomes. Pharmacotherapy includes a review of all medications, the assessment of drug-related problems, goal setting, correction of polypharmacy and PIMs, monitoring of drug prescriptions, and reassessment of drug-related problems. The goal of pharmacotherapy in rehabilitation medicine is to optimize drug prescribing and to maximize the improvement of ADL and QOL as patient outcomes. The role of pharmacists during rehabilitation is to treat patients as part of multidisciplinary teams and as key members of nutritional support teams. In this review, we aim to highlight existing evidence regarding pharmacotherapy in older adults, including drug-related functional impairment and the association between pharmacotherapy and functional, cognitive, and nutritional outcomes among patients undergoing rehabilitation. In addition, we highlight the important role of pharmacists in maximizing improvements in rehabilitation outcomes and minimizing drug-related adverse effects.

Key Words: activities of daily living; convalescent rehabilitation; polypharmacy; potentially inappropriate medications; rehabilitation pharmacotherapy

INTRODUCTION

As the population ages, the number of older adults with impaired activities of daily living (ADL) requiring rehabilitation is increasing. Aging is associated with sarcopenia, frailty, and multimorbidity, all of which are widespread medical and geriatric problems that often lead to polypharmacy.^{1,2} Polypharmacy (the use of multiple medications) is a common health concern among older adults and is associated with reduced physical function, low cognitive levels, and

malnutrition.³ Prescribing a large number of drugs can lead to medication-related problems such as potentially inappropriate medication (PIM) use, duplication of therapy, adverse drug effects, drug interactions, poor adherence, unnecessary medication use, and a strain on medical resources.⁴⁻⁶

Pharmacotherapy, or medication management, is important in older patients undergoing rehabilitation. Whereas rehabilitation focuses on training for functional recovery, pharmacotherapy tends to focus on disease treatment. Older inpatients are at risk of being discharged with prescriptions

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for medications mainly used to prevent or treat the complications of acute illness, despite these medications having no documented indication for chronic use.^{7–9} These prescribing practices are associated with significant costs and may have no obvious benefit to patients; however, they may have a significant impact on subsequent rehabilitation outcomes. Indeed, the association of polypharmacy and PIMs with decreased physical function and ADL,^{10–13} cognitive decline,¹⁴ and malnutrition¹⁵ has been demonstrated in post-acute patients undergoing rehabilitation.¹⁶ Therefore, pharmacotherapy needs to be performed in the rehabilitation medicine environment by a multidisciplinary team of medical professionals led by pharmacists. However, to date, this subject has not been well studied.

In this review, we aim to highlight existing evidence regarding pharmacotherapy in older adults; drug-related functional impairment; and the association between pharmacotherapy and functional, cognitive, and nutritional outcomes among older adults undergoing rehabilitation. Additionally, we highlight the important role of pharmacists in maximizing improvements in rehabilitation outcomes and minimizing drug-related adverse effects. This review will benefit all members of the multidisciplinary teams involved in rehabilitation medicine.

PHARMACOTHERAPY IN OLDER ADULTS

Polypharmacy

Polypharmacy is classified as a geriatric syndrome and is frequently observed in older adults.^{17,18} This phenomenon is a major concern in relation to adverse health outcomes such as falls, functional impairment, adverse drug reactions, prolonged hospitalization, rehospitalization, poor rehabilitation outcomes, and mortality.^{19,20} Multiple factors positively associated with polypharmacy such as drug–drug interactions, drug–disease interactions, and PIMs may contribute to these adverse outcomes.²¹ Adverse drug events (ADEs) caused by interactions or contraindications can be misinterpreted as new symptoms or diagnoses, which may result in new drug prescriptions. This negative spiral of prescribing to treat side effects and interactions, also known as the prescribing cascade, increases the risk of polypharmacy. The risk of prescription cascades increases with an increase in drug–drug interactions and contraindications (drug–disease).^{22,23} Therefore, polypharmacy is an important issue in rehabilitation clinical practice and is considered to be a growing problem.

While polypharmacy is defined as the ingestion of a large

number of drugs, it is also used to refer to associated conditions that increase the risk of drug side effects, drug errors, and poor adherence. There is no strict definition of the number of drugs that constitute polypharmacy. A previous report found that the consumption of six or more medications was associated with an increased incidence of adverse drug reactions.²⁴ However, a recent systematic review found that the occurrence of adverse drug reactions is associated with the intake of 2–11 drugs, and that the risk of adverse drug reactions cannot be determined by the number of drugs alone.¹⁷ Furthermore, as long as the complete list of medications is reviewed and the risk/benefit ratio for each patient has been evaluated, polypharmacy is not problematic per se, and the term “appropriate polypharmacy” is applicable. Therefore, it is necessary to optimize the content of prescriptions not only in terms of the number and type of drugs, but also in terms of safety.

