Adapting the Shed-MEDS Deprescribing Intervention to Dementia Care in Assisted Living

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Original Study Protocol

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Overview and Objectives

Polypharmacy is prevalent among older adults and associated with numerous adverse outcomes. Persons with Dementia (PWD) experience even higher levels of polypharmacy compared to those without dementia.[1] PWD are also at greater risk for potential harm from polypharmacy including adverse drug reactions, falls, and further cognitive decline.[2,3] Furthermore, deprescribing decisions among PWD (and their respective caregivers) have unique factors that must be considered. First, PWD are likely to require the input of a caregiver or healthcare proxy to make deprescribing decisions. Importantly, there are measurable differences between PWD and their proxies related to their attitudes toward deprescribing, with reduced willingness to deprescribe among proxies in the population-based sample completing the National Health and Aging Trends Study (NHATS).[1] Despite the prevalence and associated risks of polypharmacy among PWD, few interventions have targeted deprescribing among the high-risk population of PWD. Importantly, deprescribing interventions, to date, among PWD largely have been implemented within outpatient clinical settings or otherwise excluded those receiving dementia care in assisted-living facilities (ALFs).[4,5] PWD, especially those with advanced disease, may commonly live in ALFs. There currently exists a substantial gap in our understanding of deprescribing among ALF residents with advanced dementia. There are a number of important considerations within an ALF dementia care facility intervention. First, family proxies play a primary role in deprescribing decisions for PWD who reside in these care settings. In addition to family proxies' unique attitudes and behaviors, one must also consider the attitudes and behaviors of the licensed caregivers (nursing and physician staff) responsible for daily care. Although unique barriers to deprescribing may exist, there also may be potential advantages of an ALF-based deprescribing intervention, most notably the ability to more frequently monitor for potential withdrawal symptoms or other impacts of deprescribing, which may address family and/or licensed caregiver concerns about the effects of deprescribing on quality of life.

Our research team recently completed a patient-centered deprescribing intervention (Shed-MEDS) that targeted older hospitalized adults that required ongoing post-acute care (PAC). The nurse-practitioner or pharmacist-led deprescribing intervention resulted in statistically significant reductions in total medications and the combined burden of anticholinergic and sedative medications as measured by the drug burden index. Reductions were achieved at the end of the intervention (at the time of PAC discharge), and up to 90 days following the end of the intervention. Despite these successes, we do not know the feasibility or effect-size of a similar intervention implemented in a memory care ALF for PWD and their proxies. Thus, we aim to perform a single-arm, repeated-measures within-subjects feasibility pilot of the Shed-MEDS deprescribing intervention among PWD experiencing polypharmacy and their caregivers at the Abe's Garden dementia care ALF. **Our overarching hypothesis is that implementing the Shed-MEDS deprescribing protocol within a dementia care ALF will be feasible and reduce medications without worsening the quality of life for PWD.**

Specific Aim 1: Determine the feasibility of implementing the Shed-MEDS deprescribing intervention among PWD residing in a dementia care ALF.

- Aim 1a. Family proxy acceptability will be measured via the revised Patient Attitudes Toward Deprescribing (rPATD) designed for surrogates and through documentation of barriers and enablers to deprescribing recommendations shared via proxy interviews.
- Aim 1b. Implementation of the Shed-MEDS intervention will be assessed by the proportion of deprescribing recommendations acceptable to primary prescribers and family proxies of PWD.

Specific Aim 2: Document the effects of the Shed-MEDS deprescribing intervention on medication burden among PWD.

- Aim 2a: Compared to a pre-intervention period, the Shed-Meds intervention will result in significant increases in the total number of medications deprescribed, as defined by terminations at the end of 90 days.

- Aim2b: Compared to a pre-intervention period, the Shed-Meds intervention will result in a significant decrease in the anticholinergic and sedative drug burden of prescribed medications at the end of 90 days.

Specific Aim 3: Document the effects of the patient-centered deprescribing intervention (Shed-MEDS) on the quality of life of PWD.

- Aim 3a: The Shed-MEDS intervention will not result in significant reductions in quality of life, as measured by Behavioral and Psychological Symptoms of Dementia (BPSD) events and DEMQOL-proxy[6] scores at the end of 90 days.

Potential for Impact: The data from this study will inform feasibility and the implementation barriers and facilitators specific to PWD, their family proxies, and dementia care ALF staff. This information will inform tailored adaptations to the Shed-MEDS intervention in preparation for a multi-center R01 trial to test the clinical effectiveness of deprescribing among PWD in ALF care settings.

Study Design and Outcomes Overview

This is a single arm pilot and feasibility study to adapt the Shed-MEDS intervention to the memory care setting. The Shed-MEDS intervention is a multistep deprescribing protocol which considers patient and disease factors, life expectancy, goals of care, and appropriate treatment targets. Medication-specific factors such as drug-drug interactions, drug-disease interactions, and drug-specific safety profiles are also incorporated. Finally, patient preferences and primary prescriber input are key to final deprescribing actions by identifying the medications patients are willing to deprescribe and seeking their primary prescriber's agreement. In this intervention, deprescribing is defined as either stopping a medication or reducing the dose/frequency of a medication.

The primary study setting is two assisted living facilities (ALFs) with dedicated memory care units.

Eligible residents are ALF residents aged 65 years or older with a dementia diagnosis and experiencing polypharmacy as defined by 5 or more medications.

Primary Outcome is the number of medications deprescribed, either stopped or reduced dose, 90-days after intervention completion.

Secondary Outcome is the impact of deprescribing on behavioral symptoms of dementia and resident quality of life.

BACKGROUND AND SIGNIFICANCE

Polypharmacy, most commonly defined as the concurrent use of five or more prescription and over the counter (OTC) medications,[7–9] affects 40%–50% of older adults in the United States and is associated with geriatric syndromes, decreased medication adherence,[10] increased adverse drug events,[11–13] and increased health care utilization and costs.[10,14–17] Deprescribing, the systematic process of medication cessation, has been identified as an effective way to mitigate polypharmacy and inappropriate medication use.[18] Furthermore, patients' attitudes toward their medications and willingness to deprescribe often vary by medication.[19] To understand medication-specific barriers and enablers, clinicians need to engage patients in deprescribing conversations to ensure that their preferences, goals of care, and concerns are known.[20–23] Recent studies suggest that the majority of adults aged 65 and older express a willingness to deprescribe a medication if their clinicians agree, and that they wish to be involved in the decision-making process.[22,24,25]

Although people with dementia (PWD) are more likely to have polypharmacy and to take unnecessary medications, few studies have assessed attitudes toward deprescribing in this population. A recent study on deprescribing attitudes in PWD showed that the majority of participants were agreeable to stopping a medication if advised by their physician.[1] Proxy respondents in this study were less agreeable to deprescribing, echoing previous findings that have shown caregiver resistance to deprescribing of antipsychotics due to concern about the management of behavioral and psychological symptoms of dementia (BPSD).[26,27] Further, deprescribing interventions for PWD have been focused on particular medication classes and have been conducted in the hospital and skilled nursing facility (SNF) settings.[28–31] To date, we have found no published deprescribing studies of PWD residing in an assisted living facility (ALF).

