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Prevalence of Potentially Preventable Unplanned Hospitalizations Caused by Therapeutic Failures and Adverse Drug Withdrawal Events Among Older Veterans

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Background. Studies of drug-related hospitalizations have focused on adverse drug reactions, but few data are available on therapeutic failures (TFs) and adverse drug withdrawal events (ADWEs) leading to hospitalization among community-dwelling older adults. Thus, we sought to describe the prevalence of unplanned hospitalizations caused by TFs and ADWEs. In addition, we evaluated factors associated with these events in a nationally representative sample of older Veterans.

Methods. This study included 678 randomly selected unplanned hospitalizations of older (age ≥ 65 years) Veterans between December 1, 2003, and November 9, 2006. The main outcomes were hospitalizations caused by a TF and/or an ADWE as determined by a pair of health professionals from review of medication charts and application of the Therapeutic Failure Questionnaire and/or Naranjo ADWE algorithm, respectively. Preventability (ie, medication error) of the admission was also assessed.

Results. Thirty-four TFs and eight ADWEs involving 54 drugs were associated with 40 (5.9%) Veterans' hospitalizations; of these admissions, 90.0% (36/40) were rated as potentially preventable mostly due to medication nonadherence and suboptimal prescribing. The most common TFs that occurred were heart failure exacerbations ($n = 8$), coronary heart disease symptoms ($n = 6$), tachyarrhythmias ($n = 3$), and chronic obstructive pulmonary disease exacerbations ($n = 3$). Half (4/8) of the ADWEs that occurred were cardiovascular in nature. Multivariable logistic regression modeling indicated that black Veterans (adjusted odds ratio 2.92, 95% *CI* 1.25–6.80) were significantly more likely to experience a TF-related admission compared with white Veterans.

Conclusions. TF-related unplanned hospitalizations occur more frequently than ADWE-related admissions among older Veterans. Almost all TFs and/or ADWEs are potentially preventable.

Key Words: Drug-related problems—Hospitalizations—Veterans.

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DRUG-RELATED hospitalizations are common among older adults and are often preventable (1). Most previous studies of drug-related hospitalizations have assessed only adverse drug reactions (2,3). However, two other important drug-related problems can occur: therapeutic failures (TFs) and adverse drug withdrawal events (ADWEs; 4). A TF can be defined as "a failure to accomplish the goals of treatment resulting from inadequate or inappropriate drug therapy and not related to the natural progression of disease" (eg, heart failure exacerbation in a patient not receiving an angiotensin converting enzyme inhibitor who has no contraindications; 5,6). An ADWE can be defined as "a clinical set of symptoms or signs that are related to the removal of a drug" (eg, physiological withdrawal reaction to the abrupt discontinuation of a β-blocker; 5). As the U.S. population ages and overall medication use rises, it is

expected that drug-induced morbidity and mortality will also increase. Thus, understanding the magnitude of these drug-related problems and the reasons for their preventability is critical.

Unfortunately, limited research is available to understand the epidemiology of TF- and ADWE-related hospitalizations in older adults (7–16). Specifically, to the best of our knowledge, there have been only five previous studies assessing TF- and/or ADWE-related hospital admissions (7–11). Moreover, TF- and ADWE-related hospitalizations determined by the use of reliable causality algorithms and their potential preventability have never been studied concurrently in the same population. This latter point is important because both types of drug-related problems can be caused by medication errors.

Thus, the main objectives of this study were to describe the prevalence of any and potentially preventable unplanned hospitalizations caused by TFs and/or ADWEs among a nationally representative sample of older Veterans and to examine the factors associated with these events. We also aimed to extrapolate the study findings to the population of older Veterans who receive care within the Veterans Health Administration.

Methods

Study Design, Setting, and Sample

A retrospective cohort study was conducted using data from all Department of Veterans Affairs (VA) Medical Centers nationwide. The sample consisted of Veterans 65 years of age or more by October 1, 2003 (beginning Fiscal Year 2004 [FY04]), who received VA care (inpatient or outpatient) at least once per year for two consecutive years between FY03 and FY06 (n = 2,430,186). The VA Fiscal Year is from October 1 to September 30. From that population, we restricted the sample for the current study to those Veterans who were hospitalized at a VA Medical Center at least once from any care setting between FY04 and FY06 (n = 328,166). From this sample, we randomly selected 1,000 hospitalizations, and we included only those patients who were hospitalized directly from an ambulatory care setting for an *unplanned* admission (n = 678). Only the first admission was included for those Veterans with more than one admission during the study period. The study was approved by the Pittsburgh and Bedford VA Institutional Review Boards and the University of Texas at San Antonio Institutional Review Board.