Potentially Inappropriate Medications

Drugs with a high risk of ADEs are commonly referred to as inappropriate prescriptions for older adults.^{4,6} Inappropriate prescription practices include both potentially inappropriate medications (PIMs) and potential prescription omissions (PPOs).²⁵ PIMs are defined as drugs that are associated with more clinical risks (including drug–drug and drug–disease interactions) than benefits.²⁶ The two most frequently used quality criteria are the Beers criteria and the Screening Tool of Older Persons’ potentially inappropriate Prescriptions (STOPP) criteria.^{6,27,28} These tools were developed in the United States (US) and Europe; however, because they can be applied in a short time and include many drugs approved in Japan, they are being used in Japan as screening tools for PIMs in older adults. The most frequently prescribed PIMs included vasodilators, benzodiazepines, antidepressants, cardiac medications, and anticoagulants. PIMs are associated with older age, frailty, and polypharmacy.^{29,30} A review of all medications is recommended in older adults, particularly if more than 10 drugs are prescribed in combination; such combination prescriptions increase the likelihood of PIMs.³¹

PIMs are associated with poor outcomes in older adults in clinical practice including rehabilitation medicine. Hyperpolypharmacy (use of >10 drugs) or PIMs in post-acute older adults is associated with a decline in basic ADL.^{32–34} The use of PIMs in patients with hip fractures delays full functional recovery.³⁵ Increased PIM use during rehabilitation hospitalization is associated with decreased functional improvement in geriatric patients after a stroke.³⁶ In addition, PIMs are associated with psychological problems,

poor quality of life (QOL), and unplanned readmissions in hospitalized older patients.^{12,37,38} These findings suggest that PIMs may negatively impact the outcomes of patients undergoing rehabilitation. Furthermore, the use of PIMs in older adults tends to increase after hospitalization,³⁹ especially in convalescent rehabilitation settings where antipsychotics, antidepressants, and first-generation antihistamines are administered more frequently during hospitalization.³⁶ Therefore, pharmacists and physicians need to collaborate in a multidisciplinary manner to screen for PIMs and to provide appropriate pharmacotherapy for hospitalized older adults undergoing rehabilitation.

Potential Prescribing Omissions, or Underuse

Inappropriate prescribing in older adults includes PIMs and potential prescription omissions (PPOs); a PPO, or the underuse of medication, is defined as “not prescribing a beneficial medicine for which there is a clear clinical indication²⁵” and may be related to increasing numbers of hospital admissions and falls, exacerbation of chronic conditions, and the development of secondary diseases.^{40,41} The Screening Tool to Alert to Right Treatment (START criteria) has been developed to identify PPOs in older adults and to encourage physicians to prescribe the correct treatment; START has been validated and its use is recommended in clinical practice.²⁷ A previous study reported that PPOs were found in nearly half of all community-dwelling older adults,⁴² and that the probability of PPOs increased significantly with the number of medications.⁴³ In older adults, PPOs are more common in patients with cardiovascular disease, hyperlipidemia, osteoporosis, chronic obstructive pulmonary disease, depression, and cancer.⁴⁴ It can be assumed that physicians are unwilling to prescribe more drugs to patients with polypharmacy because of the complexity of drug therapy, ADEs, drug–drug interactions, and fear of poor adherence. However, pharmacists and physicians should be cautious in pharmacotherapy, especially in older patients with multimorbidity, because PPOs may be associated with a poor prognosis in these patients.