This proposed pilot study will enable investigators to expand upon knowledge gained during the Shed-MEDS randomized clinical trial and allow examination of this deprescribing intervention in the ALF setting, something that has never been done before. There are an estimated 29,000 assisted-living facilities (ALFs) nationwide serving approximately one million older adults.[32] ALFs are group residential care facilities not licensed as nursing homes, although 34% of ALF residents have a diagnosis of Alzheimer's Disease or a related dementia and need assistance with daily care.[32,33] A recent nationwide survey of 30,000 ALFs revealed dementia as one of the most prevalent chronic conditions, with nearly two thirds of all residents requiring caregiver assistance with 3 or more ADLs.[32,33] The average length of stay in an ALF is 28 months, and most residents (59%) will eventually transition to a nursing home for care.[34] Given these demographics, we believe an ALF may be an ideal setting for deprescribing interventions for PWD.

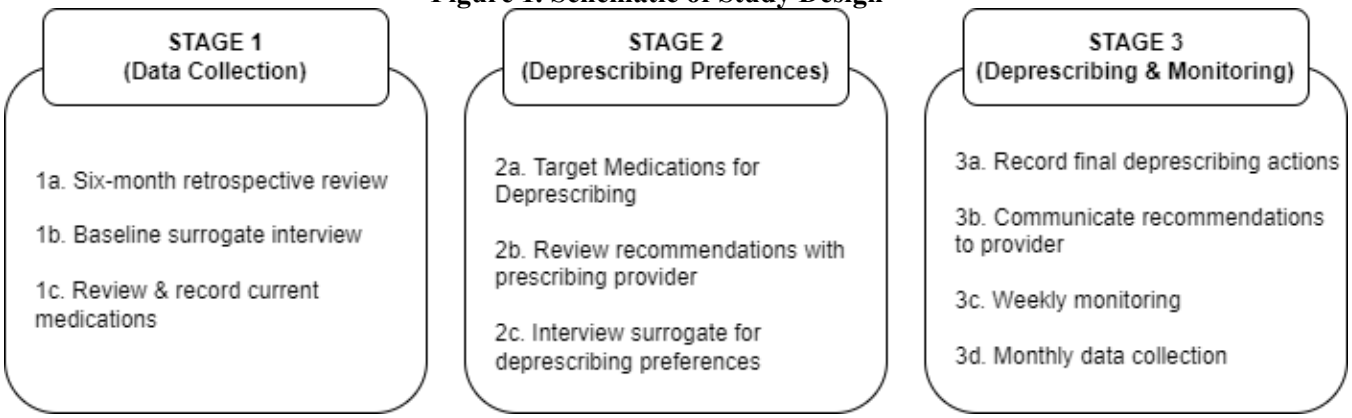
Shed-MEDS clinical trial was a patient-centered hospital-based deprescribing trial.[35,36] Although the Shed-MEDS intervention showed medication reduction in hospitalized older adults discharging to a post-acute care facilities, its feasibility of use for older adults in other clinical settings is unknown. Participants in the Shed-MEDS clinical trial had many similarities to residents living at Abe's Garden, a licensed ALF in Nashville, TN that provides memory care for all residents: 21% had Brief Intervention for Mental Status (BIMS) 30 scores suggestive of dementia, 13% were living in an ALF setting prior to hospitalization, and 15.6% of participants were residing in an ALF at the time of study completion. The Shed-MEDS trial was unique in that it also measured deprescribing attitudes of surrogate decision makers of patients who were unable to consent.

Although PATD[22] scores obtained during the study showed surrogates to be more hesitant about deprescribing,[37] surrogates agreed to a higher percentage of deprescribing recommendations (64% v. 50%) than participants making their own medical decisions (64% to 50%) during the study's patient-clinician interviews. This suggests that surrogates who have an opportunity to engage with providers and receive medication education may be more amenable to deprescribing. Further, 23% of Shed-MEDS participants who did not finish the study dropped because of Hospice admission (exclusion criteria). This proposed pilot study includes Hospice beneficiaries, thus allowing investigators to examine the value of deprescribing in this population and to understand surrogate's deprescribing attitudes in PWD that receive subsequent hospice care.

STUDY DESIGN

Overview of Design

Figure 1. Schematic of Study Design



Study Setting

The study was initially implemented at a single ALF; however, due to low enrollment, a second ALF was added six months into recruitment.

Abe's Garden is an ALF in Nashville, TN that provides long-term memory care for up to 42 PWD. At the time of the project inception, there are 41 residents, 12 of whom are Hospice beneficiaries. The average age of residents is 81 years, and their average length of stay is 1.6 years. Residents take an average of 7.78 medications, with 13 residents taking nine or more medications. On-site medical care is provided by a gerontological nurse practitioner and geriatrician, both of whom are employed by Vanderbilt University Medical Center (VUMC).

NHC Place at the Trace is a continuing care community in Nashville, TN, which includes Way Point ALF/ Memory Care. This memory care unit provides care for up to 32 residents, all of whom have dementia, and at time of the project there were 27 residents. Medical care is provided both in the outpatient setting, and by a gerontological nurse practitioner and geriatrician.

Interventions and Duration

The Shed-MEDS Intervention (Figure 1. Stage 2) includes identification of medications for deprescribing, a surrogate preference interview, and discussion with residents' primary care providers (ALF and outside providers). The intervention ends after the final agreed upon deprescribing actions were communicated to the ALF providers. Follow-up data collection and assessments were conducted at 30-, 60-, and 90-days after completing intervention.

Study Population and Sample Size

The eligible patient population are ALF residents with a dementia diagnosis, age $\geq$ 65 with polypharmacy as defined by $\geq$ 5 medications (or the presence of at least 1 PIM). The expected enrollment is 40 PWD with an estimated attrition rate of 10-15%.

