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Original Research

Intervention for Cognitive Reserve Enhancement in Delaying the Onset of Alzheimer's Symptomatic Expression (INCREASE) Study: Results from a Randomized Controlled Study of Medication Therapy Management Targeting a Delay in Prodromal Dementia Symptom Progression

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Abstract

BACKGROUND: Cognitive reserve has been hypothesized as a mechanism to explain differences in individual risk for symptomatic expression of Alzheimer's Disease (AD). Inappropriate medications may diminish cognitive reserve, precipitating the transition from preclinical AD (pAD) to a symptomatic state. To date, there is limited data on the potential impact of medication optimization as a potential tool for slowing the symptomatic expression of AD.

OBJECTIVES: (1) To test the efficacy of a medication therapy management intervention designed to bolster cognitive reserve in community-dwelling older adults without dementia. (2) To evaluate the efficacy of intervention by baseline pAD status.

DESIGN: A 1-year randomized controlled trial was conducted in community-dwelling older adults without dementia. Randomization was stratified by amyloid β positron emission tomography levels.

SETTING: Community-based, Lexington, Kentucky.

PARTICIPANTS: Adults 65 years or older with no evidence of dementia and reporting at least one potentially inappropriate medication as listed in the Beers 2015 criteria were recruited. The study aimed to enroll 90 participants based on the a priori sample size calculation.

INTERVENTION: Medication therapy management versus standard of care.

MEASUREMENTS: Primary outcomes were: (1) one-year changes in the Medication Appropriateness Index; (2) one-year changes in Trail Making Test B under scopolamine challenge.

RESULTS: The medication therapy management intervention resulted in significant improvement in Medication Appropriateness Index scores. Overall, there was no beneficial effect of the medication therapy management on Trail Making Test B scores, however stratified analysis demonstrated improvement in Trail Making Test B challenged scores associated with the medication therapy management for those with elevated amyloid β positron emission tomography levels consistent with pAD.

CONCLUSIONS: Medication therapy management can reduce inappropriate medication use in older adults at risk for AD. Our study indicated beneficial cognitive effects in those with preclinical Alzheimer's Disease. No statistically significant effects were evident in the study group as a whole, or in those without preclinical cerebral amyloidosis. Further work designed to improve the effectiveness of the medication therapy management approach and defining other preclinical pathologic states that may benefit from medication optimization are readily achievable goals for promoting improved cognitive health and potentially delaying the onset of symptomatic AD.

Key words: Medication therapy management, cognitive reserve, randomized controlled trial, Beers criteria, deprescribing.

Introduction

It is estimated that about 40% of the risk for Alzheimer's Disease and Related Dementias (ADRD) may be due to modifiable, lifestyle-based, and medical risk factors (1). The biological disease course of AD includes a 10–20-year preclinical period (pAD) during which time amyloid plaques and neurofibrillary tangles accumulate in the brain leading to neuronal injury and loss without apparent cognitive or functional decline (2, 3). The time of onset for the clinical signs and symptoms may be dependent on the balance of the underlying pathologic burden and compensatory mechanisms, collectively referred to as cognitive reserve (CR) (4).

While hypothesized modifiable risk factors are numerous, one that been less explored from an intervention standpoint are medications (5-9). Specifically, those medications shown to increase the risk of ADRD diagnosis, perhaps by compromising CR mechanisms, should be targeted for treatment optimization (7, 8). Age-related changes that increase susceptibility to adverse effects of medications include the decrease in renal and

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Figure 1. Study Procedures and Timeline

		STUDY PERIOD								
		Enrolment	Pre-randomization	Randomization	Follow-up					End of Study
	TIMEPOINT (week)	$-t_2$ -5 ± 2	$-t_1$ -4 ± 1	0	t_1 0 ± 1	t_2* 13 ± 1	t_3 26 ± 1	t_4* 39 ± 1	t_5 52 ± 1	t_6 56 ± 1
Enrollment	Eligibility screen	X								
	Informed consent	X								
	Demographics	X								
Health information	*Health History*	X	X		X	X	X	X	X	X
	ECG	X								
	Physical Exam	X								X
	Neurological exam	X								X
	Gait and balance	X	X				X		X	X
SF-36		X								X
Medication Review		X	X		X	X	X	X	X	X
Randomization	*Aβ-PET imaging*		X							
	Random Allocation			X						
Intervention	*MTM Intervention*				X		X		X	
	Educational materials	X								
Cognitive testing	Scopolamine challenge		X						X	
	Non-challenged				X					X

*follow-up visits conducted via telephone; ECG= electrocardiogram; Aβ-PET= amyloid beta positron emission tomography; Screening and baseline testing were completed prior to randomization and intervention. Challenged testing always preceded unchallenged testing by 4 weeks to limit learning effects that would be maximized in an unchallenged state. The intervention was reinforced at 3-month intervals over the one-year study period.

hepatic function affecting drug metabolism and clearance, the increased permeability of the blood-brain barrier, and the increase in the brain's sensitivity to drugs (5, 6, 8, 10, 11).

