REVIEW

Medication Adherence: Expanding the Conceptual Framework

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Interventions targeting traditional barriers to antihypertensive medication adherence have been developed and evaluated, with evidence of modest improvements in adherence. Translation of these interventions into population-level improvements in adherence and clinical outcomes among older adults remains suboptimal. From the Cohort Study of Medication Adherence among Older adults (CoSMO), we evaluated traditional barriers to antihypertensive medication adherence among older adults with established hypertension (N = 1,544; mean age = 76.2 years, 59.5% women, 27.9% Black, 24.1% and 38.9% low adherence by proportion of days covered (i.e., PDC <0.80) and the 4-item Krousel-Wood Medication Adherence Scale (i.e., K-Wood-MAS-4 ≥1), respectively), finding that they explained 6.4% and 14.8% of variance in pharmacy refill and self-reported adherence, respectively. Persistent low adherence rates, coupled with low explanatory power of traditional barriers, suggest that other factors warrant attention. Prior research has investigated explicit attitudes toward medications as a driver of adherence; the roles of implicit attitudes and time preferences (e.g., immediate vs. delayed gratification) as mechanisms underlying adherence behavior are emerging. Similarly, while associations of individual-level social determinants of health (SDOH) and medication adherence are well reported, there is growing evidence about structural SDOH and specific pathways of effect. Building on published conceptual models and recent evidence, we propose an expanded conceptual framework that incorporates implicit attitudes, time preferences, and structural SDOH, as emerging determinants that may explain additional variation in objectively and subjectively measured adherence. This model provides guidance for design, implementation, and assessment of interventions targeting sustained improvement in implementation medication adherence and clinical outcomes among older women and men with hypertension.

Keywords: blood pressure; conceptual model; hypertension; medication adherence; older women and men

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The US population ≥65 years is projected to increase from 56 million in 2020 to 86 million in 2050, with parallel increases expected in the prevalence of hypertension,[1] the key modifiable risk factor for cardiovascular disease, the leading cause of death and major contributor to disability in older adults.[2] Antihypertensive medications control hypertension and reduce cardiovascular disease risk[3–6]; however, clinical benefit is dependent on patient adherence to prescribed therapy. The odds of good health outcomes are nearly 3 times higher for adherent vs. nonadherent patients.[7] Low medication adherence is prevalent in the elderly,[8,9] accounting for up to 10% of hospitalizations,[10,11] and is estimated to cost the US healthcare system between $100 and $300 billion or more annually.[12,13] Importance of antihypertensive medication adherence and blood pressure (BP) control to build patient resilience in preventing adverse effects of other diseases is further highlighted by higher mortality in older adults with hypertension who were infected with COVID-19.[14]

Accordingly, improving medication adherence has been identified as a priority by the Lancet Commission on Hypertension[15] and the World Health Organization[16] with the latter citing inadequate medication adherence as the single most important modifiable aspect of management of chronic diseases such as hypertension.[16] Modest changes in adherence can lead to clinically significant reductions in BP.[17,18] In turn, relatively small reductions in BP are associated with improvements in mortality.[19,20]

Because of the major health benefits of good adherence, cognitive and behavioral interventions targeting various patient, healthcare system, and disease-specific barriers to adherence have been developed and tested.[21] While the positive impact of interventions focusing on changing

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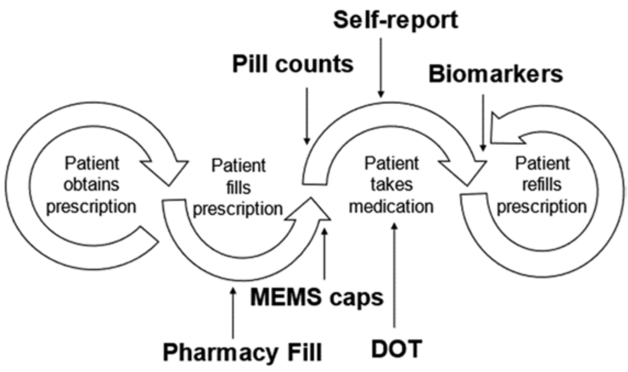