PARTICIPANT RECRUITMENT AND ENROLLMENT

Eligibility Screening and Recruitment

The Vanderbilt University Institutional Review Board (IRB) requires a multi-stage recruitment process that allows residents and/or their surrogates the opportunity to opt out of contact with the research team. The research team is not permitted to screen ALF records for eligibility or reach out to residents and/or their surrogates directly. The ALFs are responsible for distributing project information to eligible residents' designated surrogates. Inclusion Criteria: (1) a documented Alzheimer's Disease or Related Dementia (ADRD) diagnosis; (2) resident is aged 65 years or older; (3) taking 5 or more medications OR at least 1 potentially inappropriate medication as defined by the Beers criteria[38], STOPP criteria,[39] and RASP list.[40]

Enrollment Procedures

The first step of the recruiting process is for the Facility Administrator to notify surrogates that the study will take place. The administrator will send a letter (via email) to each resident's legally authorized representative and, if applicable, the resident. The letter will contain information about the study (e.g., eligibility criteria), the PI's contact information, and the date/time of the Town Hall meetings where the study will be discussed. The letter will let surrogates know that neither Town Hall attendance nor study participation are mandatory. It will also ask surrogates to notify the facility if they wish not to be contacted by the research team.

Additionally, the surrogate decision maker of each respective resident will receive a study information packet that includes a cover letter, two (2) copies of the consent documents, a study brochure, a release of information (ROI) authorization form, and a self-addressed and stamped envelope. The study team will create these packets, and facility staff will mail them to all surrogate decision makers of residents. Surrogates may sign a consent form and return to the research team in the envelope provided, or they may contact the PI for further discussion about participation. If the surrogate indicates interest in participating in the study but would like to discuss it with PI or KSP via a face-to-face meeting, the study team will arrange a time to meet at the facility to further discuss participation and sign the consent form.

The facilities regularly host Town Hall-style meetings for family members to facilitate communication between the staff and family members. The Principal Investigator and key study personnel (KSP) will attend Town Halls to explain the study in lay terminology emphasizing that participation is voluntary and choosing not to participate will not impact the resident's care. During the Town Hall meeting, residents and their surrogates will be given an opportunity to ask any questions they may have about the study and to provide comments; also, the study brochure will be made available. We will emphasize that all deprescribing decisions require both resident/surrogate agreement and the agreement of the facility clinicians. At the Town Halls, study team members will ask residents' surrogate decision makers if they would like to enroll their resident or be contacted by phone with more information about the study.

Any member of the research team can obtain written informed consent from an eligible resident and/or their surrogate using the IRB stamped and current dated copies of the informed consent document. Consent can be obtained either via mail (see packets mailed above) or in-person at the facility. When reviewing the consent document with the resident and/or surrogate, the research staff will give them time to review the document before the staff summarizes each section and addresses frequently asked questions. Staff should provide a second copy of the consent form to leave with the resident and/or surrogate.

During the informed consent process, study personnel will continuously reiterate the following:

- Data is collected only for research purposes.
- There is no obligation to participate and refusal to participate will not affect the resident's routine care.
- Residents/surrogates can withdraw from the study at any time

STUDY PROCEDURES

Data collection includes resident descriptive data as well as four groups of outcomes: medications, quality of life, safety, and feasibility. Table 1 shows a summary of the study timepoints along with the corresponding assessments. Upon enrollment, residents and their surrogate complete interviewer-administered questionnaires, which require approximately 30 minutes. Descriptive, medication, and safety data are obtained via records request from the ALF at enrollment and the three follow-up time points. Interviewer-administered questionnaires are conducted again 90-days after intervention ends. All interview assessments are completed by a trained research geriatric nurse practitioner.

Schedule of Assessments

Table 1. Data Collection Schedule

Measures	3-month Retrospective Review∞	Enrollment	30- & 60-day Follow-up	90-day Follow-up
Demographics and Health Status				
Age, Gender, Race/Ethnicity, Education Level*		X		
Comorbidities*		X		
Cognitive Impairment (BIMS)	X*	X		X
Status: Long-Term Care, Hospice, Death*	X	X		X
Medications				
Total number of medications*	X	X	X	X
Sedative & Anticholinergic Drug Burden Index	X	X	X	X
Quality of Life				
DEMQoL-Proxy		X		X
BPSD*	X	X	X	X
Safety				
Falls*	X	X	X	X
Emergency Room Visits & Hospitalizations*	X	X	X	X
Feasibility				
RPATD (surrogate)		X		
Surrogate agreement w/ deprescribing recommendations		X	X	
Provider agreement w/ deprescribing recommendations		X	X	
Total number of conversations w/ prescribing MD/NPs		X	X	X
Total number of conversations with surrogates		X	X	X

Descriptions of Assessments

Demographic and Administrative Data: The sociodemographic data collected during this investigation is obtained from the ALF medical record. Utilizing a standardized form to abstract information from the electronic medical record, a member of the project team collects age, gender, race/ethnicity, insurance status, outpatient providers, and highest education level. These data are verified with the surrogate during the baseline interviews.

Charlson Comorbidity Score[77] ranges from 0 to 31, with a higher score indicating more comorbid illness. There is an additional one-unit increase in the weighted score for every decade starting from age 50. Data sources for comorbidities are the ICD-9 and ICD-10 diagnostic criteria found on the patient's Problem List in the EMR from the last 12 months.[41]
Cognitive Impairment: The Brief Interview for Mental Status (BIMS) is a short, validated assessment of cognitive impairment with a total score range from 0 to 15 (0-7: severe impairment; 8-12: moderate impairment; 13-15: cognitively intact).[42] The BIMS is routinely used in the SNF and long-term care settings.

Primary Outcomes - Medications
Total number of Medications: The primary data source is the resident's ALF medication administration record (MAR). We include both prescription and over-the-counter medications (OTC) (vitamins, herbal supplements also included) administered by the following routes: oral, intravenous, intramuscular and ophthalmologic medications. All surrogates receive a baseline structured interview with specific prompts for OTC medications they may be providing directly (and not administered by the facility).

PIMs are defined by previously published lists including the recently updated Beers criteria,[38] the STOPP criteria,[39] as well as the RASP list,[40] for which there is a large degree of overlap. The total number of PIMs is the sum of medications that are found on any of these explicit lists.

Drug Burden Index (DBI): A DBI score is calculated separately for anticholinergic (DBI_{AC}) and sedative medications (DBI_S), which have been strongly linked to functional impairment, falls, and delirium.[43–45] The drug burden is the sum of each individual anticholinergic/sedative medication's prescribed daily dose divided by the sum of the minimum effective dose (as estimated by the FDA minimum recommended dose) and the patient's daily dose. The DBI includes over-the-counter medications. We will calculate the DBI at baseline and all follow-up timepoints. Importantly, the DBI captures reductions in dose, even when total number of medications is not reduced.

