FULL PROTOCOL TITLE

A Patient-facing Tool to Reduce Opioid-Psychotropic Polypharmacy in People Living with Dementia.

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Protocol: Pro00065204
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Study Chairman or Principal Investigator:

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Study Intervention Provided by:

National Institute on Aging (NIA) IMbedded Pragmatic Alzheimer's disease (AD) and AD-Related Dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory

Sponsor of IND/IDE:

n/a

Protocol Changes:

Version 2
September 19, 2022

- **Updated recruitment and screening details to include contact with care partners in addition to people living with dementia for Aim 1 focus group participants.**

Version 3
October 17, 2022

- **Updated focus group recruitment to include mailing to participants in addition to email recruitment**
- **Removed irrelevant mention of care partners in section 10.1 page 22.**

Version 4
January 27, 2023

- **Updated recruitment protocol to add that clinicians will be given the opportunity to identify potential participants appropriate for the study than an EHR search may have overlooked**
- **Added draft of opt out letter to be shared with clinicians**

TABLE OF CONTENTS

Page

PRÉCIS

Study Title

A Patient-facing Tool to Reduce Opioid-Psychotropic Polypharmacy in People Living with Dementia.

Objectives

Establish:

1. Implementation feasibility: after sending the tool, the proportion of enrollees with documentation in the EHR of discussion regarding CNS-active medications with a prescribing clinician (or pharmacist).
2. Pilot ascertainment of the primary clinical outcome for a future intervention trial: using EHR to measure change in the total standardized daily dosage (TSDD) of the medication classes contributing to CNS polyRx from baseline to 4 months after sending the adapted intervention.

Design and Outcomes

Aim 1: successive rounds of virtual focus groups conducted over Zoom to adapt the EMPOWER educational tool for people living with dementia (PLWD) receiving CNS polyRx and their care partners (CPs). Brief follow-up phone calls with select care partners who participated in the focus group discussion in order to reflect on and clarify any feedback and insight that emerged during the group discussion.
Aims 2 and 3: use the electronic health record (EHR) to identify a list of PLWD experiencing CNS polyRx and (b) a randomized-controlled clinical trial implementing the adapted EMPOWER intervention in two primary care clinics using pragmatic methods at University of Michigan Health and Henry Ford Health (n=120 PLWD). We will also interview prescribing clinicians to obtain their perspectives on barriers and facilitators to the intervention.

Interventions and Duration

Participants (i.e., PLWD experiencing CNS polyRx) will be mailed the educational tool. Four months after sending the tool, we will do a final EHR query for all participants to assess the burden of CNS polyRx (i.e., total standardized daily dosage) and determine whether the prescribing regimen changed from the medications prescribed at baseline. Participation will be over after the 4 months.

Sample Size and Population

Our goal is to include 4 participating clinics with at least 30 PLWDs with active CNS polyRx per clinic, for a total of about 120 eligible PLWDs.

STUDY TEAM ROSTER

Principal Investigator: **Donovan Maust, MD, MS**

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Main responsibilities/Key roles:
As the Principal Investigator, Dr. Maust will take primary responsibility for overall scientific direction and oversight of the project. Dr. Maust will: 1) lead the development of the educational tool for Aim 1; 2) work with Drs. Blow and Vordenberg to oversee quantitative data collection and analysis for all aims, supported by data analyst; 3) work with Dr. Leggett to oversee focus group and qualitative interviews and analysis, supported by study qualitative coordinator; 4) along with Co- Investigators, prepare research reports and manuscripts for peer-reviewed publication; 5) provide overall supervision of study staff.

Co-Investigators: **Frederic Blow, PhD**

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Ann Arbor, MI 48109
734-845-3657
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Main responsibilities/Key roles:
As a Co-Investigator on this project, Dr. Blow will: 1) assist with oversight of the development of the educational tool for Aim 1; 2) assist with research design and measurement issues; 3) assist with interpretation of Aims 2 findings; 4) collaborate with other study team members on research reports and scientific manuscripts for peer-reviewed publication. Dr. Blow also has a VA appointment. Division of his time between the University and the VA is formally described in a written Memorandum of Understanding. All his time on this project will come from the University of Michigan component of his appointment.

Myra Hyungjin Kim, ScD

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myrakim@umich.edu
Main responsibilities/Key roles:
For this study, Dr. Kim will: 1) provide input to Dr. Maust and study analyst as all quantitative analyses are planned and

implemented; 2) provide regular biostatistical consultation across the duration of the proposed study, specifically related to obtaining the necessary data for a subsequent R01 proposal; and 3) participate in final manuscript preparation.

Amanda Leggett, PhD

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Main responsibilities/Key roles:
As a Co-Investigator on this project, she will: 1) assist with the design and development of recruitment methods and materials for Aims 1 and 2; 3) participate in focus groups and qualitative analysis for the development of the educational tool; 4) assist Dr. Maust with the supervision of the Qualitative Coordinator; 5) collaborate with other study team members on research reports and scientific manuscripts for peer-reviewed publication.

Sarah Vordenberg, PharmD, MPH

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Main responsibilities/Key roles:
As a Co-Investigator on this project Dr. Vordenberg will: 1) provide input into the development of the educational tool in Aim 1; 2) assist with sample design and selection for Aim 2; 3) collaborate with other study team members on research reports and scientific manuscripts for peer- reviewed publication.

