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Medication Use and Functional Status Decline in Older Adults: A Narrative Review

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Abstract

OBJECTIVE—To critically review published articles that have examined the relationship between medication use and functional status decline in the elderly.

METHODS—The MEDLINE and EMBASE databases were searched for English-language articles published from January 1986 to December 2010. Search terms included *aged, humans, drug utilization, polypharmacy, inappropriate prescribing, anticholinergics, psychotropics, antihypertensives, drug burden index, functional status, function change or decline, activities of daily living, gait, mobility limitation, and disability*. A manual search of the reference lists of the identified articles and the authors' article files, book chapters, and recent reviews was conducted to retrieve additional publications. Only articles that used rigorous observational or interventional designs were included. Cross-sectional studies and case series were excluded from this review.

RESULTS—Nineteen studies met the inclusion criteria. Five studies addressed the impact of suboptimal prescribing on function, three of which found an increased risk of worse function in community-dwelling subjects receiving polypharmacy. Three of the four studies that assessed benzodiazepine use and functional status decline found a statistically significant association. One cohort study identified no relationship between antidepressant use and functional status while a randomized trial found that amitriptyline, but not desipramine or paroxetine, impaired certain measures of gait. Two studies found that increasing anticholinergic burden was associated with worse functional status. In a study of hospitalized rehabilitation patients, users of hypnotics/anxiolytics (e.g., phenobarbital, zolpidem) had lower relative Functional Independence Measure motor gains than nonusers. Use of multiple central nervous system (CNS) drugs (using different definitions) was linked to greater declines in self-reported mobility and Short Physical Performance Battery (SPPB) scores in two community-based studies. Another study of nursing home patients did not report a significant decline in SPPB scores in those taking multiple CNS drugs. Finally, two studies found mixed effects between antihypertensive use and functional status in the elderly.

CONCLUSION—Benzodiazepines and anticholinergics have been consistently associated with impairments in functional status in the elderly. The relationships between suboptimal prescribing,

antidepressants, and antihypertensives and functional status decline were mixed. Further research using established measures and methods is needed to better describe the impact of medication use on functional status in older adults.

Keywords

drug utilization; activities of daily living; aged

INTRODUCTION

Functional status is the cornerstone of geriatric care and serves as an indicator of general well-being. The World Health Organization's International Classification of Functioning, Disability, and Health describes the health status of a person in terms of body functions and structures, activities, and participation in life situations. An impairment or limitation in any of these functional capacities, whether due to underlying illness or personal or environmental factors, can be problematic for older adults.¹ Specifically, a decline in function can increase healthcare utilization, worsen quality of life, threaten independence, and increase the risk of mortality.²⁻⁵ As such, functional status has been recognized as a relevant and important treatment outcome in the elderly population.^{4,6-9}

There are two primary ways to measure functional status: self- or caregiver-reported or performance-based measures. Three of the most commonly used self- or caregiver-reported measures are: 1) basic activities of daily living (BADL—bathing, dressing, getting around the house, toileting, feeding, grooming¹⁰ 2) instrumental activities of daily living (IADL— using the telephone, paying bills, taking medications, preparing light meals, doing laundry, shopping, housekeeping, mode of transportation, ability to handle finances¹¹ and 3) mobility (i.e., walking one-half mile, walking up and down stairs, doing heavy work around house).¹² Typically, mobility is the first functional status measure to show decline whereas BADL is the last. Derivations of these self- or caregiver-reported measures include the 36-Item Short Form Health Survey (SF-36) Physical Functioning domain, which combines four scales (i.e., physical functioning, physical role, bodily pain, self-rated health) with scores from 0 to 100 (higher scores indicate better function).¹³ The Karnofsky Performance Status measure assigns scores ranging from 0 (dead) to 100 (perfect health).¹⁴ Finally, persistent lower extremity limitation is operationally defined as two reports over a 6-month period of difficulty walking one-quarter mile or climbing 10 steps without resting.¹⁵

Performance-based measures may be particularly useful in evaluating older adults at the upper end of the functional spectrum who would otherwise report little or no physical limitation.¹⁶⁻¹⁷ One such measure, gait speed, is both a predictor of adverse outcomes and an indicator of physical frailty in older adults.¹⁸⁻¹⁹ A recent pooled analysis of over 34,000 older adults found a significant association between gait speed and survival.¹⁶ Gait speed can be analyzed alone²⁰ and/or as part of the short physical performance battery (SPPB).²¹⁻²² The SPPB evaluates balance, gait, strength, and endurance by testing one's ability to stand with feet together in three positions (i.e., side-by-side, semi-tandem, and tandem), time required to walk eight feet, and time required to rise from a chair and return to the seated position five times.¹⁷ Timed chair stands have been used alone to measure functional status²³ though the clinical significance of this measure by itself is unclear.²⁴ Lastly, the Functional Independence Measure (FIM) is a widely-accepted functional assessment measure in the rehabilitation community.²⁵ Of the FIM's 18 items, 13 address physical domains and comprise the motor portion of the FIM.²⁵⁻²⁶ Each item is scored based on the observed level of assistance required to perform BADL and IADL, with lower scores indicating the need for more assistance.²⁶ Progress may be described in terms of relative FIM motor gains (FIM gain/(maximal possible FIM—actual admission FIM)).²⁷

