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## Reducing Anticholinergic Medication Exposure among Older Adults using Consumer Technology: Protocol for a Randomized Clinical Trial

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### Abstract

**Introduction:** A growing body of scientific evidence points to the potential harmful cognitive effects of anticholinergic medications among older adults. Most interventions designed to promote deprescribing of anticholinergics have directly targeted healthcare professionals and have had mixed results. Consumer-facing technologies may provide a unique benefit by empowering patients and can complement existing clinician-centric efforts.

**Methods:** We initiated a randomized clinical trial to evaluate the effectiveness of a patient-facing mobile application (Brain Safe app) compared to an attention control medication list app in reducing anticholinergic exposure among community-dwelling older adults. Study participants are

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#### Trial Status

The study is currently recruiting participants. At the time of manuscript submission, approximately 125 participants have been enrolled.

Clinical Trial Registration: Registered at [ClinicalTrials.gov](https://clinicaltrials.gov) on October 10, 2019. Identifier number: [NCT04121858](https://clinicaltrials.gov/ct2/show/study/NCT04121858)

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adults aged 60 years and above, currently using at least one prescribed strong anticholinergic, and receiving primary care. The trial plans to enroll a total of 700 participants, randomly allocated in 1:1 proportion to the two study arms. Participants will have the Brain Safe app (intervention arm) or attention control medication list app (control arm) loaded onto a smartphone (study provided or personal device). All participants will be followed for 12 months and will have data collected at baseline, at 6 months, and 12 months by blinded outcome assessors. The primary outcome of the study is anticholinergic exposure measured as total standard daily dose (TSDD) computed from medication prescription electronic records. Secondary outcomes of the study are cognitive function and health-related quality of life.

**Discussion:** A consumer-facing intervention to promote deprescribing of potentially high-risk medications can be part of a multi-pronged approach to reduce inappropriate medication use among older adult patients. Delivering a deprescribing intervention via a mobile app is a novel approach and may hold great promise to accelerate deployment of medication safety initiatives across diverse patient populations.

## Keywords

Polypharmacy; deprescribing; anticholinergics; mHealth; aging; medication safety

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## 1. Introduction

Aging scholars and healthcare professionals treating older adults have long recognized the risk posed by medications with anticholinergic effects.<sup>1</sup> For example, the Beers List<sup>2</sup>, first published in 1991, contained the first explicit list of medications to avoid or use with caution among older adult patients, including medications with anticholinergic effects. Potential harmful effects that have been reported with this class of medications include delirium and confusion<sup>3, 4</sup>, and several studies have associated anticholinergic use with an increased risk of mild cognitive impairment and Alzheimer's disease and related dementias.<sup>3, 5, 6</sup>

Despite accumulating evidence on their potential for harm, anticholinergic medications are consistently prescribed to community-dwelling older adults.<sup>7, 8</sup> Previous studies have reported annual prevalence rates for prescription anticholinergic medications ranging from 20% to over 50% among older adults.<sup>7-12</sup> Given such high burden of use, deprescribing has been proposed as a key strategy to avoid potential harm.<sup>13-16</sup> Deprescribing has been defined as "the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes."<sup>17</sup>

A growing number of aging studies have tested effectiveness of various deprescribing strategies with different rates of success.<sup>18-20</sup> Some studies have focused on the use of healthcare professionals to educate patients or fellow healthcare professionals.<sup>21-23</sup> In one study, a pharmacist-led intervention to educate patients and their physicians led to a 43% discontinuation rate for potentially inappropriate medications at 6 months compared to 12% in the control group.<sup>19</sup> Other studies have examined the impact of deploying electronic clinical decision support (CDS) tools to alert clinicians about potentially inappropriate medications and suggest safer alternatives.<sup>24, 25</sup> For example, a recent multi-country

randomized controlled trial evaluating effectiveness of a CDS resulted in a reduction of 0.42 drugs per patient with no difference in mortality and unplanned hospital admission between the intervention and control groups.<sup>26</sup> Another study utilizing CDS showed no effect on deprescribing of potentially inappropriate medications among older adults.<sup>25</sup> The varying rates of deprescribing across multiple studies may represent the many recognized barriers to deprescribing and clinical considerations in the evaluation of inappropriate medication use among older adults.<sup>27–30</sup>