PARTICIPATING STUDY SITES

Site Principal Investigator: Esther Akinyemi, MD

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Main responsibilities/Key roles:
Research will collaborate to carry out the goals and objectives of this project including overseeing development of the EMPOWER brochure, identifying potential clinics for the project, oversee the ongoing EHR data pulls and data transfers and ensure other project tasks are completed. Dr. Akinyemi

will assure that work is congruent with the desired objectives of the study. Dr. Akinyemi will participate in regular team meetings, contribute to analysis, reports, manuscripts, and dissemination of information

Site Co-Investigator: **Brian Ahmedani, PhD**

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One Ford Place
Detroit, MI 48202
313-916-2600
bahmeda1@hfhs.org
Main responsibilities/Key roles:
Dr. Ahmedani will oversee the work of the ongoing EHR data pulls and data transfer tasks to ensure these are completed in a timely manner and congruent with the desired objectives of the study. He will also participate in reviewing the analysis and dissemination of the result and he will participate in regular conference calls.

1 STUDY OBJECTIVES

1.1 Primary Objective

The primary clinical outcome will be change in the total standardized daily dosage (TSDD) of the medication classes contributing to CNS polyRx as measured in the EHR, from baseline to 4 months after sending the adapted intervention. We hypothesize that the TSDD of the medication classes contributing to CNS polyRx will decline from baseline to 4 months in participants receiving the nudge intervention (though this pilot study is not designed [or powered] to detect a statistically significant change).

1.2 Secondary Objectives

- Adapt an educational nudge intervention to help motivate CNS polyRx deprescribing among PLWD
- Establish mailing of the educational brochure within the clinic workflow by engaging clinicians and pharmacists at each of the identified clinics
- Establish implementation feasibility: after sending the tool, the proportion of enrollees with documentation in the EHR of discussion regarding CNS-active medications with a prescribing clinician (or pharmacist).

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The number of people living with Alzheimer's disease or a related dementia (PLWD) in the U.S. is projected to grow to 50 million people by 2050. Although cognitive impairment is the clinical hallmark of dementia, behavioral and psychological symptoms of dementia (BPSD) such as apathy, delusions, agitation, and sleep disturbances are exceedingly common, occur in all forms of dementia, and often dominate disease presentation.[1-5] Nearly all patients will exhibit these symptoms at some point in the course of dementia.[3,6] Such symptoms, as opposed to core cognitive symptoms, are particularly vexing and create the most difficulties for patients, caregivers, and clinicians, leading to earlier nursing home placement.[7-13] Central nervous system-active medications are widely prescribed to PLWD in the community to address these symptoms. In a recent *JAMA* publication by Dr. Maust's team analyzing all traditional Medicare beneficiaries living with dementia who had Part D prescription drug coverage, 73.5% filled a prescription for at least one CNS medication, despite the minimal evidence of efficacy among PLWD while 13.9% of community-dwelling PLWD were exposed to CNS polyRx, defined as >30 days of concurrent exposure to ≥3 CNS medications.[14] CNS medication use—singly and in combination—poses specific risks for older adults overall and PLWD specifically given the adverse impact on cognition and potential for harms including fall-related injury and death.

2.2 Study Rationale

The health care system is poorly equipped to deal with the growing number of persons living with dementia (PLWD) and their complex medical and psychosocial needs, which may help explain their high rate of potentially inappropriate psychotropic and opioid polypharmacy. However, there is potential for direct-to-patient education to promote deprescribing. The power of a direct-to-patient educational nudge approach has been highlighted by the EMPOWER intervention, which specifically focused on and successfully achieved sedative-hypnotic (e.g.,

benzodiazepines) deprescribing in older adults. Critically for this proposal, a *post hoc* analysis found no difference in efficacy between participants with and without mild cognitive impairment. Based on the potential demonstrated by EMPOWER, a direct-to-patient approach may be a helpful mechanism to prompt CNS polyRx deprescribing among PLWD. Therefore, we will adapt direct-to-PLWD educational nudge to address such polypharmacy. This educational intervention poses minimal risks to participants, particular given that the "usual care" being targeted (CNS polyRx) in fact poses significant risks to PLWD.

3 STUDY DESIGN

- *Type/design of trial (e.g., placebo-controlled, double-mask, parallel design, open-label, dose escalation, dose-ranging)*
  This is an educational nudge intervention with two intervention clinics and two control clinics.
- *Specific statement of the primary and secondary outcomes (must be consistent with Study Objectives)*
  The primary clinical outcome will be change in the total standardized daily dosage (TSDD) of the medication classes contributing to CNS polyRx as measured in the EHR, from baseline to 4 months after sending the adapted intervention. We hypothesize that the TSDD of the medication classes contributing to CNS polyRx will decline from baseline to 4 months in participants receiving the nudge intervention (though this pilot study is not designed [or powered] to detect a statistically significant change).

  Secondary Objectives are:
  a. Adapt a patient- oriented educational nudge intervention to help motivate CNS polyRx deprescribing among PLWD
  b. Establish mailing of the educational brochure within the clinic workflow by engaging clinicians and/or pharmacists at each of the participating clinics
  c. Establish implementation feasibility: after sending the tool, the proportion of enrollees with documentation in the EHR of discussion regarding CNS-active medications with a prescribing clinician (or pharmacist).
- *Study population and groups/arms including sample size (including a table, if appropriate)*
  We will identify 120 PLWD experiencing CNS polyRx across participating clinics to receive the intervention.
- *Study location (e.g., in-patient or out-patient, clinic, community)*
  A total of four primary care clinics at University of Michigan Health and Henry Ford Health; potentially more clinics will be engaged if necessary to reach the goal of N=120 PLWD.
- *Approximate duration of enrollment period and follow-up (specify individual participant vs. entire trial)*
  Approximately 6 months accounting for EHR review, sending the nudge tool, and then allowing several months (4) afterwards for dyads to discuss with clinicians and make medication changes.
- *Description of intervention and administration*
  An adapted EMPOWER brochure that will specifically be modified to address CNS polyRx (as opposed to the single-class focus of the original). The intervention will be adapted based

on input from successive rounds of focus groups and then administered by mail through the clinic. There is no direct interaction between the study team and PLWD

- *Randomization, blinding and any stratification*
  There is no patient-level randomization. Within each health system (University of Michigan and Henry Ford), we will randomly select one of the clinics where patients will receive the nudge intervention.
- *Other protocol specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans).*
  n/a

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Aim 1: Focus Group Research

The inclusion criteria for the Person living with Dementia (PLWD) will be:

(1) Individuals with a self-reported diagnosis of dementia of any type and experiencing no more than mild dementia;
(2) Individuals that are able to read, speak and understand English;
(3) Individuals that have a care partner (CP)
(4) Individuals that are 50 years of age or older.