Risk factors for functional status decline are numerous and include advanced age, low income, poor self-rated health, presence of comorbidities or certain medical conditions (e.g., arthritis, cognitive impairment, depression), lifestyle habits (e.g., lack of physical activity, current or past smoking, no or excessive alcohol consumption), and medication use.^{28–29} Multiple potential physiological explanations exist to elucidate the impact of medications on functional outcomes.^{9,30–31} For example, it has been suggested that specific medications may increase risk for impaired functional status by adversely affecting such domains as alertness, vision, and muscle strength.^{30–31} With medication use being a potentially modifiable risk factor for functional status decline, it is important to understand whether there is consistency across studies. Given this background, the objective of this study was to examine the potential risk of medication use on functional status decline in the elderly.

MATERIALS AND METHODS

The MEDLINE and EMBASE databases were searched for English-language articles published from January 1986 to June 2011. Search terms included *aged, humans, drug utilization, polypharmacy, inappropriate prescribing, anticholinergics, psychotropics, antihypertensives, drug burden index, functional status, function change or decline, activities of daily living, gait, mobility limitation, and disability*. A manual search of the reference lists of the identified articles and the authors' article files, book chapters, and recent reviews was conducted to retrieve additional publications. Only articles that used rigorous observational or interventional designs were included. Cross-sectional studies or case series were excluded from this review.^{32–41} This review will not cover use of medications designed to improve functional status or those that may have a direct detrimental effect on muscles and nerves. The reader may find information elsewhere on the following potential drug targets for preventing or treating functional status decline (and their corresponding drugs): hormonal dysregulation (growth hormone,^{42–45} testosterone,^{46–47} dehydroepiandrosterone⁴⁸), sarcopenia (vitamin D^{49–52} angiotensin-converting enzyme inhibitors^{53–55}), and inflammation (HMG-CoA reductase inhibitors⁵⁶).

RESULTS

Two thousand one hundred fifty-seven articles were identified by the literature search. Nineteen studies were identified for inclusion in this review. The individual studies were categorized into the following subsections: suboptimal prescribing, benzodiazepines, anticholinergics, nonbenzodiazepine psychotropics, multiple central nervous system (CNS) drugs, and antihypertensive drugs. These studies are summarized in Tables 1 through 6 by categories. Below we provide a brief annotation for each study, and each subsection ends with a summary of study strengths and weaknesses.

Suboptimal Prescribing

Suboptimal prescribing may be defined by underuse or overuse of medications or by prescribing potentially inappropriate medications.⁵⁷ The association of different measures of potentially suboptimal prescribing and functional status has been examined in four studies (Table 1), all of which used self-report to measure medication use.

Magaziner et al. examined the relationship between multiple medication use (i.e., polypharmacy) and self-reported BADL and IADL outcomes in older adults.⁵⁸ The random sample included 609 women living in Baltimore, Maryland, who provided information at baseline and a 1-year follow-up home interview. Control variables included demographics (i.e., age, education) and number and severity of chronic diseases. Using multivariable linear regression models, they found that with increasing number of prescription medications there was greater decline in BADL and IADL.

A 2002 study by Hanlon et al. examined two standard sets of explicit criteria for potentially inappropriate drug use and their association with functional decline in the elderly.⁵⁹ One set of explicit drug utilization review (DUR) criteria considered potential prescribing problems with dosage, duplication, drug-drug interactions, duration, and drug-disease interactions for eight medications/classes (i.e., digoxin, calcium channel blockers, angiotensin-converting enzyme inhibitors, histamine₂ receptor antagonists, nonsteroidal anti-inflammatory drugs, benzodiazepines, antipsychotics, and antidepressants).⁶⁰ The other set of explicit criteria included Beers' drugs-to-avoid in older adults.⁶¹ The primary outcomes were four self-reported indicators of functional status based on BADL, IADL, and mobility. No statistically significant relationship was seen between drugs-to-avoid and any of the functional status measures. They did find though that subjects exposed to potentially inappropriate drugs due to drug-drug or drug-disease interactions had a higher risk of decline in BADL (adjusted odds ratio=2.04, 95% confidence interval [CI]=1.32-3.16). A study of hospitalized elders also found no statistically significant relationship between drugs-to-avoid criteria and change in functional limitations determined by a 7-item BADL measure.⁶² The lack of association remained even after controlling for potential confounders, including adverse drug reactions (ADRs).