Figure 1. Adherence behavior cascade. Abbreviations: DOT, directly observed therapy; MEMS, Medication Event Monitoring System. (Adapted from ref. [96].)

behavior rather than those focusing on increasing knowledge has been appreciated since 1985,[21–23] according to a 2014 Cochrane review of interventions to enhance medication adherence, the most effective interventions are complex and, even so, are not associated with large improvements in health outcomes.[24] Furthermore, the translation of these interventions into population-level improvements in adherence and health outcomes among older adults in clinical practice remains suboptimal.[23,25]

Given that low adherence and uncontrolled BP remain clinical and public health challenges among older adults with established hypertension, there is a need to integrate novel determinants of medication-taking behavior into existing conceptual frameworks and capture and specify associations with subjective and objective adherence measures, which assess medication-taking behavior across the adherence cascade (Figure 1). Therefore, we propose an expanded conceptual framework that incorporates emerging risk factors, including patient implicit attitudes toward medications, time preferences, and structural social determinants of health (SDOH), with their relationship to objective and subjective measures of medication adherence. This updated framework may provide guidance for design, implementation, and assessment of medication adherence interventions to improve implementation adherence[26] and advance the field of adherence research by elucidating pathways for the sustained improvement in medication adherence and clinical outcomes among older women and men with hypertension.

TRADITIONAL BARRIERS TO MEDICATION ADHERENCE

Low adherence to antihypertensive drugs has been conceptually linked to social, patient, healthcare system, and disease and treatment barriers, which include, but are not limited to:

Social barriers: caring for dependents,[27] and inadequate social support or coping.[28–31]

Patient barriers: demographics (e.g., race, age, and sex),[27,32,33] behavioral (e.g., depression[29,34,35] and self-efficacy[31]), stress,[29,30] comorbidities,[35] health status,[30,31] lack of knowledge about hypertension,[30] beliefs about hypertension,[31] forgetfulness,[8,30] poor quality of life,[18,36] and lack of motivation for self-care.[37]

Healthcare system barriers: poor healthcare system perceptions,[16] poor patient–provider communication,[30,31] and trust.[38]

Disease and treatment barriers: asymptomatic nature and chronic duration of hypertension,[39] complexity and cost of drugs,[31,33,40] complementary and alternative medicine use,[41–43] sexual dysfunction,[32] and side effects and inconvenience of medications.[30,31,44–46]

Barriers that have been reported in recent and other relevant reviews and meta-analyses are listed in Table 1. While the associations between these barriers and medication-taking behavior are well recognized, few datasets include the breadth and depth of variables to analyze the combined effect of these social, patient, healthcare system, and disease and treatment factors on objective and subjective adherence measures among older adults. One such dataset, the Cohort Study of Medication Adherence among Older adults (CoSMO), includes data from each of these barrier domains as well as both objective and self-report adherence measures.[9]

The CoSMO—proportion of variance in adherence explained by traditional risk factors

Study population and timeline

We conducted a secondary analysis of data from CoSMO, a prospective *co*hort *s*tudy of *m*edication adherence among *o*lder adults with hypertension, which investigated factors associated with antihypertensive medication adherence (CoSMO study design and baseline characteristics published previously).[9] In brief, 2,194 patients who were 65 years of age and older, from a large managed care organization, and taking antihypertensive medication were recruited and enrolled between August 2006 and September 2007. Data were collected from telephone surveys administered 3 times at yearly intervals, medical records, pharmacy claims, and administrative databases from the managed care organization. CoSMO was approved by the Institutional Review Board and the privacy board of the managed care organization. This analysis used data from the first follow-up survey when the self-report adherence items were collected. Overall, 2,003 participants completed the first follow-up survey. Of these participants, 227 did not have complete self-report adherence data, an additional 164 did not have complete pharmacy refill data available from the administrative databases and an additional 68 had missing data for one of the predictors and were excluded from the analysis, yielding a sample of 1,544 for this analysis.