Secondary Outcomes – Quality of Life, Safety, and Feasibility
Dementia Quality of Life Instrument – Proxy Version (DEMQOL- Proxy: The DEMQOL-Proxy scale is used to evaluate health-related quality of life in participants with severe dementia as rated by their caregivers. It is a 31-item version (DEMQOL-proxy, rated by the caregiver). Both versions are recommended for evaluating participants (and their caregivers) with mild to moderate dementia. The DEMQOL total score ranges from 28 to 112. The DEMQOL-proxy has 31-items which are reported on a four-point Liker scale (a lot/quite a bit/a little/not at all) with a total score range from 31 to 124. Higher scores indicate a better health-related quality of life.

Behavioral & Psychological Symptoms of Dementia (BPSD): The total number of BPSD episodes recorded. The following portions of the medical chart should be requested for review: nurses notes and incident reports. To tally the total number, the reviewer (KSP) should highlight each individual episode that requires intervention or redirection from staff, or accounts for declining care (such as refusing a shower). Documented episodes may mention physical or verbal aggression or agitation, episodes of wandering into others' rooms, or off the unit, episodes of packing up belongings or taking items belonging to others.

Falls: Falls are highly prevalent in this population and lead to fatal and non-fatal injuries. To determine the total number of falls, the following portions of the medical chart should be requested for review: Nursing notes, incident reports, monthly falls report. KSP should compare each event's source with other sources to avoid double-counting falls.

Unplanned Healthcare Utilizations: Request incident reports and nursing notes of all residents who visited the emergency department or had a hospitalization. All documented emergency department visits and hospitalizations need to be tallied and recorded on the chart abstraction data sheet.

Revised Patients' Attitudes Toward Deprescribing (rPATD) is a 19-item survey with 5-point Likert scale ranging from 'strongly agree' to 'strongly disagree.' Examples include: "I feel that I am taking a large number of medicines" and "I believe that all my medications are necessary." There is not an overall, global score for the assessment. Instead, a score ranging from 1-5 is assigned for each of the five factors: Burden, Appropriateness, Concerns about stopping, and Involvement. Higher scores in the burden, concerns about stopping, and involvement in treatment domains indicate a greater burden, concern, involvement. Questions regarding the appropriateness factor are scored in reverse.[23] Thus, higher scores in the appropriateness domain indicate a participant's/surrogate's belief in the appropriateness of their medications. This tool was validated for use with surrogates.

Surrogate agreement with study deprescribing recommendations: The total number of medications the surrogate agrees to deprescribe will be totaled. For analysis purposes, medications will also be organized into medication classes.

Provider agreement with study deprescribing recommendations: The total number of medications the medical provider (i.e. Abe's Garden MD/NP or outside provider) agrees to deprescribe will be totaled. For analysis purposes, medications will also be organized into medication classes.

Total number of conversations with surrogates: We will record the total number of conversations with surrogates about the resident and the deprescribing process.

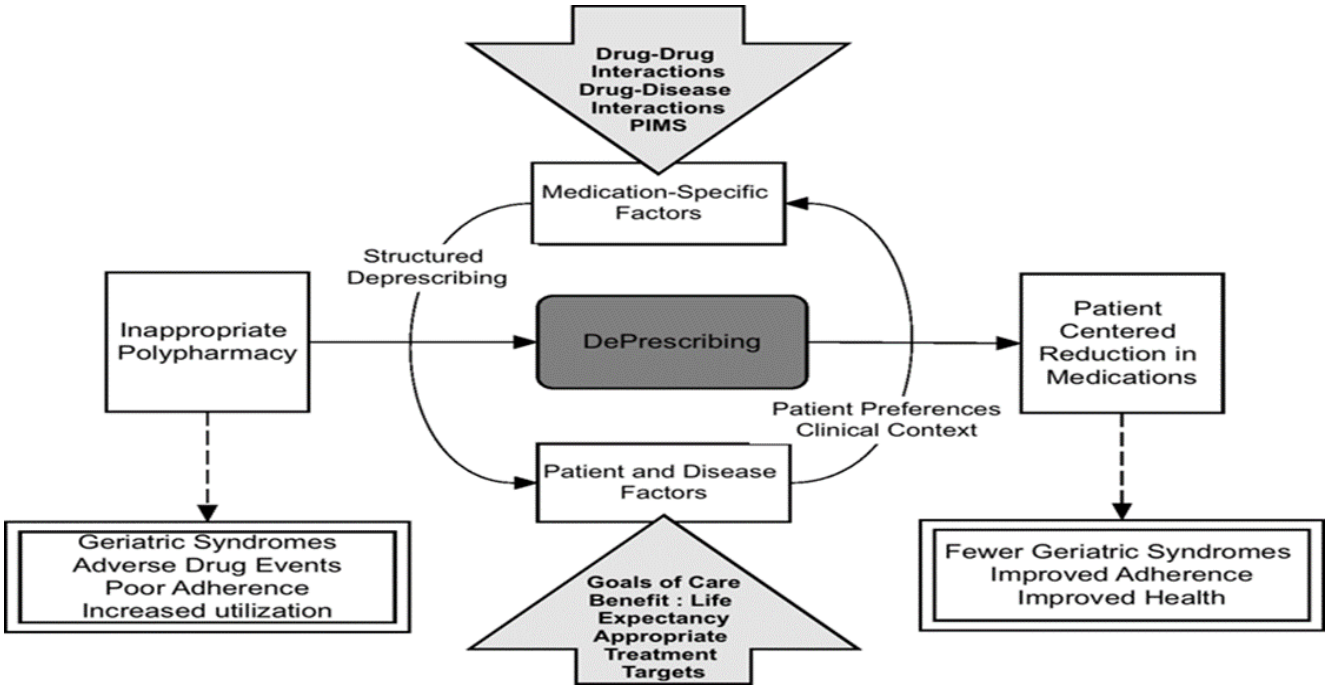
Total number of conversations with prescriber: The total number of conversations with the prescribing MD/NP as they are related to the deprescribing process will be recorded.

STUDY INTERVENTION

Our deprescribing protocol is based on a conceptual framework by Holmes that considers patient and disease factors, goals of care, appropriate treatment targets, and the duration of treatment required for benefit (Figure 2).[46] We also incorporated medication-specific factors from Scott's framework for minimizing inappropriate medication use, such as drug-specific safety profiles and drug-drug and drug-disease interactions.[47] Finally, patient preferences were viewed as a key component that informs final deprescribing actions by identifying medications the patient is willing to deprescribe (e.g., due to lack of efficacy, poor compliance, side effects, or cost burden) as well as potential barriers to deprescribing (e.g., concerns about worsening of symptoms). Specifically, our goal was to identify opportunities for deprescribing wherein clinical evidence aligned with patient preferences.