Inappropriate medication use in the aging population often leads to polypharmacy and prescribing cascades that result in drug interactions and adverse drug effects (5, 6, 8, 10, 11). This suggests that inappropriate medications, alone or in combination, might compromise CR, thus leading to an earlier clinical expression of cognitive and functional impairment (i.e., core clinical features of overt ADRD) (4-7, 9, 10, 12, 13). Older adults at risk for such complications, and who have biomarker evidence for pAD—defined as elevated brain amyloid beta positron emission tomography (Aβ-PET) standardized uptake value ratios (SUVr)—CR may be even more vulnerable (2, 14-17).

The present study was a proof of concept, phase IIa-style, randomized controlled trial (RCT) of a multidisciplinary medication therapy management intervention targeting potentially inappropriate medication use in older adults without dementia. We designed the study to test the following hypotheses: (1) the intervention targeting potentially inappropriate medication will optimize medication treatment regimens in older adults without dementia; (2) optimizing medication treatment regimens will augment CR; and (3) the impact of medication optimization on CR will be different based on baseline pAD status (i.e., SUVr ≥ 1.4 vs SUVr < 1.4). We saw the testing of these hypotheses as necessary first steps in investigating the potential for medication optimization to prolong the asymptomatic pAD phase and delay the onset of clinical signs and symptoms of ADRD in this at-risk population. In this manuscript we report results related to the primary outcomes in the INCREASE study.

Methods

Study design

We conducted a one-year, 1:1 RCT to test the effects of using comprehensive medication reviews and medication therapy management for the optimization of medication appropriateness in older adults without dementia (N=90). Following the baseline assessment, participants were randomized to the intervention or the standard of care group (see the "Randomization" section below for details).

The study was approved by the University of Kentucky Institutional Review Board (IRB) and monitored by an expert independent Data Safety and Monitoring Board (DSMB) consisting of a geriatrician, a pharmacist board certified in geriatrics, and a trial statistician, as well as representatives from the National Institute on Aging. This study was registered on https://clinicaltrials.gov NCT02849639. Figure 1 above provides a schematic of study design and conduct. Additional details on the INCREASE study design and the protocol design used in conducting the study have been published previously (18).

Participant characteristics

Volunteers were recruited from the Lexington, Kentucky area and met the following eligibility criteria: (1) age 65 years or older; (2) no evidence of dementia; (3) reporting at least one potentially inappropriate medication as listed in the Beers 2015 criteria; (4) living in the community; (5) medically stable and able to complete all study activities, as determined by the investigators; (6) able to identify a study partner to drive the participant to and from the scopolamine-challenged visits; (7) willing to participate in this intervention study. Exclusion criteria included: (1) previous reaction or contraindication to scopolamine patch, or medical condition warranting dose adjustment in scopolamine, including but not limited to: open angle glaucoma, gastrointestinal or urinary outlet obstructions, seizures, or psychosis; (2) contraindications to Aβ-PET scan including hypersensitivity to PET ligand (florbetapir) or radiation exposure in the past year that would exceed acceptable safe annual exposure in combination with the Aβ-PET.

Randomization

Randomization occurred following the baseline assessment under challenged conditions and prior to the intervention. While we hypothesized that the impact of medication optimization on CR will be different based on baseline pAD status (i.e., SUVr ≥ 1.4 vs SUVr < 1.4), for randomization we chose to further stratify SUVr < 1.4 at SUVr = 1.2 to promote balance between the treatment groups at baseline with regard to amyloid burden. (2,14,17,19,20) No hypotheses were associated with this stratification scheme and the two sub-strata (i.e., SUVr < 1.2 and 1.2 ≤ SUVr < 1.4) were not further considered in the analysis. Within SUVr strata, participants were randomized to the intervention or standard of care with equal probability.