Study measures

Outcome: antihypertensive medication adherence

Antihypertensive medication adherence was measured via self-report using the 4-item Krousel-Wood Medication Adherence Scale (K-Wood-MAS-4) and using objective pharmacy refill data from the pharmacy claims database of the managed care organization. The K-Wood-MAS-4

Table 1. Factors associated with worse or better adherence: summary of evidence from recent reviews and meta-analyses

Worse adherence	Better adherence
Social factors	
• Perceived stress[31,a] • PTSD symptoms[29,30] • Lower practical support[29] • Lower levels of social support[29] • Life chaos (i.e., chaotic lifestyle and environment)[29]	• Higher subjective norms[31,d] • Perceived good relationship with spouses[31] • Perceived strong family support[31] • Increased support from the next of kin[30] • Higher levels of care received at home[30]
Patient factors	
• Poorer language or planning/organization skills[30] • Emotional dyscontrol[30] • Perceived helplessness or illness worries[30] • Memory deficits[30] • Depression[29,a] • Type D or distressed personality[29,c] • Negative affectivity[29]	• Higher self-efficacy[31,b] • Higher internal locus of control[31] • Perceived good general health[30,31] • Stronger beliefs about HTN severity[31,b] • Knowledge (i.e., understanding purpose, how to refill and side effects of medications)[30] • Perceived symptoms of HTN[46]
Healthcare system factors	
• Inadequate interaction and communication between patient and provider[16] • Perceived discrimination from health system due to race, ethnicity, education, or income[30] • Limited access to care[100]	• Perceived good relationship with health providers[31] • Greater communication (i.e., receiving medication instructions)[30]
Disease and treatment factors	
• Beliefs in barriers (e.g., bad taste, harmful effects)[31] • Medication side effects[31,a] • High cost of medications[31,a] • Mistrust of or concerns about medication (over)use[30,46] • Concern beliefs (concerns about a range of potential adverse consequences)[29,30,80,81]	• Beliefs about anti-HTN medication effectiveness[31,b] • Perceived medication necessity[29–31,80,81] • Perceived medication safety[31] • Greater perceived benefit of medications[30]

Abbreviations: HTN, hypertension; PTSD, post-traumatic stress disorder.
[a]Inconsistent evidence (some studies showed associations with worse adherence, others indicated no relationship).
[b]Inconsistent evidence (some studies showed associations with better adherence, others indicated no relationship).
[c]Type D personality includes negative affectivity and social inhibition.
[d]Subjective norms refer to beliefs that taking medications is important because significant others believe it is important.

predicts pharmacy refill adherence in older adults taking antihypertensive medications,[50] with moderate discrimination (*C* statistic of 0.704) and sensitivity and specificity of 67.4% and 67.8%, respectively. A higher K-Wood-MAS-4 score indicates worse adherence. Low adherence assessed with a K-Wood-MAS-4 score ≥1 has been associated with uncontrolled BP (adjusted odds ratio = 1.29, 95% confidence interval (CI) 1.01, 1.65), incident cardiovascular disease (adjusted hazard ratio = 2.29, 95% CI 1.61, 3.26),[8] and decline in mental health-related quality of life (adjusted odds ratio = 1.32, 95% CI 1.08, 1.62).[51]

Using all antihypertensive medication prescriptions filled in the year prior to survey administration, prescription-based proportion of days covered (PDC) was calculated as the number of days with medication available to take divided by the number of days between the first and last pharmacy refills in the time period.[47] PDC was calculated for each antihypertensive medication class separately and then averaged across classes to generate an overall mean PDC (range 0–1) for antihypertensive medications; a higher mean PDC indicates better adherence.[8,52]

Predictors: social, patient, healthcare system, hypertension disease, and treatment factors[9]

Social factors included low social support,[53] low hypertension knowledge,[54] low coping,[55] and exposure to stressful life events.[56] *Patient* factors included self-reported individual SDOH (e.g., age, sex, race, marital status, and education), health behaviors (e.g., smoking history, alcohol consumption, home BP monitoring, healthy lifestyle modifications for BP control such as weight control, salt reduction, and fruit and vegetable consumption),[57] depressive symptoms,[58] the Charlson Comorbidity Index,[59] the health-related quality of life[60] Physical Component Summary score, duration of hypertension, and body mass index based on self-reported height and weight. *Healthcare system* factors included number of visits to a healthcare provider in the year prior to survey administration as well as low healthcare satisfaction, overall and with respect to communication.[61] *Disease and treatment* factors included number of classes of antihypertensive medications filled in the year prior to survey as well as complementary and alternative medicine use[62] for managing hypertension, reduction in medications due to cost, and reduction in medications due to self-reported side effects.