Conceptual Model

Figure 2. Deprescribing Framework



As shown in Figure 1, the study has three stages with intervention occurring in Stages 2 & 3. Each step is described in detail below, and Figure 3 shows the order of the intervention.

Pre-Review (Target Medications for Deprescribing)

Using medical record data only, a study NP will gather the following information for each medication: (1) Medication – Indication pairing: For each medication, an indication (i.e., diagnosis or symptom) will be identified. If an indication does not exist, "no indication indicated" will be specified; and, (2) De-prescribing rationale: Each medication will be assessed for the potential rationales for deprescribing shown in Table 2, indicating all applicable rationales.

All medications, both prescription and OTC including vitamins and herbal supplements, are reviewed for potential deprescribing. Select medication classes will not be under consideration for active deprescribing, which include the following:

- Anti-rejection medications for organ/ bone-marrow transplantation
- Chemotherapeutic medications for the treatment of known solid organ or hematologic malignancy.

The above medications may be deprescribed during the study period; however, it would solely be under the direction of the primary prescriber of the medication.

Deprescribing Priority*:* Although any rationale may be appropriate for deprescribing medications, a study NP will establish a priority level of 1 (low) to 10 (high) for discussing deprescribing recommendations. Priority will consider potential harm of the medication and potential effects on geriatric syndromes. It may be inappropriate to deprescribe multiple medications simultaneously; thus, prioritization may guide the surrogate interview and the deprescribing order.

Deprescribing Action Recommendations**:** For any medications recommended for deprescribing, the study NP will recommend a deprescribing action: (1) Stop now without need for monitoring; (2) Stop with symptoms/physiologic monitoring; (3) Stop at specified time point; (4) Reduce over time with monitoring until medication is stopped; (5) Reduce to lower dose without need for monitoring; (6) Reduce to lower dose with symptoms /physiologic monitoring. All recommendations will be discussed with primary prescribers **(Step 2b)** and surrogate decision-makers **(2c)**.

Table 2. Deprescribing Rationale

A. No indication for medication / Indication not clear B. Wrong dose or directions for medication C. Inappropriate for current indication due to: 1. Indication has resolved 2. Patient is below treatment threshold 3. Treating guidelines have changed, medication no longer indicated 4. Wrong Indication for medication D. Medication is ineffective as evidenced by no change in symptom or condition E. Duplicate medication for same indication	F. High risk medication based on: 1. Potential drug-drug interaction 2. Potential drug-disease interaction 3. On explicit PIMs list (i.e., Beer's, STOPP, or RASP) G. Medications are inconsistent with goals of care H. Risk > benefit given patients limited life expectancy I. Evidence of poor adherence or high risk of poor adherence (directions impractical, high cost) J. Medication currently indicated, however is time-limited and expect indication to resolve

Incorporate Resident/Surrogate Preferences

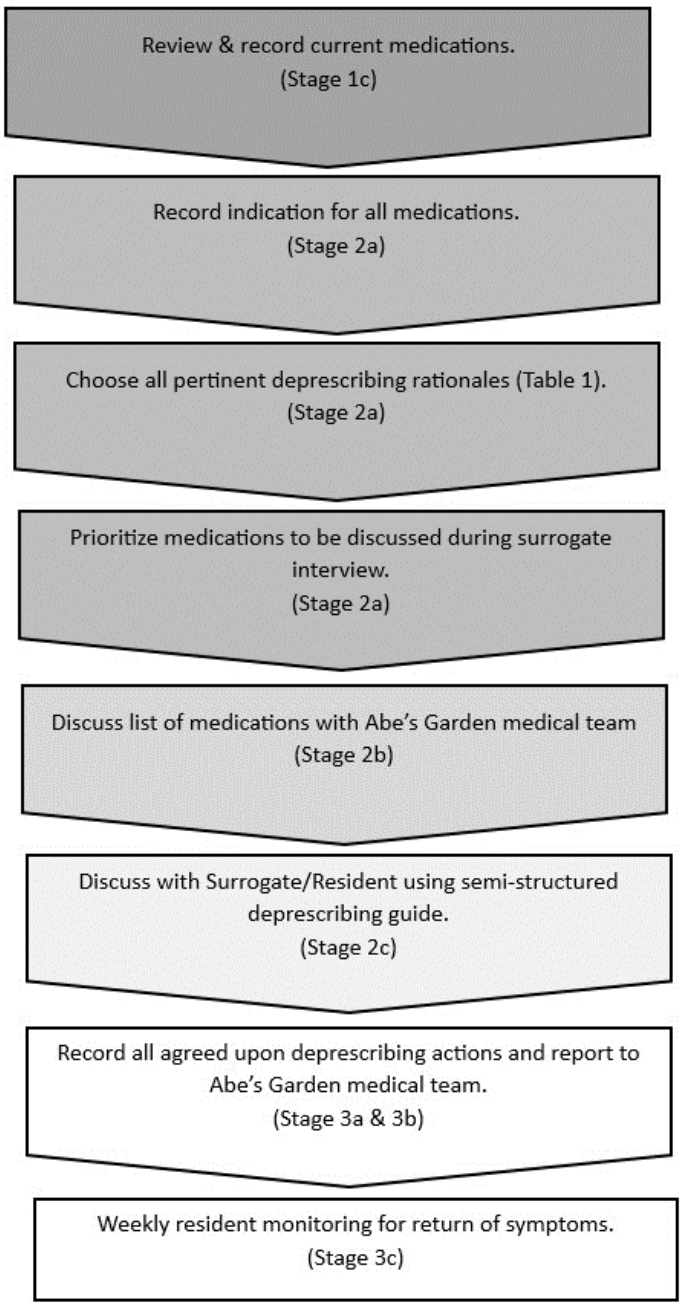
Following identification of medications for potential deprescribing, residents/surrogates will have a semi-structured interview by the study NP to elicit their preferences regarding medications identified for deprescribing (see "Deprescribing Conversation Guide" supplement). The following will be assessed for each targeted medication: medication adherence, side effects, perceived benefit/harm of the medication, cost, and level of interest in stopping or reducing the medication on a scale of 1 to 10. As part of this interview the NP may need to provide education about individual medications (e.g., side effects, risk-benefit, current evidence) and address any questions or concerns before asking if the surrogate agrees to deprescribe. If the surrogate raises a concern about a medication which the study team did not target for deprescribing, the NP should still address these concerns and note them in communications with the ALF medical team.