The inclusion criteria for the care partner (CP) will be:

(1) Individuals who are 18 years of age or older or considered legal adults in their state of residence;
(2) who are able to read, speak and understand English;
(3) Individuals who are identified as the CP to the PLWD.

Aim 2 and 3: Intervention

The inclusion criteria for the Person living with Dementia (PLWD) will be:

(1) Individuals who are receiving care at the one of the selected primary care clinics at Michigan Medicine and Henry Ford Health System;
(2) Individuals who have a diagnosis of dementia or mild cognitive impairment (MCI) of any type based on ICD-10 codes;
(3) Individuals who have been prescribed ≥3 of the medications that contribute to CNS polyRx (e.g., antidepressants, antipsychotics, anti-epileptics, benzodiazepines, non-benzodiazepine benzodiazepine receptor agonist hypnotics, or opioids) based on chart review;
(4) Individuals that are 50 years of age or older.

4.2 Exclusion Criteria

Aim 1: Focus Group Research

The exclusion criteria for PLWD will be:

(1) Individuals who do not read, speak, or understand English;
(2) Individuals with a diagnosis of dementia that is in severe stage;
(3) Individuals with visual impairment that would prohibit viewing study materials;

(4) Individuals with hearing impairment sufficient to prohibit participation in a focus group.

The exclusion criteria for CPs will be:
(1) Individuals who do not read, speak or understand English;
(2) Individuals with any visual impairment that would prohibit viewing study materials;
(3) Individuals with any hearing impairment that would prohibit participation in a focus group.

Aim 2 and 3: Intervention
(4) After identifying potential participants through EHR at the intervention and control clinics, we will provide the list to their primary care clinicians to review and opt-out potential participants for whom they feel the intervention is not appropriate. (While the control clinics will *not* receive the intervention, we will still allow their clinicians to indicate PLWD for whom the think the intervention would be inappropriate in order to have the most comparable groups.) At intervention sites, clinicians will also be given the opportunity to suggest any additional patients at the clinic who meet the inclusion criteria and may have been missed by the EHR search. The opt out letter and responses will be sent by email to/from the research assistant or coordinator at each respective site and the clinic liaison. If doctors wish to suggest any additional patients, those patients will be added to REDCap by the health system's own research team. Patients selected in this way will be noted in REDCap as having been selected through this alternate method.

4.3 Study Enrollment Procedures

Aim 1: Focus Groups

Identifying and recruiting trial participants: Participants will be identified and recruited through various organizations including Michigan Medicine entities (e.g., the CTSA recruitment portal, Pepper Center, and ADRC, UMHealthResearch), the Henry Ford Health System (HFHS), and community dementia organizations with which Drs. Maust and Leggett have partnered with previously (Alzheimer's Association and Dementia Minds). Study staff will distribute flyers via mail and/or email to the organizations and individuals with mild cognitive impairment/early-stage dementia and care partners from an existing list of participants in our previous work who have indicated interest in being contacted again for future research to maximize exposure. Anyone who thinks they may qualify for the study can call or email a study team member to inquire. Staff will use a screening log to document participant contact information and any reasons for ineligibility. The screening log will be stored on a RedCap (Research Electronic Data Capture) database. Focus groups will be virtual and conducted over Zoom. Each participant will receive the focus group questions and the brochure ahead of time. The virtual format will ensure a diverse sample and reduce participant burden. Following the group discussion, the study team will conduct brief follow-up phone interviews with select, individual focus group participants. The purpose of these follow-up phone calls is to allow participants and researchers time to reflect on the discussion and clarify any insights that emerged. Not all focus group participants will be asked to participate in a follow-up phone call.

Eligibility and Ineligibility criteria: Focus group PLWD participants will have no more than mild dementia based on the CP and/or PLWD self-report. Eligibility will be based on self-report and the dyad's availability and willingness to participate in the group discussion. Participation in the focus group will present no more than minimal risk to the participants and the probability of experiencing minimal risks associated with this project are not greater than risks encountered in daily life.

Consent procedures: Please see section 11 for consent procedures.

Aim 2: Pilot feasibility of (a) using the electronic health record (EHR) to identify PLWD experiencing CNS polyRx and (b) implementing the adapted EMPOWER intervention in two primary care clinics using pragmatic methods.

Identifying and recruiting trial participants: Patients in Aim 2 and 3 will not be recruited directly to participate.

Eligibility and Ineligibility criteria: We will use the electronic health record (EHR) to identify patients living with dementia prescribed these problematic medication combinations (2a). Team data analysts will use DataDirect—the portal for researchers into the Michigan Medicine and HFHS EHRs—to identify PLWD seen in primary care with CNS-active polyRx. ICD-10 codes will be used to identify PLWD (including MCI) with an ambulatory care encounter with a primary care clinician (internal medicine, family medicine, or geriatrics) during the preceding 12 months. Within each system, we will identify a pair of clinics that have relatively similar panel characteristics (similar volume overall; PLWD with similar distributions of gender, race/ethnicity) to serve as the paired intervention-control sites. Among PLWD, we will use current outpatient medications data to identify those with ≥3 active prescriptions of the medications that contribute to CNS polyRx (e.g., antidepressants, antipsychotics, anti-epileptics, benzodiazepines, non-benzodiazepine benzodiazepine receptor agonist hypnotics, or opioids). We will contact the primary care clinicians of eligible PLWD once by email to offer them the opportunity to exclude potential PLWD participants for whom they think the intervention would be inappropriate; clinicians will have one week to opt potential participants out, or to suggest an eligible patient we may have missed (if they do not reply, we will assume that we can proceed).