A study of older community-dwelling Mexican Americans by Pugh et al. from 2007 examined the relationship between three types of potentially suboptimal prescribing (i.e., drugs-to-avoid, drug-drug interactions, and polypharmacy [5+ drugs]) and a timed performance measure of functional status (i.e., SPPB).⁶³ Controlling for specific comorbid diseases (e.g., stroke, diabetes, arthritis) and other health status and sociodemographic factors, only polypharmacy was significantly associated with a change in SPPB.

Finally, a cohort study of 294 older adult survivors enrolled in a health services intervention study examined the relationship between polypharmacy (defined as 6–9 and 10+ drugs) and IADLs.⁶⁴ They found that, compared to those without polypharmacy after controlling for demographics, self-rated health, and comorbidities, polypharmacy was associated with greater IADL decline ($P<0.01$).

These five studies share overlapping limitations. The studies by Pugh et al., Magaziner et al., and Jyrkka et al. are limited in that the polypharmacy variables may have represented both necessary and unnecessary drugs. The Beers drugs-to-avoid criteria studied by Hanlon et al., Corsonello et al., and Pugh et al. are controversial since individual patient characteristics cannot be considered before classifying a specific type of drug as potentially inappropriate. The studies by Magaziner et al., Hanlon et al., Jyrkka et al., and Corsonello et al. all utilized self-reported functional status measures, which may not be as sensitive to changes as the timed performance measure used in the study by Pugh et al. Moreover, residual confounding is a potential problem with all of these observational studies especially since different factors were controlled for across studies. Finally, none of the studies used nationally representative samples; therefore, the findings may not generalize to those living in other parts of the United States.

In summary, there was no relationship identified between Beers' drugs-to-avoid and functional status.^{59,62–63} Three studies found a relationship between polypharmacy and functional status decline,^{58,63,64} which is consistent with polypharmacy being a strong risk factor for ADRs.⁶⁵ Drug-disease interactions may also be an important risk factor for not only functional status decline but also ADRs.^{66–69}

Benzodiazepines

Table 2 summarizes four studies that evaluated the association between benzodiazepine use and BADL, IADL, mobility, and performance-based functional status measures. Two of

these studies utilized pharmacy data from a health maintenance organization (HMO) in the northwestern United States,⁷⁰⁻⁷¹ and the other two analyzed self-reported medication data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE).⁷²⁻⁷³

The objective of the study by Ried et al. was to determine the association between benzodiazepine exposure and self-reported BADL and IADL functioning in 4,192 older HMO enrollees.⁷⁰ Any benzodiazepine exposure within the past year was negatively associated with a combined measure of BADL and IADL functioning ($\beta=-0.06$, $P<0.001$).

In 2002, Gray et al. examined in older adults the association between benzodiazepine use and incident disability measured by the SF-36 Physical Functioning scale.⁷¹ Benzodiazepine use was significantly associated with incident loss of overall physical function (adjusted hazards ratio [Adj. HR]=1.51, 95% CI=1.02-2.24) in the fully adjusted model. The use of benzodiazepines was not associated with limitations in BADL specifically when adjusting for other factors (Adj. HR=1.71, 95% CI=0.87-3.34).

A 2003 study by Gray et al. investigated whether benzodiazepine use in women 70 years of age increased the risk of physical function decline as measured by the SPPB.⁷² After adjustment for potential confounders, benzodiazepine use was associated with a greater decline in physical performance over four years than nonuse ($\beta=-1.16$; $P<.001$). The use of higher-than-recommended doses was related to decline ($\beta=-2.26$; $P<.001$), but use of lower doses was not ($\beta=-0.53$; $P=.246$). Long-term use (i.e., used at baseline and three years before baseline) was also related to decline ($\beta=-1.65$; $P<.001$), whereas recent use (i.e., used at baseline only) and past use (i.e., used three years before baseline only) were not. Similar results were obtained when restricting the sample to those without disability at baseline.

Furthermore, in 2006 Gray et al. studied whether benzodiazepine use was associated with incident disability in BADL and mobility in older individuals.⁷³ In multivariable models, benzodiazepine users were 1.23 times as likely as nonusers (95% CI=1.09-1.39) to develop mobility disability and 1.28 times as likely (95% CI=1.09-1.52) to develop BADL disability. Risk for incident mobility was increased with short- (Adj. HR=1.27, 95% CI=1.08-1.50) and long-acting benzodiazepines (Adj. HR=1.20, 95% CI=1.03-1.39) and no use. Risk for BADL disability was greater with short- (Adj. HR=1.58, 95% CI=1.25-2.01) but not long-acting (Adj. HR=1.11, 95% CI=0.89-1.39) agents compared to no use.