Data Sources

We obtained national VA inpatient, outpatient, and pharmacy data from FY03 through FY06 for individuals who were 65 years of age or more at the beginning of FY04. We created a merged database using information from the Veterans Health Administration Medical SAS data sets extracted from the National Patient Care Database (NPCD) records and outpatient pharmacy prescription data from the VA Pharmacy Benefits Management (PBM) database.

Study Chart Abstracts and Screening and Evaluating Potential TFs and/or ADWEs

A research assistant was trained by two of the investigators (J.T.H. and M.V.P.) on the procedures for study chart abstraction from national VA electronic health records using VistAWeb. The study chart abstracts included outpatient medications 3 months before and after the index hospitalization; allergies, medical problem lists, emergency department, and hospital discharge summaries for the year prior to the index hospitalization; laboratory tests 6 months prior to and during the index hospitalization; and admission history and physical note, progress notes, and discharge summary associated with the index hospitalization.

To screen for potential TFs and/or ADWEs, a trained clinical pharmacist (Z.A.M.) reviewed each chart abstract using previously established and up-to-date methods (detailed instructions for the instruments are available upon request; 9,13). For TFs, the screening approach for potential prescribing medication errors included the following:

- potential drug-–drug interactions with a hepatic metabolism-inducing medication,
- omission of an evidence-based drug (17–19),
- too low of a dose (based on the accepted dosage range for the elderly; 20),
- too short of a duration of medication therapy (20),
- or sub-therapeutic level of a narrow therapeutic range medication.

Another medication error, nonadherence, was defined as a gap of 7 days or more for refills on a 30-day supply of medication per the electronic refill record (within the past 3 months) and/or documentation of medication nonadherence in the patient's electronic medical record associated with the index hospitalization (21). Evidence of medication nonadherence from either source was used to classify an admission as being caused by nonadherence. For ADWEs, the screening approach for potential prescribing errors included assessing for any medication that was recently (ie, within the past 3 months) discontinued without replacement of a drug in the same therapeutic class prior to hospitalization, either leading to physiological withdrawal signs/symptoms or return of the underlying disease.

For chart abstracts that screened positive for a potential TF and/or ADWE, two trained clinical pharmacists (Z.A.M. and J.T.H.) separately evaluated whether the hospitalization was causally related to a TF and/or an ADWE using the reliable and valid Therapeutic Failure Questionnaire and/or the Naranjo ADWE algorithm, respectively (9,12,22). Each confirmed TF and/or ADWE was also evaluated for preventability, defined as any *medication error* occurring in the prescribing, order communication, dispensing, or monitoring in

the medication use process, or medication nonadherence (4). Evaluation discordances were resolved by consensus with a clinical pharmacist and a geriatrician (S.L.A. and S.M.H.). Interrater reliability measured using the κ statistic for both TF and/or ADWE events and preventability was adequate (0.81 and 0.73, respectively; 23).

Primary Outcome

A TF- and/or an ADWE-related hospitalization based on the Therapeutic Failure Questionnaire and/or the Naranjo ADWE algorithms were used as the primary outcome of interest (9,12,13). The outcomes were dichotomized as any *possible*, *probable*, or *definite* event versus *doubtful/none*.

Primary Independent Variable

Previous research has reported mixed results regarding the association between the number of medications and the risk of TF and ADWE occurrence (9,10,12,13). Number of medications was operationally described as regularly scheduled systemic medications prescribed by a VA physician immediately prior to the time of hospitalization. For analysis purposes, we created a categorical variable for polypharmacy for each patient (ie, 0–4, 5–8, and ≥9 medications). We used the 9+ medications category of polypharmacy as the reference group because we hypothesized that there could be an inverse association between polypharmacy and TFs.

Control Variables

Previous research is sparse describing risk factors for TFs/ADWEs in older adults (7,8,12,13). Therefore, we sought to control for various demographic, health status, and access to care variables and the primary outcome.

Demographic Control Variables

We identified patient demographic characteristics (ie, age in the year of admission, gender, race, and marital status) between FY03 and FY06. Race was categorized into white, black, and other/missing.