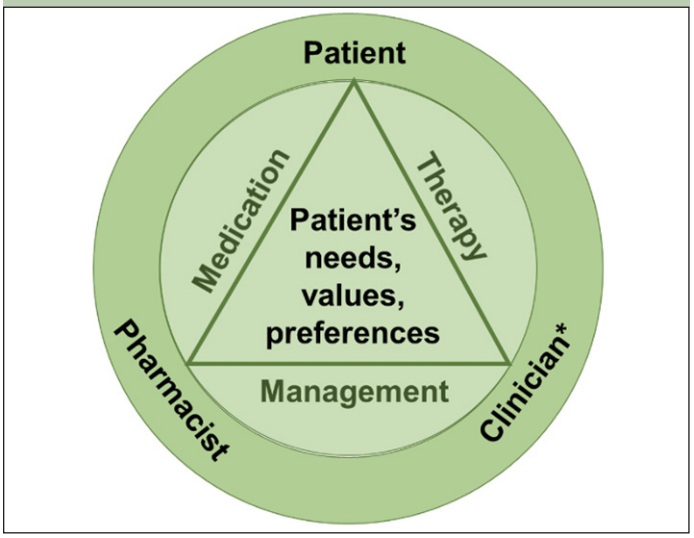
Blinding

Due to the nature of the intervention, blinding was not possible. However, to minimize the effect of the open-label design, medication review at baseline was conducted for all study participants prior to group allocation through randomization, and data analysis was blinded to the intervention.

Study Intervention: For participants randomized to the intervention, our approach focused on optimizing the individualized risk-benefit balance through a team intervention that actively involved the patient as previously described (8, 18) (Figure 2).

Demographic and health history data, as well as detailed information on every medication used by the participant, including prescription or over-the-counter medications, vitamins, and supplements were collected during screening and baseline visits. Based on the data available, the study pharmacists provided preliminary prioritized written recommendations with proposed actions for each medication taken by the participant: discontinuation, treatment modification (switch to a safer alternative or dose change), or treatment continuation when medically necessary and appropriate.

Figure 2. INCREASE Study Intervention Guiding Principles



*Physician or Advanced Practice Provider; Optimal medication therapy management requires an interdisciplinary approach partnering the patient with a physician and pharmacist team that takes into consideration and values patient needs and preferences.

During the intervention, the participant discussed the proposed changes with the pharmacist and the study clinician, and the plan was finalized, centered around the patient's needs, values, and preferences. The intervention was delivered at baseline to those randomized to the active study arm and was reinforced at 3-month intervals throughout the one-year study intervention phase (Figure 1).

All study participants, including those randomized to the control group, received educational materials on medication appropriateness and risks of polypharmacy including "Avoiding overmedication and harmful drug reactions" (www.HealthinAging.org), "Ten medications older adults should avoid or use with caution" (www.HealthinAging.org), and "Be an active member of your health care team" (https://www.fda.gov/drugs/resources-you/be-active-member-your-health-careteam-article). No active intervention was pursued by the study team to optimize medicines used in the control group, but participants and other healthcare providers were not restricted in modifying medications on the basis of this information or other changing health conditions and needs throughout the duration of the study.

Primary outcomes included measures of (1) medication appropriateness (Medication Appropriateness Index [MAI])21 and (2) CR operationalized using Trail Making Test B (TMTB) (22) under scopolamine-challenged and unchallenged conditions. We selected MAI and CR-TMTB as primary outcomes based on previously published work on inappropriate medication use and executive cognitive

function in older adults (10) and measured the 1-year change from baseline to the end of study (EOS).

(1) MAI rates medications as "appropriate", "marginally appropriate", or "inappropriate" based on ten criteria, with medications deemed inappropriate resulting in higher scores as measured by MAI (23). All medications reported by study participants at baseline and follow-up visits were evaluated by the study team and assigned a medication-specific MAI. As an outcome measure, the total MAI was obtained by adding the medication specific MAIs for all medications reported by the participant.

(2) TMTB was used to measure executive function and calculate CR. Specifically, CR was operationalized using sequential cognitive testing under scopolamine challenge, followed after four weeks by unchallenged cognitive testing at baseline and EOS visits (18, 24). Scopolamine patches (0.4mg) were applied at least 12 hours before challenged visits, and not removed until after the visit was complete to ensure stable blood levels of scopolamine during critical study conduct operations.