Randomization: We will randomly select one clinic (or more, as needed to meet the target dyad sample size) within each system as the intervention clinic; dyads in these clinics will receive the nudge intervention. Dyads within the other clinic in each system will serve as controls.

Consent procedures: We will request a waiver of informed consent for PLWD participants in Aim 2 and 3. See section 11.2 for details.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

This project will adapt the EMPOWER educational brochure for PLWD receiving CNS polyRx. The educational brochure will be mailed to intervention participants identified through EHR at Michigan Medicine and Henry Ford Health System. Prior work utilizing the EMPOWER intervention specifically focused on sedative-hypnotic (e.g., benzodiazepines) deprescribing in older adults.[15] In that EMPOWER trial, investigators developed an educational tool to "increase risk perception about benzodiazepines through knowledge acquisition and change in beliefs"[16]

(e.g., "*The dose that I am taking causes no side effects*;" [True/False]]); this tool (in the form of an 8-page brochure) was mailed to older adults on long-term benzodiazepine therapy. In the current study, this tool, to be delivered in the form of a brochure mailed to PLWD will describe what CNS polyRx is, present information about the associated risks, and suggest that they speak with their prescribing clinician or pharmacist about ways to potentially simplify their medication regimen. The tool will be adapted through three successive rounds of focus groups of PLWD and caregivers (n=5 PLWD-CP dyads per round for 15 dyads total). As part of Aim 2, we will identify eligible participants from the EHR and allow primary care clinicians to opt-out patients for whom they believe the intervention would be inappropriate. The educational tool will be mailed from the participating health systems with a cover letter from the respective clinic that includes the specific medication combination that made the PLWD eligible for the study. The goal of the educational nudge is to prompt a conversation with the PLWD's clinician or pharmacist; the material will clearly state that individuals should not make any medication changes without discussing with their clinician. The EHR will be reviewed 4 months after the brochure is mailed to determine with there has been any change to the CNS polyRx.

5.2 Handling of Study Interventions

n/a

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All usual interventions are allowed.

5.3.2 Required Interventions

None.

5.3.3 Prohibited Interventions

None.

5.4 Adherence Assessment

n/a

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Month 1-2	Month 3-4	Month 5-6	Month 7-8	Month 9-10	Month 11-12
Draft adapted tool	***x***					
Adapt content (focus groups x3)		***x***	***x***			
Follow-up phone calls		***x***	***x***			
Screen/Identify target PLWD in EHR			***x***			
Allow clinician opt-out of participants			***x***			
Clinic randomization			***x***			
Mailing of educational tool				***x***		
2-month chart review				***x***		
4-month chart review					***x***	
Clinician Interviews						***x***
Adverse Events				***x***	***x***	***x***

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Aim 1: Screening for focus groups will be based on subject's self-reported diagnosis of early-stage dementia.

Aim 2/3: Screening for the intervention will occur through electronic health record (EHR) chart review, this project does not require screening evaluations.

Consenting Procedure

Aim 1: For the focus group discussions, the consent process will be interactive and allow the participants with dementia to express understanding and interest. Before the focus groups, participants will be mailed the adapted brochure for previewing and a simplified consent form with key information about the project and their involvement. At the beginning of the focus group, which will be conducted over the Zoom teleconferencing platform, study staff will review the main tenets of the Consent Information Sheet with all participants using a comprehensive oral script and take time to answer questions. Participants will also be informed that they may be asked to participate in a brief follow-up phone call after the focus group (scheduled no later than 2 weeks following the focus group, at the selected participant's convenience). At the beginning of the focus group when staff summarizes the Consent Information Sheet, participants will be informed that they can opt out of eligibility for the potential follow-up phone call.

Aims 2/3: For the intervention we will request waiver of informed consent for PLWD intervention participants; see section 11.2.

Screening

Aim 1: Screening for focus groups will be based on subject's (PLWD and/or CP)self-reported diagnosis of early-stage dementia.

Aims 2/3: Screening to identify eligible participants will occur through electronic health record (EHR) chart. We will provide primary care clinicians the opportunity to opt-out their patients if they think the intervention is not clinically appropriate. The confirmed PLWDs will be the recipient of the nudge intervention.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Aim 1: Research staff will contact potential participants by telephone to collect basic demographic information to ensure a diverse sample and determine eligibility. Eligibility will be based on 1.) a diagnosis of dementia of any type with no more than mild dementia as reported by the PLWD and/or the care recipient and 2.) the dyad's availability and willingness to participate in the virtual group discussion.

Aim 2/3: Once a PLWD is deemed eligible based on chart review and mailed the educational tool, they are enrolled in the project.

Baseline Assessments

Aim 1: There are no baseline assessments for focus group participants.

Aim 2/3: There are no baseline assessments of the participants. Baseline information will be collected from the EHR, including basic demographics (age, gender, race/ethnicity), diagnoses, and active medications include CNS-active.

Randomization

Aim 1: n/a

Aim 2/3: We will randomly select one clinic (or more, as needed to meet the target sample size) within Michigan Medicine and Henry Ford Health System as the intervention clinics from which PLWD will receive the nudge intervention. PLWD within the other clinic in each system will serve as controls.