Anticholinergic Effects

The side effects of anticholinergic drugs are not well recognized in older adults. Such effects include headache, drowsiness, dry mouth, hand tremors, unstable movements, falls, blurred vision, and increased anxiety. Anticholinergic drugs can worsen cognitive function,⁴⁵ especially in patients with Alzheimer’s disease and other dementias in which central cholinergic neurotransmission has already been compro-

mised. Older adults are at a higher risk of anticholinergic side effects, partly because of deficits in drug metabolism, excretion, and age-related deficits in cholinergic neurotransmission.⁴⁶ Anticholinergic drugs are commonly prescribed for older adults: 23% of community-dwelling older adults and 60% of nursing home residents reportedly take anticholinergic medications, and 34% of nursing home residents and 13% of community-dwelling older adults reportedly take two or more anticholinergic medications.⁴⁷

The anticholinergic burden is independently associated with impaired physical function and ADL, e.g., gait and the ability to stand up from a chair.^{48,49} However, the extent to which this association can be attributed to anticholinergic effects versus that to related diseases and frailty is unclear. To date, there is limited evidence to indicate that reducing the burden of anticholinergic effects leads to improved function, engagement in rehabilitation, or improved habitual physical activity.⁵⁰

The total anticholinergic load (cumulative potential load) is an important consideration when prescribing anticholinergic drugs. The anticholinergic risk scale (ARS) was developed to provide a score for the strength of each anticholinergic medication.⁵¹ Drugs with high ARS scores have strong anticholinergic effects and are associated with poor prognostic outcomes in rehabilitation such as lower cognitive levels,⁵² poorer physical function,^{53,54} and a lower rate of home discharge.⁵⁵

DRUG-RELATED FUNCTIONAL IMPAIRMENT IN REHABILITATION MEDICINE

Dysphagia

Dysphagia is associated with negative outcomes such as the development of pneumonia and malnutrition in rehabilitated patients. Aging, diseases such as stroke and neurological disorders, and medications can cause dysphagia.⁵⁶ The swallowing process is divided into the antecedent, preparatory, oropharyngeal, pharyngeal, and esophageal phases, and some medications have negative effects on all these phases. Drowsiness, decreased level of consciousness, decreased cognitive function, decreased saliva secretion, inadequate food mass formation due to xerostomia, decreased swallowing clearance, and extrapyramidal symptoms are the main causes of drug-induced dysphagia.⁵⁷ In particular, drugs with anticholinergic effects exert an inhibitory effect at the level of the central nervous system and also cause dry mouth due to decreased salivary secretion.⁵⁶ The ARS score is associated with the development of aspiration pneumonia in

older adults undergoing rehabilitation.⁵⁸) Common examples of drugs with high ARS scores are anticholinergics used in the treatment of overactive bladder, anti-Parkinson's disease drugs, first-generation antihistamines used for pruritus due to skin diseases, and tricyclic antidepressants. These drugs should be used with caution, especially in patients undergoing rehabilitation. Diuretics can also cause dry mouth. Antipsychotics and antiemetics have dopamine D2 receptor-blocking effects and are prone to extrapyramidal side effects.⁵⁹) Benzodiazepines, anxiolytics, sleeping pills, and muscle relaxants can cause dysphagia due to drowsiness and weakness in the swallowing muscles caused by muscle relaxation.⁶⁰)

Some drugs may trigger the swallowing reflex and help prevent the onset of pneumonia.⁶¹) Angiotensin-converting enzyme inhibitors normalize the swallowing reflex by inhibiting substance P degradation, whereas amantadine and cilostazol normalize the swallowing reflex by increasing substance P levels.^{62–64}) The Chinese herbal medicine Banxia Houpo Tang may also improve swallowing and cough function.^{65,66})

Depression and Drowsiness

Depression and drowsiness are factors that inhibit “participation” in rehabilitation and decrease the likelihood of maximizing rehabilitation outcomes. Depression is commonly a post-stroke complication but may also be caused by medications. Psychiatric side effects such as insomnia and depression occur early during the initiation of corticosteroid therapy.⁶⁷) Central sympathetic inhibitors (central alpha 2 agonists), beta blockers, and histamine H2 receptor antagonists can also induce depression.⁶⁸)

Drugs that cause drowsiness include sedatives, antipsychotics, antidepressants, opioids, and antiepileptic drugs.⁶⁹) Sedative drugs and antipsychotics are commonly used in rehabilitation patients for the treatment of insomnia, delirium, and peripheral symptoms of dementia and can cause oversedation and somnolence. Drugs with anticholinergic effects also induce drowsiness due to their central depressant effects. The reduction or discontinuation of antipsychotics (for schizophrenia and other psychiatric disorders) and antiepileptic drugs (for epilepsy) may be difficult because of the therapeutic needs of the underlying disease. In such cases, rehabilitation should be performed with caution, taking into account all the possible side effects.