An additional approach to complement healthcare professional-centric interventions, is to use interventions targeting consumers, who serve important roles as the creators of demand for medications and the ones experiencing the symptoms for which medications are prescribed. These consumer-facing intervention strategies may empower patients by increasing access to data, information, and tools that promote health.<sup>31, 32</sup> Consumer-facing interventions are also aligned with growing calls for involving patients and families in shared decision making, using patient-generated health data during routine care, and repositioning healthcare delivery to be more patient- and family-centered.<sup>33</sup> Furthermore, consumer-facing interventions may benefit patients by supporting their self-management care work, which may remain invisible to or undervalued by healthcare professionals.<sup>34</sup> In the context of deprescribing, consumer-facing intervention is a relatively novel approach. A recent trial, the EMPOWER study<sup>18</sup>, employed a consumer-facing educational intervention using a printed booklet to educate older adults about harm associated with benzodiazepines. The authors reported a discontinuation rate of 27%, compared to 5% in the control group, of benzodiazepines during a 6-month follow-up period.

The D-PRESCRIBE randomized clinical trial, with pharmacists providing educational deprescribing brochures to older adults using certain high-risk medications, resulted in an even greater rate of deprescribing at 6 months (43% in the intervention group compared to 12% in the control group).<sup>19</sup> These findings suggest that consumer-facing interventions may open new and promising avenues to deliver deprescribing interventions, including via digital health tools.

Mobile health (mHealth) apps are part of the rapidly proliferating digital health ecosystem and can be leveraged to deliver consumer-facing deprescribing interventions.<sup>31</sup> Using such tools offers unique advantages over paper-based interventions, including the ability to deliver just-in-time information and adapt interventions based on the real-time input of end users.<sup>35</sup> They are also relatively inexpensive and offer the potential for rapid scalability, allowing health interventions and services to reach a broad group of consumers, including those who may have limited access to formal healthcare services.

Using a user-centered design approach, our team developed and usability tested a consumer-facing app called Brain Safe to empower older adults to learn about anticholinergic risk, examine alternatives, and facilitate deprescribing discussions with their clinicians. Informed by our early findings<sup>36</sup>, the primary aim of the current study is to evaluate effectiveness of the Brain Safe app for reducing anticholinergic medication exposure among older adults.

## 2. Methods

### 2.1. Brain Safe Trial Objectives and Design

This study is a randomized clinical trial evaluating the effectiveness of a consumer-facing intervention, the Brain Safe app, to reduce anticholinergic exposure among older adults, and improve cognitive function and health-related quality of life. The specific aims of the study are as follows:

- **Primary Specific Aim 1.** To test the effect of Brain Safe on anticholinergic exposure at 12 months. We hypothesize that anticholinergic exposure will be lower among older adults randomized to the Brain Safe intervention compared to those randomized to an attention control app at 12 months.
- **Secondary Specific Aim 2.** To test the effect of Brain Safe on: (a) cognitive function and (b) health-related quality of life at 12 months. We hypothesize older adults randomized to Brain Safe will have better (a) cognitive functioning measured by using an objective, performance-based composite, and (b) health-related quality of life, compared to those randomized to an attention control app, at 12 months.
- **Exploratory Specific Aim 3.** To test the effect of Brain Safe on anticholinergic exposure, cognitive function, and health-related quality of life at 6 months. This aim will explore the presence of early effects of Brain Safe at 6 months.