6.2.3 Follow-up Visits

Aim 1: Participants in the group discussion may be asked to participate in a follow-up phone call 1-2 weeks after the group discussion is over. The follow-up will allow time for researchers to reflect on the discussion and to clarify any questions that may come up after the discussion. Not every focus group participant will be asked to participate in a follow-up. After the research team reviews transcripts, the research team will clarify any questions that come up after the discussion is over. Additionally, based on the teams' previous experience in working with CP-PLWD dyads, some care participants may not be comfortable being frank with their PLWD present and the follow-up may allow care partners the opportunity to clarify anything without their PLWD present. The follow-up phone call will be brief (≤15 minutes) and not all participants will be asked to participate. Potential participants will be called or emailed after the focus group to determine if they are interested in participating and the call will be scheduled at their convenience.

The intervention does not entail any follow-up visits. For evidence of implementation feasibility, we will do a 2-month chart review of PLWD primary care and pharmacy notes to determine if there is documented evidence of conversation related to the medications of interest (i.e., did the nudge intervention have the intended outcome).

6.2.4 Completion/Final Evaluation

We will repeat a final EHR review for evidence of documented conversation related to these medications. In addition, we will review the active medications to determine the primary outcome of changes to the CNS-active medication regiment. Additionally, we will conduct informant interviews with 10 primary care clinicians across intervention clinics from U-M and HFHS. The purpose of these interviews will be to explore potential barriers with experts and will explore whether:

- PLWD discussed receiving the tool with the clinician;
- Clinician perception of whether the tool motivated:
    - discussion related to prescribing that might not have occurred otherwise;
    - prescribing changes that might not have occurred otherwise;

- Clinician suggestions for modifications to the tool;
- Clinician suggestions regarding their perceived barriers or facilitators to improving the appropriateness of CNS-active prescribing, e.g.:
    - Clinical uncertainty regarding which medications to address;
    - Lack of access to clinical pharmacists to facilitate medication changes;
    - Lack of psychosocial resources for the PLWD-CP dyad.

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

n/a

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

The intervention is presenting education, which has a benign safety profile. Should the participants, in consultation with their clinician, choose to make medication changes, then participants should be at *lower* risk of adverse events by minimizing the burden of these medications. In a recent study of deprescribing among PLWD (of any, not limited by medication class), there was no difference in hospitalization or mortality rates in intervention groups, and review of records did not "reveal any pattern of adverse drug withdrawal events associated with the intervention."[17] In the original EMPOWER intervention (deprescribing of sedative-hypnotics), "no major adverse effects requiring hospitalization were reported."[15]

Study participants will be identified using the EHRs and the intervention will consist of mailed materials to the participant—otherwise, the study team has no contact with study participants. Therefore, any potential adverse event reporting will come to the research team through clinics from which patients are identified. In the event of clinic staff notifying the study team of a serious and unexpected adverse event, the PI will follow the required reporting protocols detailed below.

7.3 Adverse Events and Serious Adverse Events

AE Definition: AE is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

SAE Definition: SAEs consist of any adverse event that results in death; is life threatening or places the participant at immediate risk of death from the event as it occurred; requires or prolongs hospitalization; causes persistent or significant disability or incapacity; is another condition which investigators judge to represent significant hazards.

Unanticipated Problem (UP) Definition: any incident, experience, or outcome that meets all of the following criteria:

- unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- related or possibly related to participation in the research;
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

AEs for this study include:

AEs for this study include a PLWD making medication changes without first consulting with a treating clinician. This may be revealed during the 2-month and 4-month chart reviews or by the prescribing clinician. Given risks associated with usual care (e.g., risk of respiratory suppression and death from common psychotropic-opioid combinations), while we will consider self-directed medication change an AE, in fact PLWD risk of medication-related adverse events would likely be lower than the risk from usual care (i.e., without change). Overall, we consider the potential for AEs to be low.

SAEs for this study include:

SAEs are not related nor anticipated as a result of this study. The study activities pose minimal risks. Death or hospitalization can reasonably be expected considering the study population includes persons living with dementia and those experiencing CNS polyRx. However, the study activities will not contribute to the death of participants; in fact, reducing burden of CNS-active medication should lower the risk of death. Prior deprescribing intervention studies in older adults demonstrate no impact on hospitalization or death.[1715]

7.3.1 Reporting Procedures

Severity of Event

All data and safety monitoring reporting will classify SAEs and AEs as to their severity, expectedness, and potential relatedness to the study intervention as per the definitions below:

Severity

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate:** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- **Severe:** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Relationship To Study Intervention

Definitely Related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

Not Related: The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

7.3.2 Follow-up for Adverse Events

Reporting Schedule:

- All adverse events that are serious (SAE) and unexpected (i.e., have not been previously reported for the study's intervention) will be reported to the IMPACT Collaboratory Regulatory and Data Team Leader (Dr. Julie Lima), NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharyya), and the IMPACT Collaboratory Safety Officer (SO) within 48 hours of the study's knowledge of SAE.
    - Only those adverse events that are serious (SAE), unexpected, and related to the intervention must also be reported to Advarra IRB. Unexpected and unrelated SAEs will be reported to Advarra IRB on a case-by-case basis if requested by the IMPACT Collaboratory Safety Officer (SO) or NIA IMPACT Collaboratory PO.
- All deaths will be reported to IMPACT Collaboratory Regulatory and Data Team Leader (Dr. Julie Lima), NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharyya), and the Safety Officer, Dr. Madhuri Reddy within 24 hours of study's knowledge of death.
    - Advarra IRB does not require the specific reporting of death outside of the SAE reporting requirement above, but they will be notified on a case-by-case basis if requested by the IMPACT Collaboratory Safety Officer (SO) or NIA IMPACT Collaboratory PO.
- All unanticipated problems (UPs) will be reported to the IMPACT Collaboratory Regulatory and Data Team Leader (Dr. Julie Lima), Advarra IRB, NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharyya), and the Safety Officer, Dr. Madhuri Reddy within 48 hours of the study's knowledge of the event.