These studies have similar limitations worth noting. Measures of benzodiazepine use differed across studies and could have led to exposure misclassification. For example, medication information was only collected at 3-year intervals in the most recent Gray et al. study. Benzodiazepine use between interviews was not assessed, and similarly intermittent use of benzodiazepines would bias the findings toward the null. In terms of outcome measures, only one study evaluated functional status with the SPPB while the others relied on self-report measures. Adjusting for confounding by indication was a challenge across all four studies. For example, anxiety, a potential independent risk factor for disability and a common indication for benzodiazepine use, could not be controlled for in the Gray et al. 2003 and 2006 studies because the EPESE survey did not ask about this condition. Finally, generalizability of these studies' results may be limited, as the populations of interest were specific to each study.

To summarize these four studies, benzodiazepine use defined by different measures was consistently associated with worse functional status regardless of the approach used to ascertain the outcome. It is biologically plausible that high-dose and/or long-term use may explain at least some of the negative association between benzodiazepines and functional status in the elderly⁷² but further research is needed to substantiate this relationship.

Anticholinergics

Anticholinergics were evaluated in two studies to describe their impact on functional status (Table 3). To determine medication exposure, Agar et al.⁷⁴ relied on self-report while Han et al.⁷⁵ utilized records from patients' primary care visits.

Han et al. identified 544 community-dwelling men with hypertension from the Connecticut Veterans Longitudinal Cohort and tested them at three time points over two years.⁷⁵ To measure the potential anticholinergic effects of each drug and determine an overall anticholinergic drug burden, the previously validated Clinician-Rated Anticholinergic Scale was used.⁷⁶ During follow-up, 66.9% (n=364) used at least one anticholinergic drug in year one and 69.5% used at least one in year two. An increase in total anticholinergic burden by one unit per three months increase was associated with a decrease in IADL scores by 0.10 points ($P=0.001$). After adjusting for demographic and health behavioral factors, cumulative anticholinergic exposure was associated with poorer self-reported IADL performance.

Agar et al. conducted a secondary analysis of 304 participants from the randomized Palliative Care Trial.⁷⁴ Australian palliative care patients with any form of pain in the three months preceding the trial were eligible for inclusion, and the mean age of participants was 71 years. Consistent with Han et al., a modified version of the Clinician-Rated Anticholinergic Scale was used to measure exposure. Medications were further divided into three categories: 1) those for comorbid conditions, 2) those indicated for symptom control of the life-limiting illness, and 3) those that may be used for both purposes (e.g., tricyclic antidepressants, antiepileptics). On average, subjects survived 107 ± 103 days (range: 11–752 days) from study entry. As death approached, there was a slight trend toward increased total anticholinergic scores. Anticholinergic scores for drugs indicated for symptom control increased as death approached ($P<0.001$). Increasing total anticholinergic load by one unit was associated with increased odds of being in a lower Australia-modified Karnofsky Performance Status (AKPS) category by a factor of 1.18 (95% CI=1.11-1.23). Anticholinergic load associated with symptomatic treatments was higher in subjects with lower AKPS scores.

A limitation of the studies by Han et al. and Agar et al. is that anticholinergic effects are considered additive and linear by the Clinician-Rated Anticholinergic Scale. Agar et al. only studied palliative care patients with pain complaints, which could have led to overestimation of the total anticholinergic burden since regularly scheduled opioids were included in this measure.

In sum, two studies found that total anticholinergic load was negatively associated with functional status measures. These findings were consistent across two unique study populations.

Nonbenzodiazepine Psychotropics

Antidepressants were evaluated in three studies to describe their impact on functional status (Table 4). To determine medication exposure, Penninx et al.⁷⁷ relied on self-report, Shiri-Sharvit et al.²⁷ utilized records from participants' hospitalizations, and Draganich et al.²⁰ only included subjects who self-reported that they did not use CNS drugs within the past 30 days.

Penninx et al. published a 4-year prospective study of 1,286 participants 71 years of age from the Iowa EPESE cohort.⁷⁷ Antidepressant use over the past two weeks (primarily with amitriptyline) was not associated with a change in physical functioning measured by BADL, mobility, and SPPB.

The study conducted by Draganich et al. was a randomized crossover, 4-period, double-blind laboratory trial in 10 men and two women aged 65–72 years.²⁰ Test subjects were given one of three antidepressants (i.e., amitriptyline 50mg, desipramine 50mg, or paroxetine 20mg) once daily or placebo four hours before testing their gait. The washout period was six days between each treatment. Paroxetine and desipramine did not significantly affect unobstructed (walking without encountering obstacles) or obstructed (walking and stepping over obstacles) gait compared to placebo. Single-dose amitriptyline impaired the following measures during obstructed gait testing: gait speed in meters per second (impaired by up to 8%, $P=0.028$), gait cadence in steps per minute (impaired by up to 4.9%, $P=0.012$), angular velocity of hip flexion in degrees (impaired by up to 10%, $P=0.004$), and angular velocity of knee flexion in degrees (impaired by up to 8.3%, $P=0.018$).