Health Status Control Variables

We used VA ICD9-CM codes (one inpatient or two outpatient) from the year prior to admission to create physical and psychiatric comorbidity indices. These indices have been previously validated in studies of U.S. Veterans (24). For physical conditions, we used a continuous count of the number of chronic diseases (range 0–30). We also identified six psychiatric conditions (ie, schizophrenia, bipolar disorder, depressive disorder, posttraumatic stress disorder, substance abuse disorder, and anxiety disorders). Due to the highly skewed distribution of these data, we dichotomized this variable (0 vs ≥1 psychiatric conditions). These measures of comorbidity have been previously associated with mortality, measures of health status, and potentially inappropriate prescribing (24–26).

Access to Care Control Variables

Categorical access to care variables included measurements of geriatric care in an outpatient or inpatient setting (yes/no) and primary care outpatient visits (0–1, 2–4, and ≥5) in the previous year. A dichotomous variable for copayment exemption was included using the VA priority group. Veterans with a service-connected disability 50% or more or individuals who were catastrophically disabled, very low income, or had specific war-related experiences generally receive a waiver for copayments associated with the VA care (26). In addition, dichotomous variables for an emergency department visit or hospitalization in the year prior to admission were included. Finally, we controlled for the year of hospitalization (2004, 2005, or 2006).

Statistical Analysis

Descriptive statistics (means and percentages) were used to summarize the primary dependent, independent, and control variables for the sample. Also, TFs/ADWEs were categorized by the major organ system/condition using ICD9-CM codes and the medication involved using the VA Drug Class Index (27). Also, for descriptive purposes, the preventability and stage of errors in the medication use process were assessed.

Bivariate analyses using logistic regression were conducted to assess the association of the primary independent variable and other control variables with the primary outcome. Control variables significant at the $\alpha = 0.15$ criteria in bivariate analysis were included in the final multivariable logistic regression model; the customary $\alpha = 0.05$ level was used in all other analyses to determine statistical significance. The primary independent variable was forced into the final model. The underlying statistical assumption of collinearity was evaluated using variance inflation factors, and the regression diagnostic of goodness of fit was verified using Hosmer–Lemeshow testing (28). Of note, due to the small number of ADWE-related admissions, we were not able to conduct multivariable statistical analyses for this outcome. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

The mean age of the sample was 76.4 years, and polypharmacy was common (ie, 44.8% took ≥9 outpatient medications and 35.4% took 5–8; Table 1). Most Veterans were white (75.5%) and male (98.5%). Table 2 describes the organ systems, specific conditions, and medications involved in TF-related hospitalizations. Overall, 34 patients were hospitalized with a TF involving 46 specific medications/classes for 15 specific conditions and involving eight major organ systems. The most common organ system involved

Table 1. Characteristics of the Sample ($N = 678$)

Variable	*n* (%)
Demographic variables	—
Age (y), *M* (*SD*)	76.4 (6.5)
Female gender	10 (1.5)
Race	—
White	512 (75.5)
Black	87 (12.8)
Other/missing	79 (11.7)
Not married	347 (51.2)
Health status variables	—
Number of regularly scheduled medications	—
0–4	134 (19.8)
5–8	240 (35.4)
≥9	304 (44.8)
Selim physical comorbidity index, *M* (*SD*)	4.0 (2.2)
Selim psychiatric comorbidity index	160 (23.6)
Access to health care variables	—
Geriatric Evaluation and Management clinic visit in previous year	50 (7.4)
Number of primary care visits in previous year	—
0–1	93 (13.7)
2–4	275 (40.6)
≥5	310 (45.7)
Nonexempt copayment status	84 (12.4)
Emergency room visit in previous year	344 (50.7)
Hospitalization in previous year	218 (32.2)
Year of index hospital admission	—
2004	138 (20.4)
2005	281 (41.4)
2006	259 (38.2)

in TF-related admissions was the cardiovascular system (20/34, 58.8%), with the most common specific condition being heart failure (8/34, 23.5%) and the most common medication class being β-blockers (11/34, 32.3%). Overall, 32 of 34 TFs were preventable, with the most common reasons being medication nonadherence (18/32, 56.3%) and suboptimal prescribing (12/32, 37.5%). Thus, medication nonadherence accounted for 2.7% (18/678) of all unplanned admissions. More specifically, in assessing three common symptomatic chronic conditions found to cause the admission (ie, heart failure, chronic obstructive pulmonary disease, and diabetes; $n = 13$), approximately half (6/13) of the TFs were due to nonadherence (6/678, 0.9% for overall sample).