Antidepressants may be useful for treating depressive symptoms. Tricyclic antidepressants have potent antidepressant effects; however, they should be administered cautiously

to older patients because of their strong anticholinergic effects.⁷⁰) Selective serotonin reuptake inhibitors (SSRIs) are associated with a risk of falls and gastrointestinal bleeding, and caution is required while prescribing these drugs to high-risk patients.⁷¹) Antidepressants are associated with drowsiness, and the risks and benefits of treating depression and drowsiness should be carefully considered.⁷²)

Falls and Fractures

Falls occur at least once a year in 29% of community-dwelling older adults aged ≥ 65 years (rate of 0.67 falls per person per year).⁷³) It is estimated that 10% of older adults fall at least twice a year, and patients who visit the clinic regularly are more likely to belong to this high-risk group because they have more diseases and disabilities that increase their risk of falling.⁷⁴) Serious complications such as fractures, joint dislocations, sprains, and concussions occur in approximately 10% of falls.⁷⁵) Among these complications, hip fracture is one of the main factors causing older patients to become bedridden and to need nursing care; hip fracture accounts for the majority of conditions that require convalescent rehabilitation in Japan.

Factors associated with falls include sarcopenia,⁷⁶) impaired balance,⁷⁷) gait disturbance,⁷⁸) visual impairment,⁷⁸) orthostatic hypotension,⁷⁹) decreased ADL,⁷⁸) decreased instrumental ADL,⁷⁸) and medications. Medication issues that increase the risk of falls include polypharmacy as well as the prescription of antipsychotics, antidepressants, benzodiazepines, and loop diuretics.^{80,81}) Medication-related side effects such as sedation, impaired balance, decreased responsiveness, dizziness, syncope, postural hypotension, and drug-induced parkinsonism have been identified as potential causes of falls.⁸²)

Constipation and Fecal Incontinence

Constipation, diarrhea, and fecal incontinence are commonly observed geriatric syndromes in rehabilitation patients, and defecation control is one of the most important tasks for healthcare providers and caregivers.⁸³) Anticholinergic drugs are the most important among the many drugs that cause constipation and should be prescribed as little as possible to older adults owing to their side effects; if needed, these drugs should be used with caution.⁸⁴) Magnesium oxide has been widely used as a laxative and is considered to be convenient, inexpensive, and relatively safe to administer. However, while prescribing magnesium oxide, optimal dosing, serum concentrations, drug–drug interactions, and potential side effects such as hypermagnesemia need to be

considered; this is especially of consequence in older adults and in patients with renal impairment. Because older patients are prone to dehydration, if diarrhea persists, the dose of the causative drug should be reduced or discontinued; if necessary, intravenous fluids should be used to stabilize circulation and correct electrolyte abnormalities.⁸⁵⁾ Fecal incontinence significantly impairs the QOL of older adults, and non-pharmacological therapies such as diet, skin care, and support for defecation activities should be given priority over pharmacological therapies such as laxative revision.

Dysuria and Urinary Incontinence

Dysuria and urinary incontinence are common and often undertreated conditions that impair the QOL of older adults. These conditions are categorized as disorders of urine storage and discharge.^{86,87)} Drug-induced dysuria and urinary incontinence can be caused by various classes of drugs including cholinergic agonists, alpha-adrenoceptor blockers, anticholinergics, cold remedies, and antihistamines.⁸⁷⁾ In older patients and those with polypharmacy, it is important to check for new and regular prescriptions to avoid drug-induced urinary incontinence.⁸⁸⁾ Indeed, urinary incontinence is a predictor of poor rehabilitation outcomes and may contribute to the need for institutional care for many patients.⁸⁹⁾ Conversely, many medications used for urinary incontinence have anticholinergic side effects that can impair cognition and reaction time, which in turn can impair the ability to participate in rehabilitation. Therefore, it is important to address urinary incontinence in rehabilitation patients through multidisciplinary discussions; it is also necessary to share information among physicians and pharmacists through a drug management summary at the time of discharge from the rehabilitation ward or hospital.