Protocol Changes related to the COVID-19 Pandemic

In March 2020, several changes to the protocol were implemented in response to the COVID-19 pandemic. In a first phase, in-person university-wide non-essential research activities for non-drug interventional studies were suspended with restart planned in a phased manner. During this transition we modified the protocol to allow for remote data collection while maintaining the study windows for each visit. For instance, medication optimization interventions and active data collection on adverse events were switched from in-person to remote using Zoom or telephone, based on each participant's preference and ability. For evaluations for which remote modalities were not feasible (e.g., cognitive testing, including those under scopolamine challenge), we extended the follow-up until in-person visits could resume. When in-person visits were resumed, COVID-19 screening of symptoms was implemented, along with social distancing, masks, and the use of PPE and plexi-glass barriers between the tester and the participant during cognitive testing. Furthermore, we shortened the visit duration to reduce in-person contact with study staff by collecting information that only required reporting rather than active study procedures beforehand over the telephone or televideo wherever possible. We also implemented COVID-19 testing for all staff and participants before entering the clinic with the goal of keeping the clinic a zero COVID zone.

Sample size

The study aimed to enroll 90 participants based on the a priori sample size calculation and accounting for potential losses to follow up based on data derived from prior studies of medication management (12, 21, 25). For MAI, 17 participants in each group were needed to detect a clinically relevant mean difference of 1.0 between baseline and follow-up assessments for the intervention group vs no change in the control group with 80% power at a significance level (α) of 0.05 (18). For TMTB, we planned to compute age- and education-adjusted TMTB z-scores based on normative data for cognitively intact older adults (22). We assumed that the scopolamine challenge would induce deficits in cognitively intact older adults at least at the levels reported in younger adults, and we determined that 32 participants per group would allow us to detect a 0.50 SD improvement in the CR change z-score with 80% power at α =0.05, and 14 per group to detect a 0.75 SD improvement with 80% power in participants with pAD (i.e., SUVr > 1.4).

Data Analysis

Medication appropriateness

We performed analysis of covariance (ANCOVA), with the dependent variables being the outcome measure (i.e., MAI) at the EOS, and the baseline measurement included as a covariate. In addition, we estimated the treatment effects controlling for pre-specified covariates age, sex, education, number of medications reported at baseline, and number of Beers medications reported at baseline. We included SUVr group (≤ 1.4, > 1.4) as a covariate to estimate overall treatment effects, and in separate analyses stratification on SUVr was incorporated into the analysis with a treatment group*SUVr group (≤ 1.4, > 1.4) cross-product term along with main effects.

Cognitive reserve

To evaluate the effect of the medication optimization intervention on CR, the planned analysis was based on the hypothesis that participants would perform the same or worse when tested under the scopolamine challenge; CR would be defined as the difference in TMTB score between the challenged and unchallenged conditions, with the analysis evaluating the difference in CR between baseline and EOS. However, about one-third of participants (non-differentially distributed across treatment groups, SUVr strata, and baseline vs. EOS TMTB scores) demonstrated better scores in the scopolamine challenged testing visit than they exhibited in the unchallenged state 4 weeks later. An explanation for this remains speculative. Because the goal of the intervention was to minimize the difference between challenged and unchallenged TMTB scores observed at study baseline, the unexpected, better performance under the challenged conditions meant that the difference in

scores (our measure of CR) could be minimized either by an increase in the challenged score if the challenged score was worse, or a decrease in challenged score if the challenged score was better. Thus, it was not possible to interpret the planned analyses. To address this problem, we restricted these analyses to the data obtained under the challenged conditions at baseline and EOS and did not use the unchallenged data. Using ANCOVA, we set the challenged TMTB z-score at EOS as the dependent variable and included the challenged TMTB z-score at baseline as a covariate. The mean and standard used to compute the TMTB z-scores were taken from a sample of cognitively intact older adult research volunteers (Weintraub et al. 2009; mean = 90.3, SD = 50) (22). Z-scores were then multiplied by -1 to facilitate interpretation, since higher TMTB scores are worse. We also included pre-specified covariates age, sex, education, baseline MAI, and baseline North American Adult Reading Test (NAART) score.

We included SUVr group (≤ 1.4, > 1.4) as a covariate to estimate overall treatment effects, and in separate analyses stratification on SUVr was incorporated into the analysis with a treatment group*SUVr group (≤ 1.4, > 1.4) cross-product term along with main effects.