Statistical analysis

Sample characteristics, including basic demographics and antihypertensive medication adherence outcomes, were described using proportions or means with SDs. Separate multivariable linear regression models were used to estimate coefficients and 95% CI for K-Wood-MAS-4 and PDC adherence measures. All social, patient, healthcare system, and hypertensive disease and treatment factors were included in the models. Adjusted *R*-squared values were used to describe the proportion of variance explained by the traditional barriers included in fully adjusted models. All analyses were performed using Stata v14.2 (StataCorp, College Station, TX).

Results

Participant characteristics and multivariable regression results are reported in Table 2. The sample was 59.5% female, 27.9% Black, with mean age 76.2 years (SD 5.5) and 24.1% and 38.9% low adherence by pharmacy refill (i.e., PDC <0.80) and self-report (i.e., K-Wood-MAS-4 ≥1), respectively. Mean PDC was 0.87 (SD 0.15; range 0.13–1) and mean K-Wood-MAS-4 score was 0.48 (SD 0.68; range 0–4).

Blacks, those with Charlson Comorbidity Index ≥2, those who indicated they had reduced medications due to cost and side effects, and those reporting 6 or more visits to a healthcare provider in the last year had, on average, lower PDC (worse adherence) than Whites, those with Charlson Comorbidity Index <2, those who did not reduce medications due to cost or side effects, and those reporting fewer than 6 visits to a healthcare provider in the last year, respectively. The social, patient, healthcare system, and disease and treatment factors included in the model explained 6.4% of the variance in PDC adherence.

Being female, being Black, having depressive symptoms, having low physical health-related quality of life, having low knowledge about hypertension, reporting a reduction in medications due to cost or side effects, and reporting low satisfaction with healthcare was associated with worse K-Wood-MAS-4 adherence. Having low coping skills was associated with better K-Wood-MAS-4 adherence. The social, patient, healthcare system, and disease and treatment factors included in the model explained 14.8% of the variance in K-Wood-MAS-4 adherence.

The relatively low proportion of variance in both objective (6.4% for PDC) and subjective (14.8% for K-Wood-MAS-4) adherence explained by traditional risk factors in this sample of older adults may provide insight into why adherence interventions to date that have addressed these traditional risk factors have resulted in only modest improvements in adherence behavior. Persistent low adherence rates coupled with the low explanatory power of traditional barriers suggest other factors may be at play, including people's implicit attitudes toward medications, time preferences, and structural SDOH (Table 3).

EMERGING DETERMINANTS OF MEDICATION ADHERENCE

Implicit attitudes toward medications

Explicit and implicit attitudes about health behaviors are distinct concepts (Table 3). Explicit attitudes guide health behavior that is more conscious or planned and are typically captured using self-report surveys assessing patients' explicit, conscious, and rational beliefs and attitudes toward disease and its treatment.[74–76] On the other hand, implicit attitudes guide health behaviors that people do not consciously monitor and are best measured using reaction time tasks which assess the absolute strength of evaluative associations.[77–79] Prior medication adherence research has investigated explicit attitudes toward medications as a driver of adherence behavior[29,30,80,81]; more recent studies have explored the potential role of implicit attitudes.[48,49,63,65,82]

Explicit attitudes have been most commonly measured using the Beliefs about Medicines Questionnaire[66,83] to determine *Necessity* and *Concern* beliefs (i.e., positive and negative attitudes, respectively) toward medication.[66] Concern beliefs, including concerns about a range of potential adverse consequences, harm or other negative effects of taking medicines are consistently associated with worse adherence[29,30,80,81] while necessity beliefs, reflecting perceptions about the personal need for treatment/medications, are typically associated with better adherence.[29,30,80,81] Further, positive explicit attitudes (measured using the Beliefs about Medicines Questionnaire *Necessity–Concerns* differential and defined as stronger beliefs in the necessity of medication relative to concerns) are associated with better adherence.[81] Interestingly, while the relationship between explicit attitudes toward medications and adherence behavior has been well established,[80] most studies have solely identified associations between explicit attitudes and subjective, self-reported adherence measures although evidence suggests that necessity beliefs, in particular, are also associated with objectively measured adherence behavior.[68]