### 2.2. Study Population and Eligibility Criteria

The study population comprises community-dwelling older adults aged 60 years and older, currently taking prescribed anticholinergic medications, managing their own medications, not cognitively impaired, and receiving primary care. Participants will be enrolled into the study using the following eligibility criteria:

#### Inclusion criteria

- i. 1 primary care visit in the past 12 months
- ii. Age ≥ 60 years
- iii. Informed consent and HIPAA authorization for the release of personal health information
- iv. English-speaking
- v. Currently using at least one strong anticholinergic medication with Anticholinergic Cognitive Burden (ACB) score 2 or 3, prescribed (new or refilled) in the prior 12 months (see Appendix for list of target medications)
- vi. Community-dwelling in Central Indiana
- vii. Not cognitively impaired, as confirmed using a six-item screener<sup>37–39</sup> administered by a research staff member
- viii. Not terminally ill, as confirmed by screening by a research staff member

- ix. Not sensory impaired, as confirmed by screening by a research staff member

#### **Exclusion criteria**

- i. Permanent resident of an extended care facility (nursing home); independent or assisted senior care living is allowed if managing own medications
- ii. Diagnosis of Alzheimer's disease or related dementia (ADRD), determined by International Classification of Diseases (ICD)-9/ICD-10 codes or current use of a medication for ADRD
- iii. Diagnosis of schizophrenia, bipolar disorder, or schizoaffective disorder defined by ICD-9/ICD-10 codes
- iv. Involvement in another clinical trial that would prevent or interfere with study objectives
- v. Sensory or other impairment prohibiting the use of a mobile touchscreen device or other study activity

### **2.3. Study Sites and Recruitment Procedures**

The study is based in Central Indiana, in the Midwest United States. Eligible participants are initially drawn from Indiana University (IU) Health primary care clinics. The study team has plans to expand recruitment geographically and to additional primary care clinics if the available pool of eligible candidates does not permit achievement of final enrollment targets.

The recruitment process begins by generating a list of individuals who meet eligibility criteria based on demographic, medication, primary care visit, and diagnostic data obtained directly from an electronic medical records system, associated electronic data warehouse, or a state-wide health information exchange database. Using this list, trained research staff conduct phone-based or in-person screenings to further assess eligibility and willingness for participation in the study. Upon consenting, participants are randomly assigned to either of the study arms (Figure 1).

### **2.4. Ethics review and approval**

All study procedures have been reviewed and received ethical approval from the Institutional Review Board of Indiana University (IRB# 1811254189; Federalwide Assurance Number, FWA00003544). The study has also been registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04121858) (Identifier: [NCT04121858](https://clinicaltrials.gov/ct2/show/study/NCT04121858)).

The study also employs an external Data and Safety Monitoring Board (DSMB) including a senior investigator trained in geriatrics (chair), a biostatistician, a pharmacist, and funding agency representatives. The DSMB approved study initiated on September 15, 2019, and meets approximately every six months to review safety and study progress, and make recommendations to continue or discontinue the trial.

## 2.5. Intervention and Control Arms

**Brain Safe Intervention Arm:** Brain Safe is a consumer-facing technology intervention designed to encourage current or potential older adult users of anticholinergic medications to learn about anticholinergic risks and self-initiate de-prescribing conversations with their treating clinicians. The Brain Safe app forms the core of study intervention (Figure 2). The app was designed and developed by the Brain Health Patient Safety Laboratory of Indiana University and through leadership of a faculty with expertise in user-centered design and medication use safety. The app's usability and feasibility were demonstrated in previously published work.<sup>36</sup>

The Brain Safe app has four key features to support the overall goal of reducing exposure to potentially harmful anticholinergic medications. The first feature includes a medication list function where users can select their medications from a searchable and browsable database. The app also allows users to manually add their medications (including strength and frequency of administration), edit and save entry details, and perform a monthly structured self-administered review of their medication list (Figure 2a). Users are prompted monthly via phone and in-app notifications to complete the medication review.

The second feature, a risk calculator, utilizes user-inputted information on the participant's medications, age, sex, history of stroke, and a weighted ACB indicator to generate a personalized risk score for brain harm (Figure 2b). The risk score is presented to the user via a traditional needle-and-gauge display along with the labels 'no', 'medium', and 'high' risk. By deselecting medications, users can see the resultant changes to their total risk score. Each medication's ACB score is also indicated.