Table 3 describes the eight cases of ADWE-related hospitalizations. Symptoms for ADWEs most commonly involved the cardiovascular system (4/8), and the most common drug class involved was diuretics (3/8). Overall, six of eight ADWEs were preventable, with the most common reasons being medication nonadherence (3/6), followed by suboptimal order communication (2/6) and suboptimal monitoring (1/6). Of note, two persons experienced both an ADWE and a TF as separate outcomes but as a part of the same index hospitalization.

Table 4 shows the bivariate analyses of the association between the primary independent variable and control variables and unplanned TF-related admission. The following variables were found in bivariate analyses to reach the a priori significance level ($\alpha = 0.15$) for inclusion in the final model: race, Selim physical comorbidity index, hospitalization in the previous year, and nonexempt copayment status (Table 4). Polypharmacy was not found to have a statistically significant association with TF-related hospitalizations in either bivariate or multivariate analyses. Race was the only significant factor associated with a TF-related admission, with blacks and other race having an increased risk when compared with whites in the final multivariable logistic regression model (Table 4). No problems with collinearity were detected, and an adequate model fit was found ($x^2 = 3.72$; $df = 8$; $p = .88$).

Discussion

To the best of our knowledge, this is the first study to describe the prevalence of any and potentially preventable

Table 2. TF-Related Hospitalizations (by major condition and therapeutic class) Among Older Veterans ($N = 678$)

Major Diagnosis Category (*n*)	Specific Conditions (*n*)	Therapeutic Classes (*n*)*
Circulatory system (20)	Heart failure exacerbation (8)	β-blocker (5), ACE inhibitor/ARB (4), nitrate/direct vasodilator (2)
	Coronary heart disease (6)	Antiplatelet (3), β-blocker (3), ACE inhibitor (1), statin (1)
	Tachyarrhythmia (3)	β-Blocker (3), digoxin (1)
	Thromboembolism (2)	Warfarin (2)
	Hypertension (1)	CCB (1), α-blocker (1)
Central nervous system (5)	Epilepsy (2)	Antiepileptic drug (2)
	Bipolar disorder (1)	Mood stabilizer (1)
	Depression (1)	SSRI (1)
	CVA (1)	Antiplatelet (1)
Respiratory (3)	COPD exacerbation (3)	Inhaled anticholinergic (3), long-acting β_2-agonist (2)
Endocrine (2)	Diabetes mellitus (2)	Hypoglycemic agents (2)
Other (4)	Renal insufficiency in transplant patient (1)	Immunosuppressant (1)
	Hepatic encephalopathy (1)	Lactulose (1)
	Osteoarthritis pain (1)	Nonopioid analgesic (1)
	Atypical tuberculosis (1)	Antitubercular regimen (4)
Overall (34)	—	—

Notes: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; SSRI = selective serotonin reuptake inhibitor; TF = therapeutic failure.

*Some Veterans experienced a TF from >1 class of medications or a TF from multiple medications in a single class.

Table 3. Cases of ADWE-Related Hospitalizations in Older Veterans ($N = 8$)

Case Number	Condition	Medication Involved
1	Tachycardia	Metoprolol
2	Angina pectoris	Metoprolol
3	Heart failure exacerbation	Furosemide
4	Heart failure exacerbation	Furosemide
5	Hypokalemia	Spironolactone
6	Increased agitation	Divalproex
7	Mental status changes	Methimazole
8	Mental status changes	Donepezil

Notes: ADWE = adverse drug withdrawal event.

Two Veterans experienced both an ADWE and a therapeutic failure (TF) as separate outcomes; thus, the total number of TF and/or ADWE-related hospitalizations was 40 (34 TFs + 8 ADWEs − 2 TF/ADWE as part of the same index hospitalization).

unplanned hospitalizations caused by both TFs and/or ADWEs. Most previous studies of drug-related hospitalizations have assessed only adverse drug reactions (2,3,29). Moreover, we used reliable and valid algorithms to detect these events in a nationally representative sample of older Veterans. We found that 5% of unplanned hospitalizations were caused by TFs, and 1% of unplanned admissions were caused by ADWEs. Our finding of a 5% prevalence rate for TF-related admissions is consistent with prior work, which has reported a range from 2.8% to 11.3% (7,9). In a study conducted by Kaiser and colleagues including 106 frail elders hospitalized across 11 VA Medical Centers, 11% of patients had 1 or more probable TF (assessed with the Therapeutic Failure Questionnaire) leading to admission (9). Similar to the study by Kaiser and colleagues, we report that congestive heart failure and chronic obstructive pulmonary disease exacerbations were some of the most common reasons for a TF-related admission (9). Furthermore, a previous study of ADWEs in community-dwelling Veterans also found that ADWEs leading to admission were rare (13). These results support the notion that most medications identified as unnecessary can be safely discontinued in older adults with careful monitoring for withdrawal symptoms and/or return of underlying disease (6,30). This is especially important for those potentially inappropriate medications with an unfavorable risk/benefit ratio or in those older adults with geriatric syndromes who may be at an increased risk for adverse drug reactions (31).