Shiri-Sharvit et al. studied the impact of three classes of psychotropic drugs (i.e., hypnotics/anxiolytics, antidepressants, and antipsychotics) on the motor portion of the FIM in 263 hip-fracture patients 75 years of age undergoing rehabilitation in the inpatient geriatric rehabilitation unit of an urban academic medical center in Israel.²⁷ Psychotropic drugs of interest were hypnotics/anxiolytics (e.g., phenobarbital, zolpidem), antidepressants (e.g., sertraline, trazodone), and antipsychotics (e.g., haloperidol, olanzapine). Users of any psychotropic drug had less relative FIM motor score improvements than nonusers (0.31 ± 0.1 vs. 0.42 ± 0.2 [$P=0.039$]), based on assessments on admission and three days before discharge. In the final linear regression model, only hypnotics/anxiolytics were associated with worse relative FIM motor score gains ($r=-2.68$, $P=0.04$).

These three studies have different limitations due to differences in exposure and outcome measures. In the study by Penninx et al., medication use was admittedly not a focus. Furthermore, drug dose, indication, frequency, and duration of use were not considered in the study by Shiri-Sharvit et al. The authors also acknowledge that the small study population led to difficulty in subgroup analyses, and one cannot tell in this study which of the hypnotic/anxiolytic drugs had the greatest impact on functional status. Sample size was also a limitation of the study by Draganich et al., as only 12 healthy, mostly male participants were studied. In addition, this study looked at the effects of select antidepressants four hours after ingestion, but long-term drug use may have yielded different outcomes. Finally, generalizability is a limitation of all of the studies in this section.

In summary, one study of EPESE participants found that the highly anticholinergic agent amitriptyline was not associated with a change in physical functioning. A 12-person randomized crossover study showed an association between amitriptyline exposure and limitations on obstructed gait testing. Finally, a study of hospitalized older adults undergoing hip-fracture rehabilitation found that use of hypnotics/anxiolytics was associated with worse FIM motor score gains than nonuse.

Multiple Central Nervous System Drugs

The rationale for assessing potential negative effects of multiple CNS drugs for research purposes is as follows: It is well known that psychotropic drugs that affect the CNS (i.e., antipsychotics, antidepressants, benzodiazepines) may by themselves increase the risk of specific geriatric syndromes (i.e., falls/fractures, delirium, urinary incontinence).^{78–80} Although there are fewer studies, opioids and anticholinergics may also be associated with these conditions.^{78–80} As such, it is logical that the duplication or combination of the aforementioned drug classes, as is often seen in clinical practice, would be of concern for the geriatric population. Three studies have addressed the impact of multiple CNS drug use on functional status decline (Table 5). All three relied on self-reported drug use to measure exposure.

Boudreau et al. evaluated whether CNS medication use in adults from the Health, Aging and Body Composition (Health ABC) study was associated with a higher risk of incident mobility limitation (i.e., persistent lower extremity limitation).¹⁵ CNS drug use was defined by the use of one or more drugs from the following four therapeutic classes: 1) benzodiazepines and benzodiazepine-like sedatives (e.g., zolpidem), 2) antidepressants, 3) antipsychotics, and 4) opioids. A standardized daily dose (SDD) was calculated by dividing a participant's daily dose of a CNS medication by the minimum effective dose per day. To develop a continuous exposure measure, the SDDs for individual CNS agents were summated. Multivariable Cox proportional hazard analyses were conducted, adjusting for demographics, health status, and health behaviors. By year six, 49% had developed persistent lower extremity limitation. CNS medication users compared to never users showed a higher risk for incident mobility limitation (Adj. HR=1.28; 95% CI 1.12–1.47). Similar findings were seen in analyses examining dose- and duration-response relationships.

Hilmer et al. conducted a 5-year longitudinal study of 2,058 subjects from the Health ABC study.²¹ The investigators created a combined measure of anticholinergic and sedative drug exposure based on pharmacokinetic and pharmacodynamic properties named the Drug Burden Index (DBI), which has subsequently been patented. This measure considered the daily dose of each anticholinergic and/or sedative medication taken by a participant and divided it by the daily dose plus the minimum effective dose of that drug. Then, cumulative exposure over six years (three points in time) was calculated by the use of area under the curve principles. Controlling for various demographic and health status factors, they found that for each 1-unit increase in area under the curve for drug burden (AUCDB) at baseline there was a significant decrease in gait speed and SPPB. The same exposure measure was applied to data collected at three points in time over a 12-month period from 602 nursing home residents >70 years of age.²² Unlike the study using Health ABC data, they found no statistically significant relationship between the AUCDB measure and gait speed or the composite SPPB.