The third feature is a multimedia library containing animated videos of about 3 to 5 minutes in length and short blog articles written for lay readers and accompanied by a short video from a pharmacist (Figure 2c). The animated videos use a storytelling approach to inform and educate users regarding indications, potential risks, and safer alternatives for anticholinergic medications. The blog articles discuss educational aspects of anticholinergic medication use, how to talk to physicians about medication safety, and answers to other frequently asked questions. Users can mark and view "favorite" videos and blog posts.

The app's fourth feature is a conversation starter and shareable report designed to elicit discussion between patients and their clinicians about the potential risks of and possible alternatives to anticholinergic medications. This feature allows users to: 1) navigate their list of anticholinergic medications in real time, select the medications they wish to discuss with clinicians, and view alternatives, and 2) generate and share a PDF report containing their personalized risk score, culprit medications, and a list of alternatives with cross-tapering suggestions for the treating physician (Figure 2d).

**Control Arm:** Participants in the control arm of the trial receive an attention control medication list app called Med Safe. This app, designed by the research team as a "stripped down" version of the intervention Brain Safe app, contains functions to create a medication list and monthly review features from the Brain Safe app as described above. To further resemble the Brain Safe app but without any anticholinergic risk related content, the control

app has similar features for account registration and log-in, access to video and blog content (selected for relative neutrality, e.g., “how to prepare a first-aid kit”), and the ability to turn the medication list into a report of the patient’s medication list that can be shared or printed.

## 2.6. Randomization and Procedures for Intervention and Control Assignment

Consenting participants will be randomized in parallel between intervention (Brain Safe app; n=350) and control (attention control medication list app; n=350) groups in 1:1 proportion. Randomization will be done using a computer-generated scheme that assigns participants to either of the study arms, is approved by the study statistician, and is loaded into REDCap by a data manager. Before randomization, a research staff member performs a baseline assessment as described in 2.7. A dedicated unmasked staff member then randomizes participants and delivers the Brain Safe or attention control app. The app is loaded by unmasked research staff onto a 5-inch smartphone provided by the study or self-installed on the participant’s personal smartphone. Participants who need internet connectivity are provided with an unlimited high-speed data plan for the study duration, purchased through AT&T. The unmasked staff member also provides verbal and written or photo/video instructions on app use, answers questions from participants, and offers synchronous or asynchronous technical support as needed.

Participants will remain enrolled in the study over a period of 12 months, with monthly phone and mail reminders to encourage app utilization and identify needs for technical support.

## 2.7. Outcomes, Instruments, and Procedures for Measurement

**2.7.1. Primary outcome**—The primary study outcome is anticholinergic exposure measured as a total standard daily dose (TSDD) during the 12 months after study enrollment. The TSDD is a measure of cumulative exposure to medications,<sup>3, 6</sup> and will sum exposure from all included anticholinergic medications with standardization of dose to account for multiple classes of anticholinergics. Medication data extracted from prescription records of the electronic medical record will be used to calculate the measure, and includes medication name, strength, quantity, and refills for each prescription. A research data analyst will extract data from prescription records on a regular basis and we will compute exposure during 6- and 12-month lookback windows.

**2.7.2. Secondary outcomes**—Secondary outcomes for the study include cognitive function and health-related quality of life, both measured at baseline, 6, and 12 months following study enrollment.

Cognitive function measures are designed to assess participants’ cognitive performance across three critical domains affected by anticholinergic medication use: 1) information processing speed, 2) memory, and 3) executive cognitive function. During scheduled in-person or telephonic/remote visits, a masked research staff member will administer performance-based measures of cognitive function, with slight variation between remote and in-person tests:

1. Information processing speed: Digit Symbol Modalities Test (remote) or Coding/ Digit-Symbol Substitution (in-person);
2. Memory: Hopkins Verbal Learning Test (remote and in-person);
3. Executive function: Semantic and Phonemic Fluency Tests and Oral Trail Making Test (remote) or Choice Reaction Time Test and Trail Making Test (in-person).

These assessments will take approximately 90 minutes to complete. The average from each measure's z-score will be used to construct a composite cognitive score.

Health-related quality of life will be measured using the 15-item Health Utilities Index (HUI) Mark 3. The HUI is a generic, utility-based self-report instrument applied in patients with a wide range of medical conditions.<sup>40</sup> It has eight attributes: vision; hearing; speech; ambulation; dexterity; emotion; cognitive function; and pain.