Importantly, the overwhelming majority (90%) of the TFs and/or ADWEs in our study were deemed to be potentially preventable largely due to medication nonadherence and

Table 4. Factors Associated with Therapeutic Failure–Related Hospitalizations in Older Veterans ($n = 678$)

Variable	Crude *OR*	95% *CI*	Adjusted *OR**	95% *CI*
Demographic variables				
Age	—	—	—	—
85+	1.0 (Reference)	—	—	—
65–74	0.91	0.29–2.84	—	—
75–84	0.84	0.27–2.60	—	—
Female gender	N/A†	N/A†	—	—
Race	—	—	—	—
White	1.0 (Reference)	—	1.0 (Reference)	—
Black	3.17	1.37–7.30	2.92	1.25–6.80
Other/missing	2.67	1.08–6.61	2.92	1.15–7.44
Not married	1.58	0.78–3.20	—	—
Health status variables				
Number of regularly scheduled medications	—	—	—	—
≥9	1.0 (Reference)	—	1.0 (Reference)	—
0–4	0.79	0.31–2.05	1.14	0.40–3.22
5–8	0.81	0.37–1.77	0.90	0.40–2.04
Selim physical comorbidity index	1.16	1.01–1.34	1.09	0.91–1.31
Selim psychiatric comorbidity index	0.54	0.21–1.43	—	—
Access to health care variables				
Geriatric evaluation and management clinic visit in previous year	0.37	0.05–2.75	—	—
Number of primary care visits in previous year	—	—	—	—
0–1	1.0 (Reference)	—	—	—
2–4	0.60	0.22–1.68	—	—
5+	0.84	0.32–2.20	—	—
Nonexempt copayment status	0.21	0.03–1.52	0.25	0.03–1.86
Emergency room visit in previous year	1.41	0.70–2.84	—	—
Hospitalization in previous year	2.20	1.10–4.41	1.61	0.69–3.75
Year of index hospital admission	—	—	—	—
2006	1.0 (Reference)	—	—	—
2005	0.86	0.42–1.77	—	—
2004	0.34	0.10–1.18	—	—

Notes: OR = odds ratio. Hosmer and Lemeshow goodness-of-fit test: $x^2 = 3.72$; $df = 8$; $p = .88$.

*Adjusted for all other variables with $p < .15$ from bivariate analyses.

†Too few females in the sample to report a meaningful *OR* and 95% *CI*.

suboptimal prescribing problems. Underuse, or the omission of indicated medications, was one of the most common suboptimal prescribing problems causing preventable TFs in our study. A previous study showed that 50% of vulnerable older adults from two managed care organizations had evidence of underuse as measured by the Assessing Care of Vulnerable Elders quality measure (32). This suggests that future research should pay equal attention to improving underuse of evidence-based indicated pharmacotherapy as has been given to reducing potentially inappropriate medications in older adults (33). Our study and the study by Kaiser and colleagues suggest that medication nonadherence is the most common cause of preventable TF-related hospitalizations (9). Moreover, previous research has shown cardiovascular medication nonadherence to be associated with increased morbidity and mortality in older adults (34). Due to the complex nature of medication nonadherence behavior in older adults, further study is warranted to improve the risk stratification of older adults for intentional and unintentional nonadherence in order to more accurately identify those patients requiring assistance with medication management, especially in older adults transitioning across the health care system (35,36).

It is interesting to note that we did not find a significant association between polypharmacy and TF-related admissions. Previous studies have reported mixed results for the association between the number of medications and TF-related health care utilization (9,10). Unexpectedly, we did, however, find that black Veterans were significantly more likely to experience a TF-related admission compared with white Veterans. This disproportionate rate of events among blacks was a surprising finding as the VA is considered an "equal access" health care system with limited patient cost sharing (37); a recent study by Trivedi and colleagues reported an improvement over the past decade in the VA's quality of care with minimal racial disparities detected in widely used process measures (eg, testing of hemoglobin A1c in patients with diabetes; 38). It is possible that this finding may indicate that race is a proxy for other unmeasured factors not assessed in this study (eg, health beliefs, health literacy). Nonetheless, our finding of racial differences in the occurrence of an important distal health outcome (ie, hospitalization) highlights the need for further study in this important area.