Safety outcomes

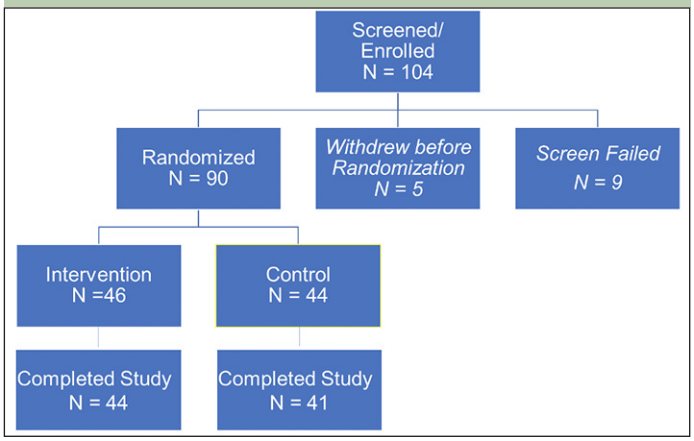
Safety outcomes were reported by randomization group, including severity and investigator evaluation of relatedness to study procedures and interventions.

Results

Consort diagram

Recruitment, randomization, and study engagement for participants is shown in the CONSORT diagram in Figure 3.

Figure 3. INCREASE Flow Diagram



Study conduct

Of the 90 participants randomized, five did not complete the study (N=2 died, and N=3 withdrew after randomization for other reasons). As described above, due to the COVID-19 pandemic, the EOS visits were modified to maximize the safety of our participants. Specifically, six participants (N=3 in the MTM group and N=3 in the control group) had the EOS cognitive testing delayed (2 - 87 days range). In addition, three participants (N=2 in the MTM group and N=1 in the control group) did not wear the scopolamine patch due to experiencing moderate nausea and dizziness during the baseline evaluation and were not tested under challenged conditions at the end of the study, therefore were excluded from the analysis of cognitive outcomes. As a result, 85 (94.44%) participants were included in the analysis related to the impact of the intervention on MAI, and 82 (91.11%) in the analysis of cognitive outcomes. All study participants were included in the descriptive evaluation of safety outcomes.

Study participants

Our participants' age ranged between 65 and 93 years, with a median age of 73.5 years. Our sample included 57 (63.33%) women and 10 (11.11%) underrepresented minority participants, with about one-third of the sample in the pAD category as indicated by a SUVr value ≥1.4. Table 1 includes more detailed information on study participants at baseline.

Safety outcomes

During the study, N=248 total adverse events (AE) were reported, of which N=17 (6.9%) were serious [SAE] (N=2 deaths, N=11 hospitalizations, N=2 injurious falls, N=1 car accident, and N=1 emergency room visit without hospitalization). None of the SAEs were related to study participation. Of the total reported AEs, N=103 (41.53%) were determined to be possibly (N=2), probably (N=15), or definitely (N=86) related to the administration of scopolamine (n=97), the PET scan (n=2), or to changes in medication due to MTM (n=3). AEs related to scopolamine included mild dizziness (N=33), dry mouth (N=39), headache (N=2), and temporary slowing of cognition (N=23). AEs related to changes in medication were mild and resolved with further medication adjustment. AEs related to the PET scan (headache, nausea) were mild and resolved without treatment. Aside from the ones caused by changes in medication due to the MTM interventions, there was no evidence of higher risk of AE in the intervention group. The DSMB monitoring the study concluded that the study procedures did not pose any significant safety risks to the participants in the study cohort.

Primary Outcome Measures

When evaluating the impact of the medication optimization intervention in reducing inappropriate medication use, those randomized to the intervention

Table 1. Baseline demographic, clinical and biomarker variables

Characteristic at enrollment		INCREASE (N=90)	Control (n=44)	Intervention (n=46)
Age	Mean (SD)	73.9 (6.0)	74.1 (6.6)	73.4 (5.6)
	Median (Min-Max)	73.5 (65-93)	73 (69-93)	72 (65-87)
Sex	Female, N (%)	57 (63.33)	23 (52.27)	34 (73.91)
Ethnicity	Not Hispanic or Latino, N (%)	90 (100)	44 (100)	46 (100)
Race	American Indian/Alaskan Native, N(%)	0 (0)	0 (0)	0 (0)
	Asian, N (%)	2 (2.22)	2 (4.54)	0 (0)
	Black/African American (%)	8 (8.89)	2 (4.54)	6 (13.04)
	Native Hawaiian or Other Pacific Islander, N (%)	0 (0)	0 (0)	0 (0)
	White, N (%)	80 (88.89)	40 (90.92)	40 (86.96)
Years of education	Mean (SD)	16.5 (2.8)	16.4 (2.6)	16.5 (3.0)
NAART	Mean (SD)	41.4 (11.5)	39.2 (12.4)	43.4 (10.2)
SUVr	≥1.4, N (%)	29 (32.22)	14 (31.81)	15 (32.61)
Total medications	Mean (SD)	12.8 (4.8)	12.9 (4.8)	12.7 (5.0)
Beers' list medications	Mean (SD)	2.4 (1.2)	2.2 (1.2)	2.5 (1.2)
MAI	Mean (SD)	12.1 (8.5)	10.6 (7.4)	13.5 (9.4)
TMTB (in seconds)	Mean (SD)	104.7 (57.5)	101.8 (60.9)	107.4 (54.7)
TMTB z-score	Mean (SD)	-0.29 (1.1)	-0.23 (1.2)	-0.34 (1.1)