**2.7.3. Other measures**—We also plan to collect data on the following: 1) demographic and clinical information; 2) health beliefs and self-initiated deprescribing behavior; and 3) technology usability, acceptance, and use. At baseline, participants will self-report information on their age, race, gender, and education. Using electronic health record data, we will compute a Charlson Comorbidity Index and number of medications for each participant. To assess adverse events, a single-item question will be asked at each follow-up assessment to determine whether participants have experienced any adverse events related to the study in the prior 6 months. Additionally, unscheduled acute care utilization (hospital and emergency department visits) will be collected to be analyzed for potential relatedness to the study.

We anticipate that participants' health beliefs and self-initiated deprescribing behavior are important mediators of the intervention's effect on the study's primary and secondary outcomes. At baseline, 6 months, and 12 months, participants in both study arms will be assessed for 1) threat awareness, using scales for risk susceptibility and risk severity; 2) deprescribing barrier and benefit knowledge, using scales for barriers and benefits to action; and 3) cues to action, using a scale for readiness to act; and 4) behavior, namely whether they self-initiated deprescribing discussion with a clinician.

For participants assigned to the Brain Safe app and attention control apps, we will assess, at 1 month, 6 months, and 12 months, the usability, acceptance, and use of the mobile app technology. We will assess usability using the simplified System Usability Scale (SUS), which is a validated 10-item instrument<sup>41</sup> modified for ease of administration for older adults.<sup>42</sup> Technology acceptance will be assessed as the mean score on a 3-item satisfaction scale.<sup>43, 44</sup> App use will be captured for both apps using in-app tracking, time-stamping, and reporting of key activities including: log-ins; medications added, removed, or modified; medication review initiation and completion; access and favoriting of videos and articles; and doctor's reports generated.

## 2.8. Sample size and rationale

Sample size is determined to ensure adequate power to test the effect of the Brain Safe app intervention on anticholinergic exposure at 12 months, measured in TSDD. Preliminary data from a previous study show that the mean daily TSDD among those using at least one strong prescription anticholinergic is 0.8 with a standard deviation of 1.7. We hypothesized that the Brain Safe app intervention will result in at least 50% reduction in the mean TSDD. To detect a 50% reduction in this mean with 80% power, using a two-sided t test at 0.05 significance level, 283 participants are needed for each treatment arm. Accounting for approximately 20% attrition, we will require approximately 350 participants enrolled per treatment arm, or 700 in total.

Although sample size determination is not done to detect a change in the secondary outcome of cognitive function, we anticipate having sufficient power to detect changes in this secondary outcome if it changes significantly during the 12-month follow-up period. With 283 subjects per group (after accounting for attrition), we will have 95% power to detect an effect size of 0.3 standard deviations in the composite cognition measure.

## 2.9. Planned Analysis

Descriptive analyses will be performed to examine participants' demographic and clinical characteristics across the two study arms (e.g, age, sex, co-morbidity index, number of medications). Doing this will also allow us to assess if the random allocation of participants was effective and key confounders are balanced across the two study arms.

The primary analysis will be focused on the TSDD, which is obtained by summing TSDD from all ACB Score 2 and Score 3 anticholinergic medications supplied by medication orders and dividing by the number of days in this period. We plan to compare TSDD from the medication orders over the 12-month trial period between the two groups using a two-tailed t-test. All analyses will be carried out in an intention-to-treat framework. For a randomized trial with moderate sample size, there is a possibility that there are imbalances in patient characteristics between the treatment groups, and that unbalanced patient-level factors such as sex, baseline health beliefs, comorbidity, or total number of medications may confound with the treatment effect. If the imbalance is of high magnitude and systematic, we will perform regression analyses by including the unbalanced characteristics as covariates. We will also perform a repeated measure analysis in a mixed effect model framework to adjust for correlations between anticholinergic exposure at 6 and 12 months; baseline levels of exposure will be included as a covariate. Early dropout and intermittent missing data can be easily handled in this analytical framework. Analysis will be implemented using either SAS or R software. P values less than 0.05 are considered statistically significant.