Study clinicians take field notes during the interview in which they detail the surrogate's general comments about medications and prescribers as well as the rationale for the agreement/disagreement with each deprescribing recommendation. After the interview these comments are coded into pre-set barriers and enablers (e.g., appropriateness, fear, process, influences, pragmatic, and dislike) from an established framework. Surrogate comments can align with more than one category for each medication and should be coded as such. A second study team member, usually the data manager, independently reviews the interview comments and coded for agreement. If there is disagreement related to categorization, the team discuss the theme assignment until a consensus is reached.

Outpatient & ALF Provider Input

The study NP will serve as a centralized source of communication. The study NP will notify the facility NP/MD of resident enrollment and will review and discuss all deprescribing recommendations to ensure they do not conflict with ongoing care. Following the resident/ surrogate interview, the study NP will contact the primary prescriber for agreed upon medications, this could be the ALF provider, an outpatient specialist, or both. The goal of these conversations is to obtain provider feedback about the proposed changes and facilitate medication updates in the medical record. Additionally, these conversations will hopefully lead to sustained deprescribing by engaging the primary provider early in the process.

Much like the patient preference interview, the study NP documents the original prescriber's agreement/disagreement and rationale for their decision. These field notes are coded into pre-set barrier and enabler categories (e.g., inertia, self-efficacy, feasibility) from a published framework.



Final Deprescribing Actions

The final step in the intervention is to review the final list of medications all parties (surrogate and provider) agreed to deprescribe with the ALF NP/MD and have them update the medication orders in the ALF EMR.

SAFETY MONITORING AND ASSESSMENTS

We have established a system to report and track adverse events (AEs) including adverse drug withdrawal events (ADWEs), serious adverse events (SAEs), and Suspected Unexpected Serious Adverse Reaction (SUSARs). In this study, an SAE is defined as an unplanned hospitalization or death, and an AE is defined as an emergency room visit that does not result in hospitalization. A SUSAR is an SAE that is suspected to be secondary to the drug withdrawal and is unexpected. Study personnel will monitor the safety of subjects and follow them until the event resolves or is explained.

Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Notification of Unplanned Healthcare Utilizations and Deaths

Unplanned healthcare utilization (intensive care unit transfers, emergency department visits and/or hospitalizations) and deaths are monitored throughout all study phases for each participant. Both the study coordinator and the data manager have access to a study patient panel in the electronic health record. As such, any time a participant is admitted to the VUMC Emergency Room, VUMC Inpatient Services, or the participant's medical record is updated to indicate death, the coordinator and data manager receive a notification. To determine if a participant had an unplanned healthcare utilization at an outside hospital (OSH), the participants are asked at each follow-up time point if they have been to an emergency room or had an inpatient stay, and if so, at what facility. The study coordinator and data manager are responsible for requesting medical records from OSHs (and SNFs) relevant to the utilization.

Review of Unplanned Healthcare Utilizations and Deaths

Any unplanned healthcare utilization (e.g., hospitalization, ER visit) or unplanned death (e.g., patient not receiving hospice care) is reviewed to determine if it was an adverse event that was serious, related to the study, and unexpected (SUSAR). Once all necessary records have been obtained and collated by the study coordinator, the case is assigned to a physician co-investigator for review. The adjudicator uses an established methodology to determine the presence of serious medication errors and will determine whether the unplanned healthcare utilization is related to medication withdrawal (i.e., ADWE) using the 10-question Drug Withdrawal Probability Scale, a scale based on the Naranjo algorithm,[48] which is a validated scoring system to assess causality of adverse drug events. ADWE will be coded as definite (>8), probable (5-8), possible (1-4), and doubtful (<1). For all ADWEs, the clinician-adjudicator will then determine whether it was avoidable by any change in management. After review by the clinician-adjudicator, the case is sent to the Principal Investigator to review. Both the PI and a co-investigator review to determine if the event was unexpected and/or study related. Should the event be determined as SUSAR (serious, unexpected, and study related) it will be reported as such to the DSMB and IRB as outlined below.

Serious Adverse Events and Reporting Procedures

To ensure proper and timely reporting of adverse events, the following communication plan is utilized. The project coordinator is responsible for reporting adverse events to the safety officer and the IRB in a timely manner and in accordance with the IRB's guidelines. Our procedures are as follows:

1. IRB: PI will notify the IRB of any Serious, Unexpected, Study Related Adverse Event within 7 days of PI notification of the event. Any noncompliance with the IRB approved protocol that increases the risk or affects the patient's rights, safety, or welfare also need to be reported within one week. At the time of the IRB annual continuing review, the IRB receives copies of the reports prepared for the safety officer. Reports that identify a new risk or a change in the risk benefit ratio must be submitted to the IRB within 10 days of receipt by the PI.
2. Safety Officer: PI will notify the safety officer of any SAEs regardless of study-relatedness. Additionally, the safety officer will receive semi-annual reports summarizing all SAEs and AEs.

Safety Officer

The SO will be the entity ultimately responsible for monitoring the safety of participants and the validity and integrity of the data. The SO is an experienced clinician-investigator with expertise in deprescribing and clinical interventions research and the clinical care of older persons with dementia in long-term care settings. The SO will maintain independence from the study and will not be involved in the conduct of the study or be a current collaborator of the PIs. The SO will be provided the study protocol and safety and data monitoring plan before study enrollment begins.

The safety officer is Paul Newhouse, MD, Professor of Psychiatry, Pharmacology, and Medicine at Vanderbilt University Medical Center and Clinical Core Director of the Vanderbilt Alzheimer's Disease Research Center. Dr. Newhouse has expertise in clinical dementia care and dementia research. As described above, Dr. Newhouse is not part of the key personnel involved in this grant. He is qualified to review the patient safety data generated by this study because of his unique and extensive clinical and research expertise in clinical interventions in long-term care and dementia care settings. The research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents will be submitted to the SO for approval prior to the beginning of the study.

The SO will review the entire IRB-approved study protocol regarding subject safety, the informed consent document regarding applicability and readability, and participant recruitment and retention milestones. Every six months, the study team will prepare safety reports to be reviewed by the SO for recommendations about modifications to the study. The report will include 1) a list of adverse and serious adverse events classified by severity and likelihood of being related to the study procedures; 2) whether adverse event rates are consistent with pre-study assumptions; 3) rates and reasons for study withdrawal; and 4) whether all participants met entry criteria. Summary reports of SO reports will be included in the annual NIH report for the project.