- The summaries of all previously reported unexpected and related SAEs, deaths, and UPs, as well as all other SAEs and AEs will be reported to IMPACT Collaboratory Regulatory and Data Team Lead (Dr. Julie Lima), Advarra IRB, NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharyya), and the IMPACT Collaboratory Safety Officer, Dr. Madhuri Reddy at a minimum every 6 months, or at a frequency requested by the Safety Officer or NIA IMPACT Collaboratory PO.

7.4 Safety Monitoring

The NIA Guidelines on Data and Safety Monitoring generally require that a NIA-appointed Data and Safety Monitoring Board or Safety Officer monitor clinical trials. Please see the Data and Safety Monitoring Guidelines .

8 INTERVENTION DISCONTINUATION

For this pragmatic intervention, there is no specific intervention discontinuation. The intervention consists of providing educational information on one occasion and it will be up to the dyad and clinician whether there are any resulting medication changes.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

For this nudge intervention, the primary clinical outcome will be change in the total standardized daily dosage (TSDD) of the medication classes contributing to CNS polyRx as measured in the EHR, from baseline to 4 months after sending the adapted intervention. We hypothesize a decline in the total standardized daily dosage (TSDD) following the nudge intervention. The presumed mechanism of the intervention is that the nudge educational tool will activate the dyad to discuss their current medication regimen with the prescribing clinician or a pharmacist. To determine whether the intervention has had this desired effect, as an implementation feasibility target, the team at each site will revisit intervention PLWD charts to complete an expedited chart review. We will complete initial reviews approximately two months after sending the tool and final review four months after sending the tool.

9.2 Sample Size and Randomization

Our goal of participants is a total of 120 PLWD (a total of 60 across 2 intervention clinics; 60 across 2 control clinics), after allowing for clinician opt-out. This will then allow us to obtain a reasonably precise estimate of the first feasibility outcome (i.e., documentation of a prescribing-related conversation in the EHR), allowing us to determine the number of clinics within each health care system needed for the future ePCT. We will also be able to estimate the lower limit of a 95% confidence interval around the implementation feasibility target (i.e., documented discussion regarding CNS polyRx) not to drop below the pre-determined target of 50%. With N=60 PLWD (i.e., the PLWD in the intervention clinics) and assuming 65% to 75% to show evidence of CNS-medication discussions, the lower limits of a 95% confidence interval for implementation

feasibility target will be 51.6% to 62.1%, respectively. Meeting the implementation feasibility target will allow us to proceed to a full ePCT.

9.2.1 Treatment Assignment Procedures

We will randomly select one clinic (or more, as needed to meet the target sample size) within Michigan Medicine and Henry Ford Health System as the intervention clinic; PLWD in these clinics will receive the nudge intervention. PLWD within the other clinic in each system will serve as controls.

9.3 Interim analyses and Stopping Rules

No interim analyses are planned.

9.4 Outcomes

9.4.1 Primary outcome

The primary clinical outcome will be change in the total standardized daily dosage (TSDD) of the medication classes contributing to CNS polyRx as measured in the EHR, from baseline to 4 months after sending the adapted intervention.

9.4.2 Secondary outcomes

n/a

9.5 Data Analyses

- **Aim 1** will involve rapid and rigorous qualitative analysis. Focus group discussions and any follow-up phone calls will be audio recorded. Following transcription of focus groups, the transcripts will be used to create summaries for each focus group, which will then be reconciled through discussion. Summary data regarding tool refinement and recipient engagement will be transferred into a matrix for interpretation and comparison across groups. This matrix will be reviewed by all pilot investigators to select final refinements of the tool as well as to finalize the Aim 2 engagement strategy. If participants selected for a follow-up phone call agree to being recorded, the brief discussion will be audio recorded for accuracy purposes.
- **Aim 2:** With **N=120** PLWD, we expect to obtain a reasonably precise estimate of the first feasibility outcome, allowing us to determine the number of clinics within each health care system needed for the future ePCT.
- **Aim 3:** Four months after sending the tool, we will do a final EHR query (**Aim 3**) for all participants to assess the burden of CNS polyRx (i.e., total standardized daily dosage) and determine whether the prescribing regimen changed from the medications prescribed at baseline. We will use each active outpatient prescription for a CNS-active medication and convert them to a standardized daily dose using the minimal effective geriatric daily dose, adding the total across all CNS-active medications at the patient level. This—change in the total standardized daily dosage (TSDD) following the nudge intervention—will be the primary outcome for the study and subsequent trial. With the expected sample size of 120 PLWD (60 per group and 30 per clinic-group), we expect to have a good estimate of the variability of the distribution of change in TSSD (clinical outcome

measure) from baseline in each group as well as within-clinic correlation of the changes in TSSD.

Data analysis will be completed by a Maust team analyst, under supervision of the study biostatistician. Because the nature of the intervention is that any changes are made by the PLWD in consultation with their treating clinician, there are not trial results or information to provide to the clinician at completion of the pilot study (i.e., the intervention does not entail treatment changes other than those made by the treating clinician).

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

To maintain the confidentiality of the intervention participants, the study team will follow strict procedures that protect subject information. Information necessary for eligibility and enrollment will be stored in REDCap. REDCap is a secure web application designed to support data capture for research studies. It provides user-friendly web-based case report forms, real-time data entry with branching logic and validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus), procedures for importing data from external sources, and advanced features such as a data quality check module. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Application and database servers are on virtual machines (VM). Surveys will capture focus group participant demographics, specific diagnosis information for PLWD including diagnosis type and date of diagnosis; this information will also be collected and stored in REDcap. Participants' names and contact information will be stored in a secure, REDCap database, separate from their study data and only accessible to members of the research team for research purposes.