*NAART: North American Adult Reading Test; SUVr: Standardized Uptake Value ratios; MAI: Medication Appropriateness Index; TMTB: Trail Making Test B

experienced a statistically significant and clinically relevant improvement in medication appropriateness. However, for the primary cognitive outcome, the results were not statistically significant when comparing the two study groups. (Table 2, top section)

Primary Outcomes Stratified by Aβ-PET SUVr

To evaluate the impact of preclinical amyloid burden on the study outcomes, a stratified analysis was conducted that indicated a significant effect on medication appropriateness and TMTB in those in the preclinical AD state with an SUVr ≥ 1.4 (Table 2, bottom section).

Discussion

These data demonstrate that targeted medication therapy management is both safe and effective in reducing inappropriate medication use in the older adults at risk for AD beyond that achieved pragmatically in routine clinical practice (5-9, 18, 26, 27). Despite myriad redundant systems built into modern day electronic health monitoring systems that engage the provider, the pharmacist, and the patient, as well as an increasing awareness of the broad spectrum of potential adverse side effects and drug interactions, a large percentage of the older adult population remain at risk for polypharmacy and inappropriate medication use (5-7, 9, 26, 27). While the present study used a targeted recruitment design to identify such individuals, it was not difficult to reach our recruitment goals. Participants in our current study required only a single questionable medication to meet enrollment criteria and yet, on average, an INCREASE participant was taking 12 medications, with approximately 2 to 3 inappropriate medications at enrollment despite increasing awareness of issues related to polypharmacy and inappropriate medication use (5-7, 9, 26, 27). These data are not significantly different from those derived from the general population of older adults in the US that are subject to polypharmacy and inappropriate medication use (5-7, 9, 26, 27).

The Beers' Criteria list of medications that should be avoided or used with caution in the older adults has provided a framework for assessing polypharmacy and inappropriate medication use in this population (11, 27, 28). This list has been popularized by health care providers with substantive older adult patients and has been updated regularly to reflective a changing pharmacopeia and treatment options for the aging population that are most in need of medical treatment for both acute as well as a chronic healthcare conditions. (11, 27, 28). Despite advances in our knowledge and awareness of such problems, the Beers' Criteria list has accomplished little in regards to stemming the tide of polypharmacy and inappropriate medication use in the aging population today (5, 26). While many clinical intervention programs have been designed to provide oversight and protections against polypharmacy and medication inappropriateness, patient specific interventional programs are few and far between and have not been proven to be superior to standard of care in successfully employed gold-standard, randomized, control interventional trials (5, 8, 26, 29, 31). The present study represents one of the first high-quality studies supporting an individualized MTM approach to optimize medications in the aging population (18).

Despite the statistically significant reduction in MAI because of the MTM demonstrated in this study,

Table 2. Primary outcome measures including change in Medication Appropriateness Index (MAI), and the change in Trail Making Test B under challenged conditions (raw and z-scores) as described above in the methods section

Primary Outcomes Measures					
Outcome (mean ± sem)		**End of Study**		**Mean difference**	**p-value tx effect**
		Control	**Intervention**		
MAI[1]		11.2±0.6	9.4±0.6	1.80±0.82	0.029
TMTB challenged conditions[2]		95.2±7.0	88.6±7.3	-6.6±10.0	0.51
TMTB z-score challenged conditions[3]		-0.10±0.14	0.03±0.14	0.13±0.20	0.51
Primary Outcomes Measures: Stratified analyses*					
Outcome (mean ± sem)	**SUVr**	**End of Study**		**Mean difference**	**p-value tx effect**
		Control	**Intervention**		
MAI[1a]	≥ 1.4	11.99±1.08	9.14±1.01	2.86±1.49	0.05
	< 1.4	10.74±0.68	9.40±0.72	1.34±0.98	0.17
TMTB challenged conditions[2a]	≥ 1.4	106.9±9.8	74.4±9.2	-31.5±13.5	0.02
	< 1.4	92.7±5.9	87.4±6.3	-5.3±8.6	0.54
TMTB z-score challenged conditions[3a]	≥ 1.4	-0.64±0.27	0.23±0.25	-0.87±0.37	0.017
	< 1.4	0.11±0.16	-0.07±0.17	-0.18±0.23	0.45