Our secondary analyses will focus on cognitive function and health-related quality of life (HRQOL). We will use t-tests to directly compare the cognitive function and HRQOL outcomes at 12 months. We anticipate that these outcomes are likely to be strongly influenced by the cognitive function and HRQOL measures at baseline. Therefore, we will carry out the analyses in a mixed effect model framework and adjust for patient-specific baseline cognitive function and HRQOL levels.

### 3. Discussion

A limited number of trials have previously demonstrated the benefits of a consumer-facing intervention in promoting deprescribing of potentially harmful medications among older adults. One landmark trial, the EMPOWER study<sup>18</sup>, used a paper-based informational booklet to empower older adults to initiate discontinuation of unsafe benzodiazepine medications. The researchers showed that the intervention increased instances of patients discussing discontinuation or dose reduction of benzodiazepines with their physicians and/or pharmacists. Our study leverages consumer-facing interventions but takes advantage of a mHealth tool (Brain Safe app) to empower and activate older adults so they can initiate deprescribing related discussions with and receive support from clinicians.

The Brain Safe app was developed through a user-centered design approach incorporating accepted design recommendations for older adults. It was also evaluated for usability and feasibility with older adults using similar recruitment criteria as in this trial.<sup>36</sup> Use of the Brain Safe app has unique advantages over a paper-based tool for several reasons. First, the app can integrate information from multiple sources, including user provided information, and generate a personalized risk score and recommendations. This can increase the likelihood of acceptance by patients as information is delivered in a context-sensitive manner as opposed to generic guidance that may contain information not applicable to a person's specific situation. The app also has the advantage of delivering multi-modal, just-in-time information (e.g., video, text) making it a media rich tool that may increase likelihood of acceptance. These features of the app make it an ideal tool for scaling up the future to reach a much broader audience and with minimal cost compared to resource-intensive strategies, such as those involving clinician-centric interventions.

Like the EMPOWER trial<sup>18</sup>, patients in our study initiate conversations on deprescribing of anticholinergics. The Brain Safe app will facilitate this by providing a personalized risk score and the conversation starter to enhance shared decision making with their treating clinicians. Although clinicians are not obligated to heed the recommendations, we believe the conversation starter provides a non-threatening yet powerful opportunity for patients to bring up the issue with their clinician.

### Acknowledgements

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### APPENDIX

Target anticholinergic medications. Note: These include several common brand names to supplement generic products when screening patient medical records.

Amantadine, Symetrel, Belladonna, Tegretol, Flexeril, Periactin, Loxitane, Demerol, Levoprome, Moban, Nefogestic, Trileptal, Orap, Carbamazepine, Cyclobenzaprine, Cyproheptadine, loxapine, Meperidine, Methotrimeprazine, Molindone, Nefopam, Oxcarbazepine, Pimozide, Amitriptyline, Amoxapine, Atropine, Benztropine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine,