These three studies have several limitations worth mentioning. Boudreau et al. looked at three distinct classes of psychotropics as well as opioids. There is limited information to show that opioids alone or in combination with other psychotropic drugs increases risk of falls/fractures and delirium^{81–86}; however, two recent studies suggested that opioids may actually improve functional status in older adults with chronic nonmalignant pain.^{87–88} While the evidence for delirium due to anticholinergic use is strong,⁸⁰ the evidence that they increase the risk of falls and functional status decline is limited.^{35,74–75} Some might question the combining of anticholinergic drugs with those that have sedative properties used in the calculation of DBI.²¹ Moreover, there are conflicting opinions and at least four other approaches regarding which drugs should be classified as anticholinergic,⁸⁹ and for many drugs it is difficult to separate anticholinergic from sedative effects (e.g., tricyclic antidepressants, skeletal muscle relaxants). Other limitations include the use of a self-reported mobility measure such as that used in the study by Boudreau et al. The studies by both Hilmer et al. and Boudreau et al. used Health ABC data and, thus, share the same limitation regarding generalizability since participants at baseline had to be at least 70 years old and without self-reported mobility problems.

In summary, two of three studies found a relationship between composite measures of exposure to medications affecting the CNS. The mobility decline findings by both Boudreau et al. and Hilmer et al. have yet to be replicated in other samples using rigorously designed observational studies. Future studies are needed to better understand this area.

Antihypertensive Drugs

Table 6 summarizes the findings of two studies investigating antihypertensive drugs and their impact on functional status in particular. The rationale for considering these drugs is that past studies have identified changes in muscle function, energy level, and cognition associated with antihypertensive agents, but data on drug effects outside the cardiovascular realm is limited.^{90–93} Both studies described below used self-report to determine drug exposure.

Applegate et al. published the results of a multicenter trial of antihypertensives in community-dwelling men and women 60 years of age.⁹⁴ The Systolic Hypertension in the Elderly Program (SHEP) study recruited 4,736 men and women with systolic blood pressures of 160–219 mmHg and diastolic blood pressures of <90 mmHg randomized subjects to active antihypertensive therapy (n=2,365) or placebo (n=2,371). Active treatment was given in a stepwise manner, starting with chlorthalidone 12.5–25mg and adding 25–50mg of atenolol in step 2. If atenolol was contraindicated or not tolerated, then reserpine 0.05–0.1mg could be used instead. ADLs were categorized as basic (e.g., bathing, dressing, eating), moderate (e.g., writing/handling small objects, walking up and down stairs, walking one-half mile) or advanced (e.g., carrying groceries, moving furniture, crouching/kneeling) and were assessed over an average follow-up of five years. In the intention-to-treat analysis, the treatment group experienced significantly less deterioration in some specific basic and moderate ADLs (i.e., personal grooming, dressing, eating, toileting, walking up and down stairs, walking one-half mile) versus placebo ($P<0.05$); however, there were no differences between the treatment and placebo groups for change over time in any of the overall ADL categories.

More recently, Agostini et al. studied 544 community-dwelling men 65 years of age with hypertension from the Connecticut Veterans Longitudinal Cohort to evaluate the association between antihypertensive medication use and functional outcomes.²³ Intensity of antihypertensive medication use was defined by: 1) number of antihypertensive classes prescribed across all four of the 3-month intervals (assigned scores ranging from zero to 20), and 2) number of antihypertensive classes subjects were exposed to for at least two of the 3-month intervals. Timed chair stands were used to measure functional status. In the multiple linear regression model (adjusted for sociodemographic, comorbidity, hypertension severity, and baseline values of the primary outcome measures), for each 1-unit increase in antihypertensive intensity score, the time to complete the chair stand test was lengthened by 0.11 seconds (95% CI=0.05–0.16). Furthermore, a linear trend was identified between number of antihypertensive classes used and time to complete chair stands ($P<0.001$) after adjusting for hypertension severity and the other aforementioned covariates.

These studies also have limitations. The design of the study by Agostini et al. was less rigorous than that of the study by Applegate et al. Also in regard to the Agostini et al. study, the clinical significance of timed chair stands beyond measuring lower body strength remains unclear.²⁴ Generalizability is problematic in both studies because subjects selected for the SHEP randomized controlled trial may not be comparable to sicker elders with multiple morbidities, and the study by Agostini et al. included only male participants.

These two studies yielded mixed results on the impact of antihypertensives on functional status in the elderly. While antihypertensive use did not significantly impact the three ADL categories from the Agostini et al. study, there was a trend toward less deterioration for some specific ADL measures with antihypertensive therapy. In the study by Applegate et al., the worsening of timed chair stands was statistically significant but of unclear clinical significance. Based on these data, additional information about the effects of specific antihypertensive classes and individual agents on functional status is needed.