Anorexia

Anorexia causes malnutrition and sarcopenia in patients undergoing rehabilitation and interferes with the improvement of physical function. Anorexia is caused by dysfunction of the oral and gastrointestinal tracts, central nervous system issues that can lead to abnormal food perception, and decreased general durability and persistence. The causes of drug-induced anorexia vary, and include dry mouth, taste disorders, peptic ulcers, nausea, constipation, diarrhea, cognitive decline, and drowsiness. Anticholinergic drugs induce constipation, dry mouth, and the suppression of gastrointestinal motility.⁹⁰⁾ Nonsteroidal anti-inflammatory drugs and bisphosphonates may cause peptic ulcers.⁹¹⁾ Opioids cause central nausea due to direct stimulation of the chemoreceptor

trigger zone in the medulla oblongata, nausea and constipation due to inhibition of gastrointestinal peristalsis, and increased anal sphincter tone.⁹²⁾ Digitalis, an inotropic drug, is likely to cause gastrointestinal symptoms in the early stages of the therapy.⁹³⁾ Biguanides should be prescribed with caution in patients with impaired renal function or dehydration because of the risk of nausea, vomiting, and diarrhea due to lactic acidosis.⁹³⁾ Anti-cancer drugs cause anorexia, nausea, and vomiting due to damage to the gastrointestinal mucosa and stimulation of the vomiting center.⁹⁴⁾ Hypercalcemia caused by active vitamin D3 preparations used in the treatment of osteoporosis and hypermagnesemia caused by magnesium preparations used as laxatives and antacids lead to nausea and anorexia.^{95,96)}

Some drugs may improve anorexia. Antipsychotic drugs such as sulpiride promote gastrointestinal motility owing to their antidopaminergic effects, leading to increased nutrient intake.⁹⁷⁾ However, caution should always be exercised as continuous use of these drugs may cause extrapyramidal symptoms. Mirtazapine, a noradrenergic and serotonergic antidepressant, increases appetite.⁹⁸⁾ The Chinese herbal medicine Rikkunshito suppresses gastric evacuation, improves upper gastrointestinal symptoms, and increases ghrelin secretion (which is an appetite stimulant).⁹⁸⁾ Hochuekkito and Ninjin Yoeito (herbal medicines) are also effective in improving appetite.⁹⁸⁾

Anemia

Severe anemia causes fatigue and breathlessness; this condition reduces activity as well as the ability to participate in rehabilitation. Low baseline hemoglobin levels are associated with sarcopenia, poorer recovery of physical function, and dysphagia in patients undergoing rehabilitation after stroke.⁹⁹⁾ Furthermore, improved hemoglobin levels are positively associated with functional recovery and a shorter hospital stay in stroke patients with anemia.¹⁰⁰⁾ Therefore, anemia should be assessed as a prognostic indicator at baseline and treated appropriately to maximize patient outcomes. Correction of the underlying disease (e.g., peptic ulcer) is important for treating anemia, and supplementation with nutrients (e.g., iron and vitamin B12) is necessary. Many older adults and those with reduced mobility have mild chronic anemia; however, there is little evidence that correction with iron is effective. Oral iron preparations have no significant effect on anemia and hemoglobin levels (a recent meta-analysis found an average increase of 0.35 g/dL¹⁰¹⁾), can cause significant constipation and nausea, and are ineffective in cases of anemia associated with chronic disease.

Parkinson Syndrome

Parkinsonism caused by medication usually develops in 60% of patients within 1 month and 90% within 3 months of starting antipsychotic treatment. Rapid progression within a few days to a few weeks is a characteristic feature. Factors such as age, female sex, amount of drug used, and treatment duration are also associated with the development of adverse reactions.¹⁰² A detailed evaluation of the history of antipsychotic treatment is warranted when the progression of symptoms is rapid.¹⁰² Because drug-induced parkinsonism is a side effect that tends to persist for a long time, it is important to detect and treat this side effect at an early stage. Prolonged symptoms may result in head trauma due to falls, bone fractures, and cognitive decline, which may interfere with daily life and rehabilitation.¹⁰³

PHARMACOTHERAPY AND REHABILITATION OUTCOMES

Activities of Daily Living

Recently, polypharmacy and PIMs have attracted considerable attention in rehabilitation medicine. Among patients aged ≥ 65 years undergoing convalescent rehabilitation after stroke, approximately 42% were taking six or more medications at the time of admission and thereby exhibited polypharmacy.¹⁰⁴ Approximately 58% of patients with polypharmacy were diagnosed with sarcopenia. Among 144 stroke patients with chronic kidney disease admitted to a convalescent rehabilitation ward, 48 (33.3%) exhibited polypharmacy and took six or more drugs; the improvement in ADL was significantly lower in these patients than that in the non-polypharmacy group.¹⁰⁵ PIMs, as assessed by the 2015 American Geriatrics Society Beers Criteria, showed an independent negative association with ADL recovery in older patients undergoing convalescent rehabilitation after stroke.³⁶ Furthermore, among those taking PIMs, patients using antipsychotics had lower ADL at admission and discharge, lower improvement in ADL with rehabilitation, and required longer rehabilitation times compared with those not taking antipsychotics.¹⁰⁶ These findings demonstrate that polypharmacy and PIMs may worsen ADL in older adults requiring rehabilitation.