Implicit attitudes may be captured using tools that measure underlying automatic evaluations,[77] such as the Single Category Implicit Association Test (SC-IAT).[78] The SC-IAT is typically administered via computer and requires participants to sort pictures representing the attitude object ("taking my pills") and words representing "Good" and "Bad" evaluations into categories. An SC-IAT difference score (*d*-score), based on response times to the assigned sorting tasks, is calculated to indicate which evaluation (i.e., "Good" vs. "Bad") has the stronger automatic association with the attitude object (i.e., "taking my pills"). Although the role of implicit attitudes in shaping health behavior has been appreciated for some time,[79,84,85] the relationship between implicit attitudes and antihypertensive medication adherence has garnered attention more recently.[82]

Individuals have both explicit and implicit attitudes toward medications; yet, these attitudes are not necessarily in sync. Recent evidence shows that discordance between explicit and implicit attitudes about taking chronic disease medications is linked to poor adherence.[63,65,86] In studies assessing medication adherence in people with rheumatoid arthritis and chronic psychiatric disorders, implicit and explicit attitudes were uncorrelated (r = 0.08, P = 0.59[65] and r = 0.003, P = 0.98,[63] respectively), and marginal associations between explicit, but not implicit, attitudes and self-reported adherence were reported (r = 0.28, P = 0.07[65] and β = 0.25, P = 0.05,[63] respectively), consistent with the idea that *self-reported* adherence behavior may not be associated with implicit attitudes. More recently, Herrera identified implicit ("anti-adherence") and explicit ("pro-adherence") motivations underlying adherence behavior in a sample of adults with hypertension, and suggested that implicit ("anti-adherence") attitudes may be working counter to

Table 2. Multivariable linear regression models predicting medication adherence based on traditional factors (CoSMO study: n = 1,544)

	% (*n*)	Proportion of days covered β (95% CI)	4-Item Krousel-Wood Medication Adherence Scale score β (95% CI)
Patient			
Age ≥75	56.0 (864)	0.009 (−0.007, 0.025)	−0.017 (−0.086, 0.051)
Female	59.5 (918)	−0.007 (−0.024, 0.010)	0.086* (0.011, 0.160)
Black	27.9 (431)	−0.048*** (−0.066, −0.030)	0.124** (0.047, 0.202)
High school education or higher	80.8 (1,247)	0.007 (−0.013, 0.027)	−0.012 (−0.098, 0.074)
Married	55.4 (855)	0.001 (−0.015, 0.017)	0.054 (−0.016, 0.124)
Depressive symptoms	12.4 (192)	−0.000 (−0.024, 0.023)	0.247*** (0.144, 0.350)
2+ lifestyle modifications	80.8 (1,247)	0.008 (−0.011, 0.027)	−0.062 (−0.146, 0.022)
2+ alcoholic drinks per week	23.7 (366)	−0.004 (−0.022, 0.015)	−0.030 (−0.110, 0.050)
Home BP monitoring at least once/month	56.5 (872)	−0.013 (−0.029, 0.002)	0.019 (−0.046, 0.085)
Charlson Comorbidity Index ≥2	56.5 (873)	−0.020* (−0.036, −0.004)	0.026 (−0.043, 0.094)
Low Physical Component Summary	35.1 (542)	−0.004 (−0.021, 0.012)	0.329*** (0.257, 0.400)
High body mass index	75.7 (1,168)	−0.001 (−0.019, 0.016)	0.037 (−0.040, 0.114)
Hypertension duration ≥10 years	63.3 (978)	0.011 (−0.004, 0.027)	−0.019 (−0.086, 0.048)
Ever smoked	49.9 (771)	−0.008 (−0.024, 0.007)	0.021 (−0.046, 0.088)
Social			
Low social support	34.6 (534)	−0.004 (−0.019, 0.012)	0.047 (−0.022, 0.116)
Low coping	48.0 (741)	0.004 (−0.010, 0.019)	−0.065* (−0.130, 0.000)
Low hypertension knowledge	29.3 (453)	−0.003 (−0.020, 0.014)	0.142*** (0.068, 0.216)
Life events			
Moderate (vs. high)	27.2 (420)	−0.007 (−0.044, 0.030)	−0.053 (−0.214, 0.108)
Low (vs. high)	68.2 (1,053)	−0.015 (−0.051, 0.021)	−0.08 (−0.237, 0.076)
Disease and treatment			
3+ classes of antihypertensive medications	46.5 (718)	0.010 (−0.006, 0.025)	0.027 (−0.04, 0.094)
Reduced medication due to cost	2.3 (36)	−0.131*** (−0.180, −0.082)	0.244* (0.030, 0.457)
Complementary and alternative medicine use	20.2 (312)	−0.004 (−0.022, 0.015)	0.031 (−0.049, 0.112)
Reduced medication due to side effects	4.1 (63)	−0.075*** (−0.112, −0.038)	0.385*** (0.225, 0.546)
Healthcare system			
6+ visits to healthcare provider in last year	29.1 (449)	−0.025** (−0.042, −0.008)	0.049 (−0.025, 0.123)
Low satisfaction with healthcare	3.6 (56)	−0.037 (−0.078, 0.005)	0.282** (0.102, 0.463)
Low satisfaction with communication	7.9 (122)	0.005 (−0.024, 0.034)	0.104 (−0.023, 0.231)
R^2	—	0.0641	0.1482