DISCUSSION

To the best of our knowledge, this is the first systematic review of the risk of medications with functional status decline in older adults. We found that for the majority of studies (i.e., 14/19), medication use, regardless of the drug class, was associated with worse functional status. Out of the 19 studies identified, only two were randomized trials.^{20,94} Of these, one found a statistically significant effect while the other did not. Fewer than half of the studies (i.e., 8/19) actually used performance-based measures to evaluate participants' functional status. Researchers reported no association in two studies^{22,77} and increased risk of functional status decline in six studies.^{20, 21,23, 27,63,72} Of the remaining 10 studies, eight assessed self-reported BADL and/or IADL,^{58–59,62,64, 70,73,75,94} one examined self-reported mobility only,¹⁵ and two evaluated self-reported SF-36 Physical Functioning or AKPS scores as functional status measures.^{71,74}

Geriatric syndromes (e.g., falls/fractures, delirium, urinary incontinence) follow a common pathway ultimately leading to functional status decline, so it is logical that medication use would be considered a contributing factor to functional decline among the elderly.^{9,95} It is interesting though that of the six major medication classes studied (i.e., benzodiazepines, antidepressants, hypnotics/anxiolytics, antipsychotics, opioids, antihypertensive drugs), only benzodiazepines had more than two published studies even though these drugs have been among the most commonly prescribed for more than 40 years.⁹⁶ All four benzodiazepine studies were prospective cohort designs, and all had negative outcomes regardless of the functional status measure employed. It is plausible that benzodiazepine-like sedatives (e.g., zolpidem), which like benzodiazepines increase the risk of falls and fractures,⁹⁷ may also adversely affect functional status in the elderly. In the absence of studies examining the impact of benzodiazepine-like sedatives on functional status, the findings presented here highlight the potential for benzodiazepines to worsen functional status and compromise independence among community-dwelling older adults.

This systematic review has several potential limitations worth mentioning. One potential limitation is publication bias because negative studies are less likely to have been published. Also, although PubMed and EMBASE were used to search for relevant articles, it is possible that some studies may have been missed if they were indexed in other databases. In order to minimize the chance of missing such studies, the authors manually searched the reference lists of the identified articles and recent reviews to identify potential studies for inclusion. The search strategy was also limited to the English language and limited to older adults because the intent of this study was to evaluate the impact of medication use on functional status decline in older adults. The use of strict inclusion criteria may limit the generalizability of this review.

CONCLUSIONS

Benzodiazepine and anticholinergic use has been consistently linked to impairments in functional status in the elderly. The impact of suboptimal prescribing, antidepressants, and antihypertensives on functional status decline was mixed. Future studies are needed to further evaluate the impact of medication use on functional status in older adults.

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Table 1
Studies Examining the Relationship between Suboptimal Prescribing and Functional Status

Author/Year	Design	Setting	Subjects/Patients	Exposure	Results
Magaziner J/1989 ⁵⁸	Longitudinal – 1 year	Community (Baltimore, MD)	609 women	65 years	Number of prescription drugs
Hanlon JT/2002 ⁵⁹	Longitudinal – 3 years	Community (Duke EPESE)	3,234 men and women	65 years	8 drug classes with dosage, duplication, drug-drug or drug-disease interaction problems; Use of high risk drugs (Beers)
Pugh MJ/2007 ⁶³	Longitudinal – 7 years	Community (Hispanic EPESE)	1,682 Hispanic men and women	65 years	Polypharmacy (5+ drugs); Drug-drug interactions; Use of high risk drugs (Beers)
Corsonello A/2009 ⁶²	Longitudinal – Duration of hospital stay (varied)	Hospital (Italy)	506 men and women	65 years	Use of high risk drugs (Beers)
Jyrkka J/2011 ⁶⁴	Prospective cohort – 3 years	Community (Finland)	294 men and women at baseline	75 years	Polypharmacy (6–9 drugs); Excessive polypharmacy (10+ drugs)

Abbreviations: BADL=basic activities of daily living; IADL=instrumental activities of daily living; Established Populations for Epidemiologic Studies of the Elderly=EPESE; DUR=Drug Utilization Review; Adj. OR=adjusted odds ratio; CI=confidence interval; US=United States; SPPB=Short Physical Performance Battery; NS=non-significant ($P>0.05$)

Table 2**Studies Examining the Relationship between Benzodiazepines and Functional Status**

Author/Year	Design	Setting	Subjects/Patients	Results
Ried LD/1998 ⁷⁰	Prospective cohort – 1 year	Community (HMO in the Northwestern US)	4,192 men and women 65 years	↑ BADL & IADL limitations, ($\beta=-0.06$; $P<0.001$)
Gray SL/2002 ⁷¹	Prospective cohort – 4–5 years	Community (HMO in western Washington state)	1,519 men and women 65 years	↓ SF-36 Physical Functioning score (Adj. HR=1.51; 95% CI=1.02–2.24)
Gray SL/2003 ⁷²	Prospective cohort – 4 years	Community (Iowa EPESE)	885 women 70 years	↑ SPPB decline ($\beta=-1.16$; $P<0.001$)
Gray SL/2006 ⁷³	Prospective cohort – 6 years	Community (4 sites of the EPESE)	9,093 men and women 65 years	↑ Mobility disability (Adj. HR=1.23; 95% CI=1.09–1.39); ↑ BADL disability (Adj. HR= 1.28; 95% CI=1.09–1.52)