Some drugs may be positively associated with improvements in ADL. Statins have been shown to have both positive and negative effects on the physical function of older adults.^{106–108} Older patients taking allopurinol who underwent convalescent rehabilitation showed greater improvement in ADL than those not taking allopurinol.¹⁰⁹

A recent systematic review found that the use of SSRIs in stroke patients with anxiety and depression improved ADL independence, disability, and neurological impairment.¹¹⁰ In contrast, however, another systematic review reported that the use of SSRIs in stroke patients without anxiety or depression was not effective in improving physical function.¹¹¹ Future studies are needed to examine the effects of drug interventions on the recovery of physical function and ADL in older patients undergoing rehabilitation.

Cognitive Level

Medications, drug–drug interactions, and medication side effects can have a significant impact on arousal and the state of consciousness, leading to decreased cognitive levels. Drug-induced depression and drowsiness reduce cognitive levels. Polypharmacy, increased use of psychotropic drugs, and increased anticholinergic load impair the improvement of cognitive function in patients undergoing rehabilitation.^{52,55} Among anticholinergics, chlorpromazine and hydroxyzine have strong anticholinergic effects and may cause drug-induced cognitive impairment. Indeed, increased anticholinergic effects reduce improvements in comprehension and memory, which are cognitive components of ADL in convalescent rehabilitation.⁵² Dose reduction or discontinuation of the drug should be considered in patients with suspected drug-induced cognitive impairment. Encephalopathy may develop or become irreversible with prolonged use; however, discontinuation of the causative agent often results in improvement. Although some drugs such as cilostazol and citicoline are expected to be effective in preventing or improving cognitive decline in rehabilitation patients,^{112,113} there is still insufficient evidence in this regard. Therefore, future research is needed to provide clearer evidence of the beneficial effects of pharmacotherapy on cognitive function in patients undergoing rehabilitation.

Nutritional Status

Medication is one of the factors that affect the nutritional status of older adults undergoing rehabilitation. Polypharmacy and malnutrition increase with age and multimorbidity, and their relationship is based on several mechanisms.¹¹⁴ Indeed, malnutrition is found in 14%–65% of rehabilitation patients and hinders rehabilitation outcomes such as improvement in ADL and dysphagia, length of hospital stay, and home discharge rate.^{115–117} Moreover, excessive polypharmacy (more than 10 drugs) is associated with an increased risk of malnutrition after 3 years in people older than 75 years.¹¹⁸ Polypharmacy is also reportedly associated with

sarcopenia,¹¹⁹⁾ which occurs frequently in rehabilitation patients and is an independent predictor of worse rehabilitation outcomes.^{120–122)} Recently, deprescribing polypharmacy in older sarcopenic patients undergoing convalescent rehabilitation was found to improve nutritional intake.¹⁰⁴⁾ Therefore, the prevention and correction of polypharmacy may lead to improvements in malnutrition,¹⁵⁾ sarcopenia, and physical function in older adults.

Many clinically important drugs that can affect nutritional status cause anorexia. These include the following: (1) non-steroidal anti-inflammatory drugs, corticosteroids, bisphosphonates, and potassium preparations that cause mucosal damage in the gastrointestinal tract; (2) opioids, anticancer drugs, and digitalis that cause nausea and vomiting; and (3) antihypertensive drugs, peptic ulcer drugs, antidepressants, antibiotics, and anticancer drugs that cause taste disorders.¹²³⁾

PIMs are associated with a number of clinical risks such as drug–drug and drug–disease interactions, leading to an increased risk of malnutrition. Increased PIM use during convalescent hospitalization was negatively associated with improved nutritional status and decreased ADL improvement³⁶⁾; benzodiazepine hypnotics, antipsychotics, and first-generation antihistamines were the most frequently used among these PIMs. The side effects of these drugs include dry mouth, extrapyramidal symptoms, and muscle relaxation. Therefore, nutritional intake may have been affected by side effects such as impaired lump formation, mouth opening and closing, and tongue movement, and dysphagia.