STATISTICAL CONSIDERATIONS

Sample Size & Attrition

Abe's Garden administration reported that all current residents lack decision-making capacity for healthcare decisions, and that all have surrogate decision makers. We estimate that the majority of the 41 residents/surrogates will participate in the study and conservatively estimate, based on investigators' work in previous studies in long term care, that attrition will be approximately 10-15%. We anticipate that some residents may die during the study and some surrogates may decline participation.

Power consideration: Given this is a pilot study, no formal power analysis will be conducted. But this pilot data would serve as a further guide for the power analysis for the following multi-center trial in preparation to test the clinical effectiveness of deprescribing among PWD in ALF care settings.

Outcomes

Aim 1: Descriptive statistics (counts and proportions for categorical variables and means and SDs for continuous ones) will be used to describe Demographics at baseline, as well as Feasibility outcomes in Aim 1 at each measurement.

Aims 2 and 3: All statistical tests will be two-sided, with alpha = 0.05. For Aims 2 and 3, we will be applying a within-subjects intervention design to estimate the effect size of Shed-MEDS deprescribing intervention on Medication and Quality of Life outcomes. This design takes advantage of the smaller sample size in this pilot intervention, with each subject's 3-month retrospective review serving as their own control, which also removes the between-subjects differences in each condition. For the Medications outcomes in Aim 2 and the Quality of Life outcome of BPSD in Aim 3a, changes during the intervention period will be modeled using GEE, where time (multiple indicators), intervention group (one indicator) and their interaction will form the predictors, controlling

for baseline demographics. Hypothesized differences between the intervention and control groups will be examined using appropriate linear contrasts. For the DEMQoL-Proxy in Aim 3a, we will use a two-sample t-test to compare measurements at baseline with the 90-day follow-up, which is robust against normality or heterogeneity of variance.[49]

Data Analyses

Missing Data: We will examine the incidence of missing data for each outcome in Table 2. We acknowledge that although the missing data could be informative due to intervention-related death or surrogate decision, we will not have enough data to formally test it due to the extremely small number of anticipated attrition (<5).

Repeated measures: Barring study withdrawal or death, main outcomes including the total number of medications, Quality of Life, and Safety will be assessed at four time points (enrollment, 30, 60, and 90 days) for each participant. We account for the anticipated positive correlations using a generalized estimating equation (GEE) framework for each repeated outcome. Unlike the parametric generalized mixed-effects models, GEE imposes no mathematical model for data distribution, thus providing valid inference for a broader class of data distributions.[50]

Limitations: There are a number of limitations that must be acknowledged in this pilot deprescribing study. The most apparent is the limited sample size. Although small, the sample size is sufficient to understand the primary feasibility aims of our study, applying Shed-MEDS in this novel population of PWD in an ALF. We have selected a within-subjects study design to maximize the power to estimate effect sizes on medication and quality of life outcomes for subsequent larger randomized trials. Without a concurrent, randomized comparator, there is a potential for time-related threats to validity, as we cannot control the effects of time on the outcomes. Furthermore, we would not be able to rule out carryover effects of earlier treatments on the outcomes.

DATA COLLECTION AND QUALITY ASSURANCE

Data Collection Forms

Data is obtained from multiple sources including residents (or surrogates) directly via standardized interview protocols and electronic medical records. All assessments, both interviews and medical record reviews, are recorded on paper forms stamped by the Vanderbilt IRB. Hardcopy forms should use the participant's randomly assigned ID number. Utilizing case report forms allows for quality assurance reviews of data entered in the electronic (REDCap) databases.

Data Management & Storage

All paper case report forms are maintained in a secure and locked file cabinet in a secure and locked office. Data collected from resident/surrogate assessment and medical records are entered directly into Research Electronic Data Capture (REDCap) databases. Use of REDCap outside the Vanderbilt server is allowable; however, it requires two factor authentication for security purposes. Assessment and interview forms are entered within the same week of data collection, and if possible, the same day.

Study coordinators will maintain SPSS databases for study tracking purposes. These databases along with data exported from REDCap for reporting and analysis purposes are maintained on a password protected VUMC secure server, which is only accessible to key study personnel registered with the IRB. Information in the REDCap databases and the secure server will be stored for an indefinite period of time to allow for subsequent data analysis and future reference.

Quality Assurance

No quality assurance training or metrics are required beyond IRB training and VUMC confidentiality standards. To reduce data entry errors, the REDCap databases have been created in a longitudinal model to match the paper case report forms and including branching logic and automated syndrome scoring. Additionally, to ensure the integrity of the data, the data manager conducts weekly data reviews to check for both completion and accuracy.

PARTICIPANT RIGHTS AND CONFIDENTIALITY

Shed-MEDS deprescribing intervention meets the criteria for human subjects research and, as such, is subject to a standard review by the institution's review board. All protocols, consent forms, and research materials were submitted to the Vanderbilt IRB. The study is subject to annual review by the IRB. In accordance with VUMC policy, all key study personnel complete human subjects training annually and Good Clinical Practice training every three years. Below is a description of the key human subjects materials submitted to the IRB.

Rationale for studying a potentially vulnerable population

Patients with cognitive impairment or dementia represent a population at potentially increased risk for worsened outcomes associated with polypharmacy. Thus, it is important to understand the effect of deprescribing on this vulnerable population. Patients with moderate impairment will likely need a surrogate to provide consent and complete some study measures. Patients with mild impairment may (not) need a surrogate to provide consent. We will complete a "standardized evaluation to sign informed consent" for all eligible patients with cognitive impairment based on the BIMS (see *Recruitment and Informed Consent Procedures*). Based on the distribution of BIMS scores, we may examine intervention effects by cognitive status via sub-group analyses.

Patients with a history of seizures on and off antiepileptics who otherwise meet study eligibility criteria will be considered eligible for enrollment. Antiepileptic medications are commonly used in the treatment of non-epileptic conditions. Although, the presence of a seizure disorder will not be a contraindication to deprescribing, patients who are currently on a therapy specifically for this indication will be continued on antiepileptic medications and managed by the medical team, as per usual care practice.