(Top section). Aβ-PET SUVr <1.4 vs. ≥ 1.4 stratified analyses. (Bottom section) ; 1. model adjusted for age, sex, education, baseline MAI, # baseline meds, # baseline Beers meds, SUVr≥1.4; 2 .model adjusted for age, sex, education, baseline challenged TMTB, NAART, baseline MAI, SUVr≥1.4; 3. model adjusted for age, sex, education, baseline challenged TMTB z-score, NAART, baseline MAI, SUVr≥1.4; *All models include amyloid*tx interaction term and main effects; 1a. model adjusted for age, sex, education, baseline MAI, # baseline meds, # baseline Beers meds; 2a .model adjusted for age, sex, education, NAART, baseline challenged TMTB, baseline MAI; 3a. model adjusted for age, sex, education, NAART, baseline challenged TMTB z-score, baseline MAI; sem: standard error of the mean; MAI: Medication Appropriateness Index; TMTB: trail making test B; NAART: North American Adult Reading Test; Aβ-PET: amyloid beta positron emission tomography; SUVr: standardized uptake value ratios

it is noteworthy that we could not reduce the MAI to zero. There are many reasons why even targeted MTM programs may fall short of their ultimate goals to eliminate all potentially inappropriate medications that deserve discussion (8, 29, 30). These include often limited therapeutic alternatives for some symptomatic disease states, as well as reticence by some prescribers and patients to alter therapy that they do not recognize as problematic (5, 6, 9, 11, 32). Many of the reasons for not seeking appropriate alternative therapy that have emerged throughout the course of the trial include the chronic use of such agents irrespective of the recognition and or education of age-related changes in cognitive sensitivity to such medications, renal and hepatic metabolism alterations, and importantly for our pre-dementia patients, a lack of perceived benefit as they continue to maintain function without repercussions of medication inappropriateness in their daily lives (1-3, 17). Further understanding and education on these critical issues is needed to support widespread changes in health behaviors for both patients and providers are needed to reduce polypharmacy and inappropriate medication use in the aging population.

Yet, for many, the opportunity to have their medications scrutinized in order to reduce the number of pills they take daily appeared to be a pivotal factor that engaged participants in our clinical study. The opportunity to engage in research that takes away medications rather than simply adding another was attractive to our recruited subjects. Balancing such desires with the need for certain medications, including some that may be considered inappropriate in a generalizable sense, yet appropriate for a specific patient's needs, is going to require further education and engagement of the patient-provider-pharmacist team (9, 32).

Deprescribing efforts are not without consequence, and potential risks of stopping and or substituting alternative medications can come with many risks (8, 9, 27, 29, 32). While such concerns should be taken seriously, the present data supports the safety of individualized MTM intervention as none of the SAEs seen in this study were related to study participation. Of the total reported AEs, only 3 were considered to be possibly related to changes in medication as a result of the MTM intervention, and all of these AEs related to changes in medication were mild and resolved with further medication adjustment. These data clearly demonstrate the safety of an individualized MTM approach to reduce polypharmacy and inappropriate medication use. The data presented further demonstrate that beneficial cognitive effects can be seen in those with preclinical AD but are not apparent in those without preclinical cerebral amyloidosis.

Use of a scopolamine challenge to unmask preclinical AD represents a novel approach to interventional trials in the area of pAD (18, 24). This approach appeared safe and effective in the majority of patients but was not without temporary consequences. While a substantial number of reported AEs, were determined to be possibly, probably, or definitely related to the administration of scopolamine (n=97), including mild dizziness, dry mouth, headache, and temporary slowing of cognition these were all considered mild and resolved with removal of the scopolamine patch. Such adverse events were anticipated to occur, and participants were monitored