Another point worth discussing regarding the combination of pharmacotherapy and nutritional management is the Medication Pass Nutrition Supplement Program (Med-Pass).¹²⁴⁾ Med-Pass suggests distributing small (60 ml) calorie-dense oral nutritional supplements (ONS) three to four times a day between meals and at the time of medication administration. This strategy avoids duplication by using existing systems, prevents malnourished patients from taking supplements instead of meals, and may promote weight gain. Med-Pass, or prescribing sip feed ONS for taking medication, increases energy and protein intake and reduces weight loss during hospital stay.^{125,126)} Thus, medication and nutritional management strategies such as Med-Pass may help address malnutrition related to polypharmacy and PIM.

ROLE OF PHARMACISTS IN REHABILITATION MEDICINE

The role of pharmacists in the healthcare system has expanded from dispensing services to direct patient care.

The perspectives of pharmacists are essential in rehabilitation medicine. ADL assessment in older adults is effective in reducing ADEs,¹²⁷⁾ and prescription review and pharmacological management by pharmacists can reduce the number of prescriptions, healthcare costs, and the frequency of drug-related problems.^{128–130)} For inpatients undergoing rehabilitation, it is important for pharmacists to monitor ADL such as eating, exercise, toileting, cognition, and sleep while monitoring the patient's vital signs and laboratory data for systemic management. While assessing patients' ADL, pharmacists' recommendations for appropriate drug prescriptions and optimization and deprescribing of polypharmacy and PIM may have a positive impact on rehabilitation outcomes. Rehabilitation is carried out by a multidisciplinary team of physicians, therapists, nurses, dietitians, and dental hygienists; however, the effects of drugs are often overlooked by professionals other than pharmacists. In patients undergoing rehabilitation, pharmacist-centered pharmacotherapy is necessary to enhance patients' life functions from the perspective of "rehabilitation pharmacotherapy" and to minimize drug-induced functional impairment.¹³¹⁾ In addition to older adults, the target population for pharmacist-centered pharmacotherapy should include all age groups that require rehabilitation. When initiating pharmacotherapy, goal setting should be aimed at maximizing the improvement of ADL and QOL of the target patients, in addition to optimizing pharmacotherapy.

Pharmacists are expected to provide patient care through a multidisciplinary team approach. The nutritional support team (NST) aims to improve ADL and dysphagia during the convalescent rehabilitation of stroke patients.¹³²⁾ Pharmacists are key members of the NST and share information on drug-related nutritional disorders through NST rounds and discussions; they also provide pharmacological and intravenous nutritional therapies that improve the quality of nutritional care.

Here, we propose a role for pharmacists in rehabilitation medicine for each of the following three stages: at the time of hospitalization, during the hospitalization period, and at the time of discharge; we focus on convalescent rehabilitation, which is an important setting for rehabilitation medicine (Fig. 1).

At the Time of Hospital Admission

When a patient is admitted, pharmacists should review all information regarding the number of prescribing physicians and hospitals, medication management practices, and adherence prior to hospitalization; they should also evaluate any