Abbreviations: BP, blood pressure; CI, confidence interval; CoSMO, Cohort Study of Medication Adherence among Older Adults.
*P < 0.05.
**P < 0.01.
***P < 0.001.

the participants' expressed explicit ("pro-adherence") attitudes.[82] Published theoretical frameworks, originating from psychotherapy research,[87,88] further support the notion that nonadherence or "resistance to change" behavior can be viewed as an expression of conflict between explicit "pro-" and implicit "anti-" adherence motivations.

In keeping with the hypothesis that *automatic* behavior (guided by implicit beliefs) and *reflective* behavior (guided by explicit beliefs) are differentially associated with nonadherence behaviors, Kleppe *et al.* found that negative (i.e., affective) associations likely influence adherence via avoidance tendencies while positive (i.e., cognitive) associations likely influence adherence via intentions, noting that the processes through which behavior is influenced might be different for positive and negative associations.[48] Researchers have also demonstrated

Table 3. Emerging determinants of adherence behavior

	Sample size	Sample characteristics	Disease condition	Adherence outcome	Association
Implicit attitudes					
Adherence voices[82] Assessed through in-depth interviews, with responses classified as either "pro-adherence" or "anti-adherence" voices	N = 51	• Age range 25–80 years • Sex not reported • Race not reported (all Chilean nationals)	Hypertension	• *Self-report* (in-depth interview) combined with BP data from medical records	This qualitative study identified pro-adherence voices and anti-adherence voices (self-worth, well-being, affiliation, autonomy, lack of motivation) underlying adherence behavior
Implicit attitudes toward medications[67] Measured with the SC-IAT [higher score = more positive attitudes]	N = 85	• Age, mean (SD): 62.3 (4.9) years • Female: 44.7% • Black: 20.0%	Hypertension	• *Objective* (pharmacy refill, PDC): mean score = 0.8, range 0.1–1.0 (higher score = better adherence); and low (vs. high) PDC adherence (43.5% low PDC) • *Self-report* (K-Wood-MAS-4): mean score = 0.5, range 0–3 (lower score = better adherence); and low (vs. high) K-Wood-MAS-4 adherence (31.8% low K-Wood-MAS-4)	*Objective PDC:* • Implicit attitudes not associated with PDC score (β = 0.13, P = 0.129) • Positive implicit attitudes associated with reduced odds of low PDC (aOR = 0.12, P = 0.029) *Self-report K-Wood-MAS-4:* • Implicit attitudes not associated with K-Wood-MAS-4 score (β = −0.05, P = 0.843) • Implicit attitudes not associated with low K-Wood-MAS-4 (aOR = 0.81, P = 0.811)
Medication-taking related associations[48] Measured with affective imagery, i.e., participants asked to write first associations about taking medicines and then evaluate their association on a scale ranging from extremely negative (−3) to extremely positive (3) [higher score = more positive affect ratings]	N = 525	• Age, mean (SD): 58.1 (11.6) years • Female: 42.7% • Race not reported	Hypertension, diabetes, and CVD	• *Self-report* (ProMAS) used to determine a mean score (higher score = better adherence)	Positive affect ratings were correlated with higher adherence (r = 0.29, P < 0.001)
Implicit attitudes toward medications[63] Measured with the BIAT [higher score = more positive implicit attitudes]	N = 85	• Age, mean (SD): 44.8 (9.7) years • Female: 32% • Black race: 58%	Schizophrenia, schizoaffective and affective disorders	• *Self-report* (single item) used to categorize adherence as high (vs. low): [n = 48 high adherence, n = 33 low adherence, n = 4 not currently prescribed medication]	Implicit attitudes not associated with self-reported adherence [β = 0.16 (i.e., OR = 1.17), P = 0.16]
Hidden motives and unrecognized assumptions underlying nonadherence[86] Assessed with established psychological interviewing method	N = 46 (construction sample) N = 17 (validation sample)	• 25–34 years: 2% • 35–44 years: 44% • 45–54 years: 54% • Female: 92% • Race not reported	Chronic disease	• *Self-report* (single item) used to assess presence of problems adhering to medications [all participants reported problems adhering to medications]	In this qualitative study, hidden motive clusters underlying nonadherence were identified: interference with other priorities, losing control, negative identity, not being one's own doctor, too close or dependent on medical establishment/medications, unpleasantness