carefully to ensure safety during the challenged phases of the study (18, 24). The majority of patients performed more poorly on cognitive testing in the challenged vs. unchallenged conditions as anticipated. However, a small subset of patients actually performed better on their cognitive testing, at least on the primary outcome measure of executive function captured by TMTB performance. This paradoxical response to cholinergic challenge was not anticipated, and an explanation for such occurrences can only be speculated. The study coordinator noted that the subjects with such a paradoxical response to cholinergic challenge appeared calmer and more comfortable during the cognitive testing procedure compared to their affective state during testing in the unchallenged condition although the study did not include measures of subjective or objective affective state that might have allowed an evaluation of such a phenomenon. Another possible explanation could be related to state-dependent learning wherein performance on the subsequent unchallenged testing might have been lowered by interference effects of initial testing in an altered state (33, 34). It is also possible that the anticholinergic properties of scopolamine contributed to enhanced extrapyramidal motor function allowing improved performance on TMTB which is reliant on motoric performance in addition to executive function (35). This phenomena created statistical problems with the preplanned analysis of a TMTB CRR, and so an alternative approach was employed using an analysis of pre-to-post MTM challenged scores alone in relation to effects of the MTM.

Detection of pAD using global Aβ-PET SUVr scores allowed stratification of participants into low risk (Aβ SUVr < 1.2), moderate risk (Aβ-PET SUVr between 1.2 and 1.4), and high risk (Ab SUVr ≥ 1.4) groups that were approximately balanced in the cohort studied (2, 14, 16). The present distribution of AD risk is similar to that seen in other studies such as ADNI and the NIH funded A4 study, further supporting prior findings of the frequency of pAD in the aging population to be approximately 30% (2, 14, 16, 20). While our primary analysis of MTM impact on TMTB CR effects failed to reach statistical significance across the combined Aβ-PET SUVr strata, there was a trend for improved cognitive performance on scopolamine-challenged TMTB performance (p=0.068), and consistent with our hypothesis, subgroup analysis using Aβ-PET SUVr cut-offs of 1.4 demonstrated cognitive benefit in the pAD group (SUVr ≥ 1.4; p=0.02). These data support the hypothesis that higher Aβ levels negatively impact cognitive reserve in a meaningful way (2, 15, 19).

Limitations of the present study included a relatively homogenous group of highly educated, predominantly White participants that may limit the generalizability of the findings. While only 10 participants who reported Black or Asian race (11% of the total cohort) were recruited into the study, this relative percentage is comparable to population demographics in our recruitment area (12.5 % non-White in Kentucky according to the 2020 US Census). Our choice of a CR challenge using an anticholinergic could also be considered a limitation as neurotransmitter imbalances and or deficits in pAD span many neurotransmitter systems including monoaminergic, glutamatergic, and others (3). Our MTM did not focus on reducing anticholinergic burden specifically, but rather targeted all potentially inappropriate medications (18). As such, it is possible that the cognitive benefits of the MTM in bolstering CR may be much broader than those identified in the current study. Furthermore, our inability to detect an effect of the intervention on the primary cognitive outcome could be explained by the broad range of medications targeted by the intervention and the limited sample size. Our sample size calculation was based on limited preliminary data to estimate a plausible effect size and was further impacted by the cost of performing amyloid PET scans on study participants. Despite its inability to determine whether an MTM intervention can improve executive function on older adults, INCREASE now stands to contribute information about potential effect sizes for cognitive outcomes that could help with the development of future studies.

Strengths of the current study include an optimized study design that addressed the use of all potentially inappropriate medications, rather than limiting the MTM to specific medication classes (18). The use of a multidisciplinary clinician-pharmacist team that partnered with study participants, encouraging engagement of the participant in medication related healthcare decisions based on our theoretical model can also be considered a major strength of our approach (18). Operationalizing CR with objective measures of actual performance rather than using surrogate measures such as education is a distinct strength of the present study (18, 36). Importantly, the safety measures incorporated in the protocol ensured participant safety and further provide a framework for the safe implementation of CR challenges that may augment further work in the area of CR (36). Further work designed to improve the effectiveness of the MTM across the continuum of dementia in persons that may benefit from medication optimization are readily achievable goals for promoting improved cognitive health and potentially not only delaying but also mitigating the symptoms that contribute to functional decline and reduced quality of life in persons with even fulminate AD.

Conclusion

A multidisciplinary medication optimization intervention can reduce inappropriate medication use for non-demented persons, irrespective of pAD status (SUVr ≥1.4). As hypothesized, some CR benefits were seen in those with pAD, but it remains unclear if the augmentation of CR by a medication optimization intervention can truly delay the onset and or progression of dementia based on the study data. Given the small sample of participants included in the INCREASE study

and the importance of this question, larger, multi-site, longer-duration studies with adequate power to evaluate the impact of the medication optimization in pAD are warranted.

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Ethical standards: Participants in the INCREASE trial provided written consent to participate with IRB approved informed consent forms.

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