Abbreviations: HMO=Health Maintenance Organization; US=United States; BADL=basic activities of daily living; IADL=instrumental activities of daily living; SPPB=Short Physical Performance Battery; Adj. HR=adjusted hazards ratio; CI=confidence interval; SF-36=36-Item Short Form Health Survey; Established Populations for Epidemiologic Studies of the Elderly=EPESE

Table 3
Studies Examining the Relationship between Anticholinergics and Functional Status

Author/Year	Design	Setting	Subjects/Patients	Exposure	Results
Han L/2008 ⁷⁵	Prospective cohort – 2 years	Community (VA primary care clinic, New Haven, Connecticut)	544 men 65 years with diagnosed hypertension	Cumulative exposure to anticholinergic medications over the past 12 months	0.10-point ↓ in IADLs per 1-unit ↑ in total anticholinergic burden per 3 months ($P=0.001$)
Agar M/2009 ⁷⁴	Longitudinal – Until death (varied duration)	Palliative care program in the outpatient, inpatient and nursing home settings (Australia)	304 men and women (mean age=71 years) from the Palliative Care Trial	Changes in anticholinergic load	↓ AKPS score (Adj. OR=1.18, 95% CI=1.11–1.23) per 1-unit ↑ in total anticholinergic load

Abbreviations: VA=Veterans Administration; IADL=instrumental activities of daily living; CI=confidence interval; AKPS=Australia-modified Kamofsky Performance Status; Adj. OR=adjusted odds ratio

Table 4
Studies Examining the Relationship between Nonbenzodiazepine Psychotropics and Functional Status

Author/Year	Design	Setting	Subjects/Patients	Exposure	Results	
Penninx BW/1998 ⁷⁷	Prospective cohort – 4 years	Community (Iowa EPESE)	1,286 men and women	71 years	Antidepressant drug use (mostly amitriptyline)	↔ SPPB (NS)
Draganich LF/2001 ²⁰	Randomized crossover trial – Laboratory testing (varied duration)	Community (Geriatric Clinical Research Center, Chicago, Illinois)	12 men and women	65–72 years	Amitriptyline 50mg, desipramine 50mg, paroxetine 20mg, or placebo	Amitriptyline ↓ gait speed ($P<0.05$)
Shiri-Sharvit OM/2005 ²⁷	Longitudinal – Hospital stay (varied duration)	Hospital (Israel)	263 hip-fracture patients undergoing rehabilitation	75 years	Hypnotic/anxiolytic, antidepressant, antipsychotic use	↓ FIM motor gains – any use ($P=0.039$); hypnotic/anxiolytic use ($P=0.04$)

Abbreviations: Established Populations for Epidemiologic Studies of the Elderly=EPESE; SPPB=Short Physical Performance Battery; NS=non-significant ($P>0.05$); FIM=Functional Independence Measure

Table 5
Studies Examining the Relationship between Multiple Central Nervous System Drugs and Functional Status

Author/Year	Design	Setting	Subjects/Patients	Exposure	Results
Boudreau RM/2009 ¹⁵	Prospective cohort – 5 years	Community (Health ABC Study)	3,055 black and white men and women 70–79 years at baseline	CNS polypharmacy (benzodiazepines, antidepressants, antipsychotics, and opioids combined)	↑ self-reported mobility decline (Adj. HR=1.28; 95% CI=1.12–1.47)
Hilmer SN/2009 ²¹	Prospective cohort – 5 years	Community (Health ABC Study)	3,055 black and white men and women 70–79 years at baseline	AUCDB (sedatives and anticholinergics combined)	↑ SPPB decline ($\beta=-0.08$; $P=0.01$)
Wilson NM/2010 ²²	Longitudinal – 1 year	Nursing homes (Australia)	602 men and women >70 years	AUCDB (sedatives and anticholinergics separated)	↔ SPPB (NS)

Abbreviations: Health ABC=Health, Aging and Body Composition; CNS=central nervous system; Adj. HR=adjusted hazards ratio; AUCDB=area under the curve for drug burden; SPPB=Short Physical Performance Battery; NS=non-significant ($P>0.05$)

Table 6
Studies Examining the Relationship between Antihypertensive Drugs and Functional Status

Author/Year	Design	Setting	Subjects/Patients	Exposure	Results
Applegate WB/1994 ⁹⁴	Randomized controlled trial – 5 years	Community (16 academic clinical trial sites)	4736 men and women with isolated systolic HTN	Chlorthalidone + atenolol or reserpine vs. placebo	↓ deterioration in BADL and mobility (all $P<0.05$)
Agostini JV/2002 ²³	Prospective cohort – 1 year	Community (VA primary care clinic, New Haven, Connecticut)	544 men 65 years with HTN	Antihypertensive intensity (# of classes prescribed)	↑ time required to complete timed chair stands per 1-unit ↑ in antihypertensive intensity ($P<0.001$)

Abbreviations: HTN=hypertension; BADL=basic activities of daily living; VA=Veterans Administration