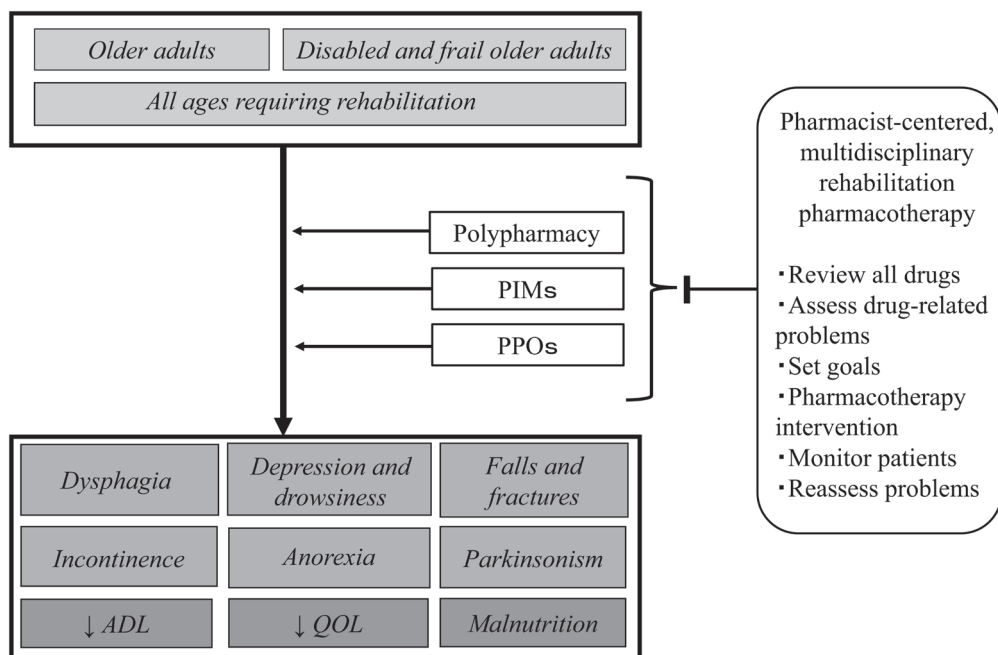


Fig. 1. Pharmacist-centered multidisciplinary rehabilitation pharmacotherapy, drug-related functional impairment, and the association between pharmacotherapy and ADL, QOL, and nutritional outcomes in rehabilitation medicine. ADL, activities of daily living; QOL, quality of life; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions.

prior history of medication-related problems. In the acute phase, all comorbidities as well as the primary disease that led to the hospitalization should be reviewed, and drugs that can be reduced or discontinued should be identified; it is also important to ensure that all necessary drugs are being prescribed. During the convalescent and chronic phases, after the acute phase treatment is completed, all prescriptions should be reviewed to identify/evaluate the following: drugs that may no longer be needed at that time, acute phase drugs that should be continued, the appropriateness of drug doses, and any necessary drugs that have not been included. Drugs that can be tapered or discontinued during rehabilitation should also be listed. It is also important to provide relevant information to physicians and other professionals if some of the prescribed drugs that are difficult to reduce/discontinue may affect rehabilitation. The appropriate time to review all prescriptions is during transitions in care, such as that from acute care to convalescent care or from convalescent care to home or chronic care.

During Hospitalization

During hospitalization, patients are generally prescribed multiple medications. In addition to regular oral medications for the treatment of existing and primary diseases, the intro-

duction of medications for patient complaints and functional disorders can easily increase the risk of polypharmacy. As patients' ADL changes significantly (and in most cases improves) as rehabilitation progresses, drug prescriptions should be reviewed periodically and opportunistically according to the ADL at that time. Considerations for pharmacotherapy include checking whether a drug is limiting activity or participation, whether the requirement for the drug has changed due to improved or increased activity or participation, and whether any appropriate non-pharmacological treatments can be applied. Pharmacists should address polypharmacy by discussing and organizing the results of prescription reviews with physicians and other professionals. If there is a risk of adverse drug reactions, the symptoms and physical dysfunction of concern should be shared with the other professionals. After the prescription is discontinued or reduced, pharmacists should follow up carefully to determine if there are any subsequent changes in the patient's condition. To assess patients' ADL, pharmacists should collect information from medical records and other professionals and visit the wards to personally check the patients' conditions. Locations for medication instruction and education for patients and their families include not only the bedside, but sometimes the training room or dining room also.

At the Time of Hospital Discharge

At the time of discharge, the prescription list should be reviewed once again according to the place of care. Drugs that may no longer be needed because of changes in the environment resulting from home discharge or institutionalization should be identified, and dose reduction or discontinuation should be considered for drugs that have a high risk of ADEs. During hospitalization, adherence is assured by the intervention of medical professionals; however, after discharge, there is a risk of decreased adherence and the development of new ADEs due to medication errors. Therefore, pharmacists should organize prescriptions with a focus on dosage (frequency and timing of taking the medication) to simplify medication management and reduce the burden of nursing care.¹³³⁾ After patient discharge, to ensure the coordination of pharmacotherapy, information should be provided to prescribers and pharmacists about the patient's progress during hospitalization and the results of prescribing interventions using tools such as drug management summaries.

CONCLUSION

This review discusses the importance of pharmacotherapy in rehabilitation medicine with a focus on pathophysiology, epidemiology, drug-related problems, and ADL decline. Recommendations on the role of pharmacists in rehabilitation medicine are also presented. Older adults undergoing rehabilitation are affected by polypharmacy, PIMs, and anticholinergics, which can limit improvements in ADL and QOL. Therefore, pharmacist-centered multidisciplinary rehabilitation pharmacotherapy is recommended. However, few studies have focused on pharmacotherapy in rehabilitation medicine. Further research on rehabilitation pharmacotherapy is required to maximize patients' physical function, activity, participation, and QOL.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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