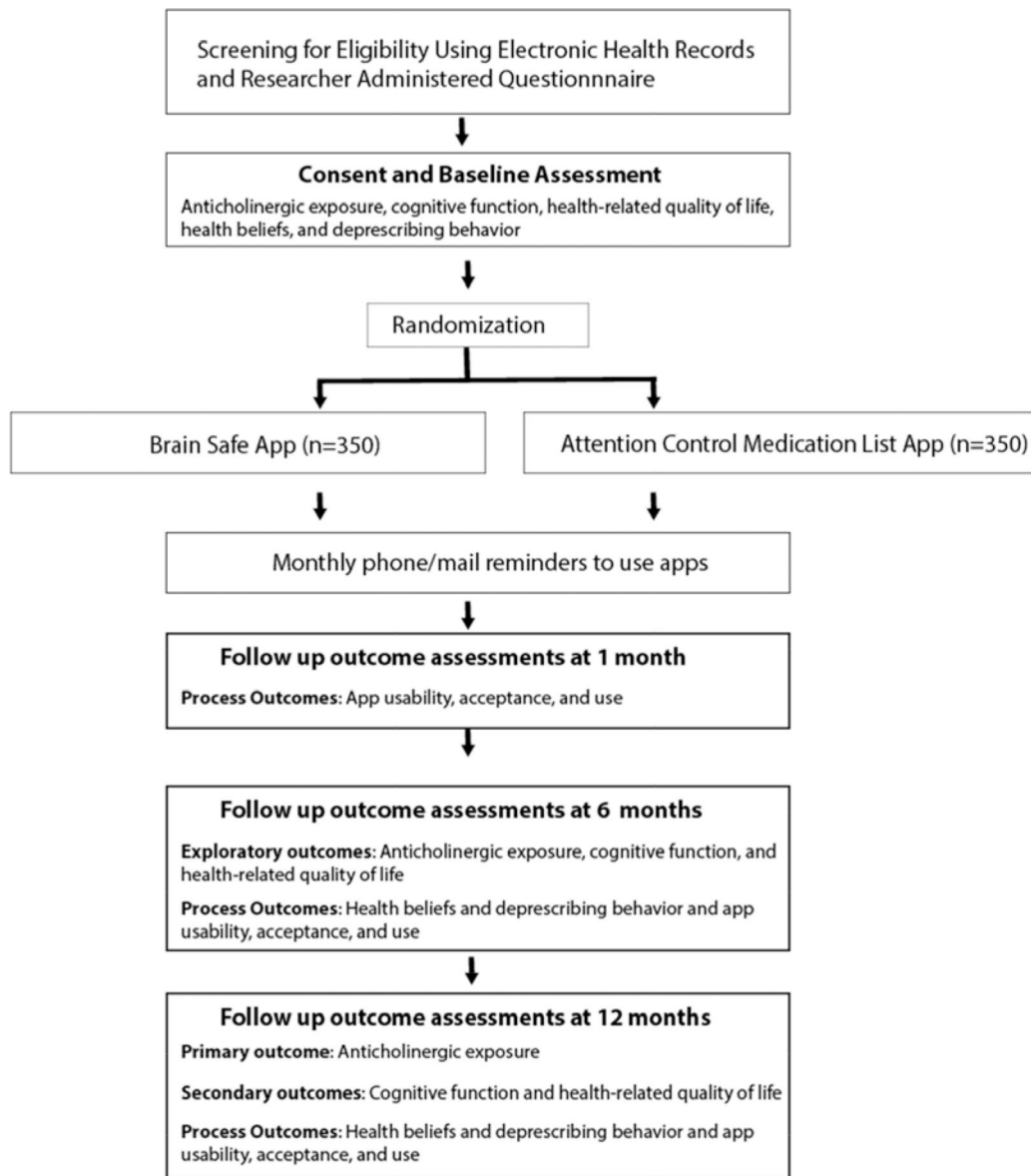
Clomipramine, Clozapine, Clozapine, Darifenacin, Desipramine, Dicyclomine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, fesoterodine, Fesoterodine, Flavoxate, Hydroxyzine, Hyoscyamine, Imipramine, Meclizine, Methocarbamol, Nortriptyline, Olanzapine, Orphenadrine, Oxybutynin, Paroxetine, Perphenazine, Promethazine, Propantheline, Propiverine, Quetiapine, Scopolamine, Solifenacin, Thioridazine, Tolterodine, Trifluoperazine, Trihexyphenidyl, Trimipramine, Trospium, Elavil, Asendin, Sal-tropine, Cogentin, Dimetapp, Histex, Carbihist, Chlor- rimeton, Thorazine, Tavist, Anafranil, Clozaril, enablex, Norpramin, Bentyl, Dramamine, Benadryl, Sinequan, Unisom, Toviaz, Urispas, Atarax, Vistaril, Anaspaz, Levsin, Tofranil, Antivert, Robaxin, Pamelor, Zyprexa, Norflex, Ditropan, Paxil, Trilafon, Phenergan, Pro-banthine, Detrunorm, Seroquel, Transderm cop, Vesicare, Mellaril, Stelazine, Artane, Surmonti, and Sanctura.