It may be of interest to clinicians and health policy makers to further understand the cost implications of our findings given the nationally representative sample studied. Between FY04 and FY06, 2,430,186 older Veterans received care in 1 of 153 VA hospitals/outpatient clinics for at least two consecutive years and 13.5% (n = 328,166) were hospitalized at least once in a VA hospital. Given this, we can extrapolate using our data that two thirds of these hospitalizations were unplanned, and 5.9% of these hospitalizations were due to TFs and/or ADWEs. Further applying our TF- and/or ADWE-related hospitalization preventability rate of 90.0%, it is estimated that more than 11,600 admissions would be preventable during this time frame. Using the average length of stay in the Veteran population of 7.4 days and applying conservative FY04 acute inpatient admission daily costs ($1,880 per day; personal communication with VA Health Economics Resource Center, January 2011), TFs and/or ADWEs cost the VA more than $160 million in preventable hospitalizations (39). It is clear to see that these costs from potentially preventable hospitalizations could be even greater if applied to more than 5,000 nongovernment U.S. hospitals (40).

There are several potential study limitations worth discussing. First, this study relied on information from VA electronic health records to assess TFs and/or ADWEs, which may have led to an underestimation of these problems if the information was missing or incorrectly/not recorded in the chart. For example, dosage changes that may have been communicated to the patient but not documented in the medical record would have been missed in the data abstract review. This situation would most likely have affected medications such as diuretics, warfarin, and/or insulin. Another potential source of underestimation was that we were not able to capture TF and/or ADWE-related hospitalizations that occurred outside the VA as electronic medical records are not available. Our measure of medication adherence was also limited in that we were not able to calculate objective measures (eg, medication possession ratio, proportion of days covered) because this was not the primary outcome or independent variable. The prevalence of nonadherence in this study is likely an underestimate. Moreover, by using a 3-month look back period for medication refills, we may have missed informative medication-related data that may have occurred outside this time frame to help assess omission of evidence-based pharmacotherapy. However, we abstracted emergency department and hospital discharge summaries for the year prior to the index hospitalization as well as laboratory tests 6 months prior to the index hospitalization. These additional clinical data, which included medication lists, informed us on the patient's overall clinical events (including any medication-related events) for the year prior to the index hospitalization. In addition, there were too few ADWE events to examine associated risk factors. As mentioned earlier, it is possible that unmeasured confounding could account for the association between race and TFs. Finally, the sample consisted mostly of older male Veterans living in the community, so the results may not generalize to older females or younger populations.

Conclusion

In conclusion, TF-related unplanned hospitalizations occur more frequently than ADWE-related admissions among older Veterans. Importantly, almost all TF- and ADWE-related hospitalizations are potentially preventable. Future research should focus on innovative solutions to improve medication

adherence and suboptimal prescribing among community-dwelling older adults in order to reduce the significant and costly morbidity associated with TF and/or ADWE hospitalizations.

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Appendix i. Therapeutic Failure Questionnaire Items (9)

1. Was drug therapy omitted for the condition?
2. Did the condition improve with drug therapy?
3. Was the drug prescribed at too low a dose by the physician or taken as too low a dose by the patient?
4. Was the drug detected in the blood in subtherapeutic concentrations?
5. Was there a drug–drug interaction that interfered with the effectiveness of the drug prescribed for the condition?
6. Did the condition improve with an increase in dose or worsen with a decreased dose?
7. Are there conclusive reports of efficacy for a drug for the condition?
8. Are there alternative causes that on their own could have caused the condition?
9. Did the patient have the same condition related to absent or inadequate drug therapy previously?
10. Was therapeutic failure confirmed by objective evidence?

Appendix ii. Adverse Drug Withdrawal Event Causality Algorithm Items (22)

1. Are there previous conclusive reports on this reaction?
2. Did the adverse event appear after the suspected drug was withdrawn?
3. Did the adverse event improve when the drug was readministered?
4. Did the adverse event reappear when the drug was withdrawn again?
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?
6. Did the adverse event appear after placebo withdrawal?
7. Did the patient previously use the drug chronically?
8. Was the reaction less severe when the dose was increased or more severe when the dose was decreased?
9. Did the patient have a reaction to the same or a similar drug in any previous exposure?
10. Was the adverse event confirmed by any objective evidence?