Implicit attitudes toward medication[65] Measured with the SC-IAT [higher score = more positive implicit attitudes)	N = 52	• Age, mean (SD): 58.3 (15.8) years • Female: 51.9% • Race not reported	Rheumatoid arthritis	• *Self-report* (Compliance Questionnaire on Rheumatology) used to calculate a mean score (higher score = better adherence)	No statistically significant correlations between self-reported adherence and implicit attitudes (r = 0.059, P = 0.70)

Table 3. Continued

	Sample size	Sample characteristics	Disease condition	Adherence outcome	Association
Time preferences (TP)					
Scenario measures of TP[92] *Health (i.e., chest pain) scenario TP* • I would want to have relief right away • The medication that takes 6 months to work is more effective in reducing pain, so worth waiting for *Monetary scenario TP* • Waiting for the delayed money is like earning a high rate of interest • The delayed amount is more money, so worth waiting for	*N* = 195[a]	• Age, mean: 79.2 years • Female: 65% • Race not reported	Hypertension	• *Self-report, specific* (4 questions) used to calculate mean score (higher score = better adherence) • *Self-report, summary* (3 summary items) used to calculate mean score (higher score = better adherence) • *Pill count* used to calculate mean score (higher score = better adherence) • *Systolic BP, interview* used to determine mean BP value (higher value = worse adherence) • *Systolic BP, doctor's visit* used to determine mean value (higher value = worse adherence)	*Self-report, specific:* • Health TP: $r = 0.17$; $P < 0.06$ • Monetary TP: $r = -0.04$; $P > 0.1$ *Self-report, summary:* • Health TP: $r = 0.13$; $P > 0.1$ • Monetary TP: $r = -0.03$; $P > 0.1$ *Pill count:* • Health TP: $r = 0.21$; $P < 0.05$ • Monetary TP: $r = 0.06$; $P > 0.1$ *Systolic BP, interview* • Health TP: $r = -0.01$ $P > 0.1$ • Monetary TP: $r = 0.07$; $P > 0.1$ *Systolic BP, doctor's visit* • Health TP: $r = 0.18$; $P < 0.1$ • Monetary TP: $r = 0.04$; $P > 0.1$
Health discount rates[71] Determined using a hypothetical temporal choice (i.e., respondents were asked if, having won a lottery, they would prefer $1,000 today or $1,500 in 5 years)	*N* = 422	• Mean age: 57.4 years • Female: 76.3% • Black: 70.47%	Hypertension	• *Self-report* (selected items from the PEPPI questionnaire) used to assess likelihood of engaging in preventive health practices (33% of patients reported nonadherence to self-management and pill taking)	A 1 percentage point increase in the discount rate was associated with a 3.5 percentage point decrease in the likelihood of checking BP at home ($P = 0.003$)
Future time perspective[90] Measured using the ZPTI subscale reflecting an individual's orientation to future time perspective (mean (SE) score = 3.67 (0.04); higher score = more of the construct)	*N* = 178	• Age, mean (SE): 62.9 (1.20) years • Female: 61.2% • Black: 30.3%	Hypertension; diabetes	• *Self-report* (MMAS survey-4 item) used to create 5 adherence groups, ranging from completely nonadherent (3.7%) to completely adherent (59.9%) [higher score= better adherence]	Increase by a single unit in future time perspective was associated with a 0.32 SD increase in reported adherence ($P < 0.05$)
Disruption in time projection[101] *Impatience for monetary choice* • Determined using a simple fictive monetary scenario (i.e., preferring to receive €500 today (impatient) or €1,500 in 1 year) [63.3% impatient, 36.7% patient] *Temporal horizon (≥5 years)* • Based on greater or lesser ability to imagine future events [median = 2.5 years]	*N* = 120	• Age, mean (SD): 58.6 (8.9) years • Female: 45.8% • Race not reported	Hospitalized patients with Type 2 diabetes	• *Self-report* (French 6-item validated, Girerd questionnaire, e.g., "Do you think that you have too many tablets to take?") used to create adherent (<3 positive answers) vs. (≥3 positive answers) nonadherent groups [39.2% adherent]	In multivariate analysis, 2 factors were significantly associated with adherence to medication: impatience (OR = 0.20; $P = 0.006$) and long temporal horizon (OR = 1.17; $P = 0.006$)