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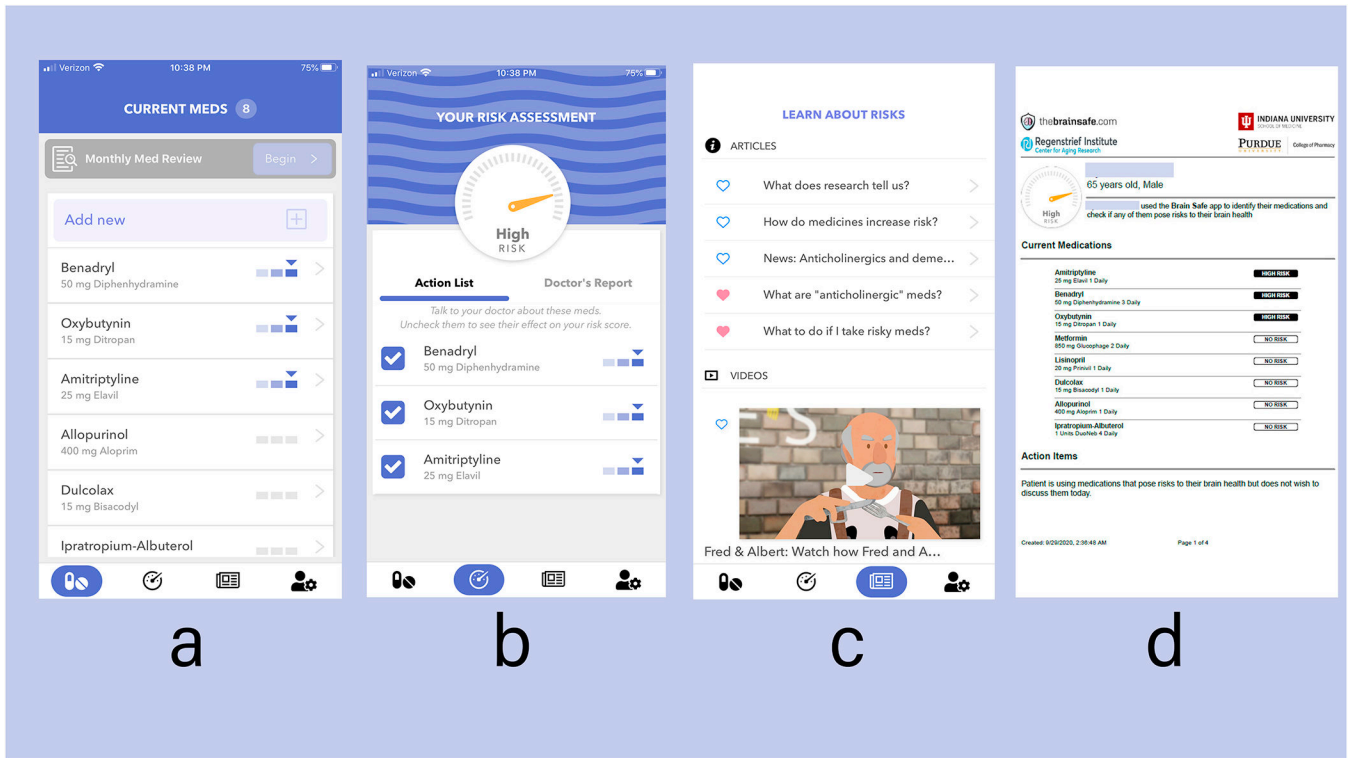
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**Figure 1:**  
Study Flowchart



**Figure 2:**  
Brain Safe app select static screen captures

**Table 1:**

Overview of data collection and measurements

Measure/Assessment	Baseline (T0)	1 Month (T1)	6 months (T2)	12 months (T3)
Demographic characteristics	X			
TSDD			X	X
Cognitive function measures	X		X	X
HRQOL (HUI Mark 3)	X		X	X
Health beliefs and self-initiated deprescribing behavior	X		X	X
Technology usability, acceptance, and use		X	X	X

TSDD: Total Standard Daily Dose; HRQOL: Health-Related Quality of Life; HUI: Health Utilities Index.