Approach to potential risks of the proposed study

The proposed research study has been designed based on input of experts in geriatrics, pharmacology, psychiatry, LTC nursing and medicine, and clinical trials. In order to assure appropriate research subject selection and high quality data collection, all study personnel will undergo training in the study protocol. Exclusion criteria have been carefully considered to help minimize patient risk prior to enrollment. In addition, our deprescribing intervention protocol is a carefully developed, multi-stage process that includes the independent review of multiple clinicians, each of whom has the ability to stop any recommended deprescribing action. This includes the study nurse practitioner, the facility medical team, the outpatient prescribing clinician, as well as the patient/surrogate. Each recommended medication for deprescribing will be considered for its potential for physiologic withdrawal, pharmacokinetic/pharmacodynamic effects, and medical condition exacerbation. For each medication for which any one of these is a potential concern, a medication titration protocol will be recommended, rather than full drug withdrawal, with appropriate monitoring of signs and symptoms. In addition, following the deprescribing intervention, systematic safety assessments and data recording will be done.

Steps Taken to Reduce Risks and Increase Impact of Study: The following are actions to minimize risk for the study population and maximize the impact of this study in deprescribing:

1. Intervention protocols included in this study are supported by a well-grounded conceptual framework, clinical evidence and, although not yet proven, the potential to benefit older person with dementia living in an assisted living facility.

2. The study protocol has been informed by a broad range of expertise including geriatrics, gerontology, pharmacology, LTC nursing and medicine, psychiatry, and implementation science methodologists.
3. Deprescribing actions and decisions will be guided by a clear and explicit protocol that will enable transparency and explanation of results and allow for broader generalizability.
4. The intervention protocol is general in its approach, however all deprescribing decisions are individualized to the patient, after considering the input from the NP expert, the resident, the Abe's Garden care team, and outpatient prescribers.
5. In the event that medications have increased potential for physiologic withdrawal, pharmacokinetic / pharmacodynamics effects, or medical condition exacerbation we will implement a titration protocol to minimize risk.
6. We have designed our trial with weekly follow-up of residents throughout the study period, thus allowing for robust follow-up for any potential adverse drug withdrawal events.
7. All protocols, consent forms, and research materials will have been submitted to the Vanderbilt IRB as part of the pilot intervention and will be approved.

Participant Confidentiality

Confidentiality: Research subjects' identities will be kept confidential at all times. Subject identifiers will never be revealed in publication, presentation, or other scientific purpose. All de-identified data will be maintained in locked file cabinets and locked offices at the Vanderbilt University Medical Center (VUMC) Center for Quality Aging and only accessible by the research team. All study subjects will be assigned a unique study identification number for use in computer database and analytic work. Linkage of patient study IDs to patient identifiers will be maintained by the PI and Project Coordinator only, with username/password protected access. All electronic data is kept in password-protected computer files on secured VUMC servers that is username and password protected. Study tables for data gathering will have two layers of password protection. De-identified data will be shared between VUMC and Vanderbilt University (VU) via the REDCap electronic database.

This study has support from the National Institutes of Health (NIH). Study information is protected by a Certificate of Confidentiality. This Certificate allows the research team, in some cases, to refuse to give out participant information even if requested using legal means. It does not protect information that must be reported by law, such as elder abuse or some infectious diseases. The Certificate does not prevent researchers from disclosing participant information if the team learns of possible harm to participants or others, or if a participant needs medical help. The National Institutes of Health & Aging and/or the Vanderbilt research team may share participant information, without identifiers, with others or use it for other research projects not listed here. The National Institutes of Health & Aging, and the research team will comply with all laws regarding the privacy of such information. There are no plans to pay participants for the use or transfer of this de-identified information.

Disclosures that participants consent to in the consent form are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that a participant makes him/herself are also not protected.

Privacy: All efforts, within reason, will be made to keep research health information (RHI) private. Some of the RHI will include medical information shared with VUMC from Abe's Garden. All research data will be locked in file cabinets and locked offices at the Vanderbilt University Medical Center (VUMC) Center for Quality Aging and only accessible by the research team. All electronic data is kept in password-protected computer files on secured VUMC servers that are username and password protected. Study tables for data gathering will have password protection. De-identified data will be shared between VUMC and Vanderbilt University (VU) via the REDCap electronic database.

Potential Benefits of the Proposed Research to the Subject and Others

The risks to study participants are reasonable in relation to the anticipated benefits. Although deprescribing is a well-known concept, the safety of such practice has not been closely evaluated as will be done in this study, which will advance our knowledge of how best to manage polypharmacy in clinical practice. In the absence of this study, a primary care provider or the Abe's Garden medical team may elect to deprescribe without consideration of withdrawal effects, pharmacokinetic / pharmacodynamic changes or exacerbation of an underlying medical condition. We will proactively consider these potential risks and actively mitigate risks with protocolized tapers of medication, surveillance, and communication of changes to the next care provider. Because most polypharmacy goes unaddressed in routine care practice, residents who do not undergo active deprescribing would be the same as receiving placebo (i.e., usual care). Thus, the risk is not greater than current standard practice.

Importance of Knowledge to Be Gained

Polypharmacy is prevalent among older adults and associated with numerous adverse outcomes. Persons with Dementia (PWD) experience even higher levels of polypharmacy compared to those without dementia.[1] PWD are also at greater risk for potential harm from polypharmacy including adverse drug reactions, falls, and further cognitive decline.[2,3] Furthermore, deprescribing decisions among PWD (and their respective caregivers) have unique factors that must be considered. First, PWD are likely to require the input of a caregiver or healthcare proxy to make deprescribing decisions. Importantly, there are measurable differences between PWD and their proxies related to their attitudes toward deprescribing, with reduced willingness to deprescribe among proxies in the population-based sample completing the National Health and Aging Trends Study (NHATS).[1] Despite the prevalence and associated risks of polypharmacy among PWD, few interventions have targeted deprescribing among the high-risk population of PWD. Importantly, deprescribing interventions, to date, among PWD largely have been implemented within outpatient clinical settings or otherwise excluded those receiving dementia care in ALFs. PWD, especially those with advanced disease, may commonly live in ALFs.[4,5] There currently exists a substantial gap in our understanding of deprescribing among ALF residents with advanced dementia. There are a number of important considerations within an ALF dementia care facility intervention. First, family proxies play a primary role in deprescribing decisions for PWD who reside in these care settings. In addition to family proxies' unique attitudes and behaviors, one must also consider the attitudes and behaviors of the licensed caregivers (nursing and physician staff) responsible for daily care. Although unique barriers to deprescribing may exist, there also may be potential advantages of an ALF-based deprescribing intervention, most notably the ability to more frequently monitor for potential withdrawal symptoms or other impacts of deprescribing, which may address family and/or licensed caregiver concerns about the effects of deprescribing on quality of life (e.g., behavioral disturbance, activity engagement) or safety events (e.g., falls) among PWD.

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