Focus group discussions will be recorded and then transcribed with identifiers removed and audio recordings will be destroyed. Transcriptions will be stored in password protected files.

Only data necessary for the intervention will be collected through EHR for subjects in aim 2 and 3 (demographics, medications, mailing address). Study participants will be identified using the EHR and data collected will be stored in REDCap. Outcome data will be collected from the EHRs and stored in REDCap, there will not be any further contact with study participants beyond the initial mailing of the intervention materials.

10.2 Data Management

Qualitative data from focus groups in Aim 1 will be stored in password protected files. All survey data from Aim 1 and EHR data from Aims 2 and 3 will be stored in REDCap. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. The University of Michigan

team will sponsor REDCap accounts for each necessary member of the Henry Ford team. Only necessary study team members will have access. The Michigan Medicine team will lead data analysis.

10.3 Quality Assurance

10.3.1 Training

All staff have completed Program for the Education and Evaluation in Responsible Conduct of Research (PEERRS) and Good Clinical Practice trainings. Staff will follow quality assurance procedures to assure the accuracy and consistency of study data. Any adverse events that are serious and unexpected will be reported to study staff by participating clinics. Training on the importance of identifying any adverse events, including checklists, will be provided to clinic staff throughout the course of the study.

10.3.2 Quality Control Committee

The Principal Investigator, Dr. Maust, will be responsible for ensuring participants' safety on a daily basis. The study team will meet regularly to ensure safety and quality. In addition, the NIA IMPACT Collaboratory Safety Officer will oversee all data and safety monitoring activities for this study. The SO will act in an advisory capacity to the NIA Director to monitor participant safety, to evaluate the progress of the study, and to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. Advarra IRB will conduct the ethical review required for the protection of human subjects. NIA PO, in consultation with DSMB chair, will make a determination regarding the level and format of data and safety monitoring this study requires, i.e., full DSMB oversight or monitoring by an independent SO.

10.3.3 Metrics

n/a

10.3.4 Protocol Deviations

Any unplanned deviations or departures from IRB approved protocol procedures will be reported to Dr. Maust and the Advara IRB.

10.3.5 Monitoring

Both the enrollment and implementation feasibility targets from Aim 2 will entail chart reviews for patients with dementia experiencing CNS-PolyRx. For each component, research assistants (RAs) will complete the first 20 chart reviews, which will then be reviewed by Drs. Maust and Akinyemi (the UM and Henry Ford PIs, respectively) to assure appropriate and accurate data abstraction. The RAs will then complete further reviews independently.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and any future modifications will be submitted to the Advara IRB for

approval. Study team members will strictly adhere to IRB guidelines and policies.

11.2 Informed Consent Forms

Aim 1: Focus groups PLWD participants will have no more than mild dementia and participation in the focus group will present no more than minimal risk to the participants and the probability of experiencing minimal risks associated with this project are not greater than risks encountered in daily life. We will seek approval to waive documentation and include a comprehensive oral script for the PLWD-CP dyad. After completing the recruitment and screening procedures, interested and eligible individuals will have the option to receive a mailed and/or emailed a Consent Information Sheet (a simplified consent form with key information about the project and their involvement) before the focus group. At the beginning of the virtual focus group, study staff will review the main tenets of the Consent Information Sheet with all participants (PLWD-CP dyads) using a comprehensive oral script Participants will also be informed that they may be asked to participate in a brief follow up phone call after the focus group (1-2 weeks following the discussion, and scheduled at the selected participant's convenience). The study team also allow participants to opt out of a follow-up phone call at the beginning of the focus group when staff summarizes the Consent Information Sheet. Participants will be encouraged to ask questions and verbal consent will be obtained. We have chosen this consent process to minimize participant burden and to ensure the cognitively impaired participants are not overwhelmed by information. This verbal consent process will make our recruitment processes more efficient. We will maintain a spreadsheet where we track participant IDs, we include a column for date of consent and consent provider. It should not be assumed that persons with mild cognitive impairment/early-stage dementia are unable to give consent. Our approach will make the consent process interactive and provide opportunities for the individual with dementia to demonstrate capacity to understand the study while not overwhelming with information. The research includes people living with dementia who will have capacity to provide informed consent. To ensure that the individuals understand their involvement in the research, our approach to informed consent will me pragmatic and interactive. We will use Talk Back to assess comprehension we will remind participants that their participation is voluntary and they are free to leave at any time. We will use the same approach (waiving documentation and using a comprehensive oral script) for obtaining informed consent for CP participants in the focus groups.

Aims 2 and 3: We will request a waiver of informed consent for PLWD participants in for the following reasons:

- *The research involves no more than minimal risk:* This is an educational intervention to prompt a discussion with the PLWD's clinician or pharmacist. Given the inclusion criteria—these are PLWD exposed to CNS polyRx—the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life" given the adverse outcomes associated with the usual care (i.e., CNS polyRx) that establishes study eligibility.
- *The research could not practicably be carried out without the requested waiver or alteration:* Sending an informed consent document to PLWD describing the

deprescribing study could bias the control group by introducing them to the concept of deprescribing itself and interfere with the aims of this project.

- *If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format:* In order to determine feasibility, implementation, and primacy outcomes, the information must be in an identifiable format.
- *The waiver or alteration will not adversely affect the rights and welfare of the subjects*: The intervention is entirely comprised of education about appropriate medication use; generally providing additional, potentially actionable information to patients and families is a valuable goal in health care settings.
- *Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation:* At the conclusion of the study, we will send the intervention PLWD a one-page informational study summary. The summary will be written in accessible language and will include pertinent information and findings.

11.3 Participant Confidentiality

Aim 1: To minimize the violation of confidentiality for focus group participants, we will ensure that data are protected and cannot be linked to a particular person. It is not possible to guarantee confidentiality because focus group members may talk about their experience, however, participants will be asked to only disclose information that they are comfortable sharing in the group setting and we will ask that participants not disclose any information shared outside of the group. Unique identification numbers will be assigned to each participant and all forms are coded with this number, rather than by name. All data are stored in secure password protected files. Enrollment files and subject code/name sheets will be stored separately because they contain identifying information. Rigorous data security measures and staff training procedures will be put in place to minimize the risk of breach of confidentiality. The study team has considerable experience in maintaining the confidentiality of participant data and datasets, using established procedures to ensure data confidentiality. All investigators and research staff fulfill ongoing training requirements for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA).

Aim 2 and 3: A full HIPAA waiver of authorization will be sought for the use of electronic health record data. In order to fulfill requirements for a HIPAA waiver of authorization, participant's protected health information will not be disclosed unless necessary for certain individuals working on behalf of the study sponsor. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the sponsor or persons working on behalf of the sponsor (i.e. IMPACT research study staff, the DSMB and/or Safety Officer), the FDA, the NIA/NIH, and the OHRP. To maintain confidentiality of the intervention participants, the study team will follow strict procedures that protect the confidentiality of subject information; Subjects will be assigned study numbers, study records will be secured through the use of password protected files and coded by subject identification numbers so that participants

cannot be identified by their research record. Access to the EHR files will be limited to appropriate study personnel and only study team members who have completed appropriate training in the protection of human subjects will have access to the data. At the conclusion of the study, identifiers including subject tracking files will be deleted. It is necessary for the study team to access intervention participant's EHR for research activities to occur and without a HIPAA waiver of authorization for the following reasons:

- *The research involves no more than minimal risk:* This is an educational intervention to prompt a discussion with the PLWD's clinician or pharmacist. Given the inclusion criteria—these are PLWD exposed to CNS polyRx—the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life" given the adverse outcomes associated with the usual care (i.e., CNS polyRx) that establishes study eligibility.
- *The research could not practicably be carried out without the waiver:* Without access to PHI the research cannot practicably be conducted.
- *If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format:* In order to determine feasibility, implementation, and primacy outcomes, the information must be in an identifiable format. Only members of the research team will have access to PHI, all data will be stored in password protected files with limited access. Identifiable data will be deleted/destroyed at the completion of the project
- *The waiver will not adversely affect the rights and welfare of the subjects*: The intervention is entirely comprised of education about appropriate medication use; generally providing additional, potentially actionable information to patients and families is a valuable goal in health care settings.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

All study team members have appropriate training in the protection of human subjects and study team members will strictly follow IRB rules and guidelines and will adhere to data management policies.

13 COMMITTEES

Provide a list of the committees (Steering Committee or Executive Committee, Publication Committee, Adjudication Committee, etc.) and describe their roles.

Safety Officer

Madhuri Reddy, MD, MSc

Geriatric Medicine Specialist, Hebrew SeniorLife

Dr. Reddy is a geriatric medicine specialist who specializes in chronic wound care and technology. She has a fellowship in chronic wound healing and uses evidence-based care to develop methods of prevention and management of pressure ulcers. Dr. Reddy previously served as the Chair of the Institutional Review Board at Hebrew SeniorLife.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee as well as by the IMPACT Collaboratory. Any presentation, abstract, or manuscript will be made available for review by the IMPACT Collaboratory prior to submission.

15 REFERENCES

Provide the citations for all publications and presentations referenced in the text of the protocol.

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16 SUPPLEMENTS/APPENDICES

16.1 Central Nervous System-Active Classes and Medications

Class	AHFS code	Generic names
Antidepressants	28:16.04.20, 28:16.04.16, 28:16.04.28, 28.16.04.92, Trazodone	28:16.04.20: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Vilazodone 28:16.04.16: Desvenlafaxine, Duloxetine, Levomilnacipran, Venlafaxine, Milnacipran 28:16.04.28: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine 28.16.04.92: Bupropion, Mirtazapine Misc: Trazodone
Antiepileptics	28.12.XX.XX except benzodiazepines	28:12.04: Phenobarbital, Primidone, Methohexital 28:12.12: Ethotoin, Fosphenytoin, Phenytoin 28:12.16: Ethadione, Paramethadione, Trimethadione 28:12.20: Ethosuximide, Methsuximide 28:12.92: Brivaracetam, Carbamazepine, Eslicarbazepine, Felbamate, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Magnesium Sulfate, Oxcarbazepine, Perampanel, Pregabalin, Rufinamide, Sultiame, Tiagabine, Topiramate, Valproate/Divalproex/Valproic Acid, Vigabatrin, Zonisamide, Acetazolamide
Antipsychotics	28.16.08.XX	28:16.08.04: Aripiprazole, Asenapine, Brexpiprazole, Cariprazine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Pimavanserin, Quetiapine, Risperidone, Ziprasidone 28:16.08.08: Haloperidol 28:16.08.24: Chlorpromazine, Fluphenazine, Perphenazine, Prochlorperazine, Thioridazine, Trifluoperazine 28:16.08.32: Thiothixene 28:16.08.92: Loxapine, Molindone, Pimozide
Benzodiazepines	28:24.08	Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Estazolam, Flurazepam, Halazepam, Lorazepam, Midazolam, Oxazepam, Prazepam, Quazepam, Temazepam, Triazolam, Clobazam, Clonazepam
Opioids	28:08.08 and 28:08.12	Codeine, Fentanyl, Hydrocodone, Hydromorphone Levorphanol, Meperidine, Methadone, Morphine, Opium, Oxycodone, Oxymorphone, Remifentanil, Sufentanil, Tapentadol, Tramadol, Buprenorphine, Butorphanol, Nalbuphine, Pentazocine, Dihydrocodeine
Z-drugs	Subset of 28:24.92	Eszopiclone, Zaleplon, Zolpidem