Table 3. Continued

	Sample size	Sample characteristics	Disease condition	Adherence outcome	Association
Discounting of side effects[102] Derived from medical decision-making task scores [median (interquartile range): 0.17 (0.02, 0.57), higher score = higher rates of discounting side effects (i.e., devalue treatment as probability of side effects increases)]	*N* = 208	• Age, mean (SD): 46.02 (10.96) years • Female: 83.2% • Black: 7.7% (87% White)	Multiple sclerosis	• *Self-report* (Adherence Determination Questionnaire, modified) used to calculate mean score [mean (SD) = 38.00 (5.99); higher score = better adherence determination] • *Self-report*[b] (single item question) used to create nonadherent (i.e., >20% of prescribed doses missed) vs. adherent groups [12% of sample were nonadherent]	*Self-report (adherence determination):* • Discounting of side effects (R^2 change = 0.07, $P < 0.001$) accounted for unique variance in adherence determination (total $R^2 = 0.20$, $F = 15.98$, $P < 0.001$) *Self-report (adherence group status):* • Only discounting of side effects accounted for unique variance in adherence group status ($\chi^2 = 12.95$, Nagelkerke $R^2 = 0.14$, $P < 0.001$)
Social determinants of health (SDOH)—structural					
SDOH[95] Composite scores, based on data from the County Health Rankings dataset, were used to create social determinants of medication nonadherence constructs reflecting poverty/food insecurity [higher score = more food insecurity]; weak social support [higher score = fewer social supports]; and healthy built environments [higher score = healthier built environment)]	*N* = 2,067 (counties in the United States: Midwest, Northeast, South, and West)	• Age above 65 years, per geographic region: Midwest = 17.1%; Northeast = 17.2%; South =16.7%; West = 16.6% • Female, per geographic region: Midwest = 50.0%; Northeast = 51.0%; South = 50.4%; West = 49.7% • Black, per geographic region: Midwest = 3.3%; Northeast = 5.2%; South = 16.3%; West = 1.7%	Hypertension	• *Objective* (<80% PDC with BP medication during a 365-day period; weighted mean prevalence of nonadherence = 25%, SD = 18.8%)	After multivariate adjustment, poverty/food insecurity (β = 0.38, $P < 0.01$) and weak social supports (β = 0.12, $P = 0.05$) were positively associated, and healthy built environments (β = −0.13, $P < 0.01$) inversely associated, with nonadherence; together, these social determinants explained 30.3% of the total variation in county-level nonadherence to BP medication
SDOH index[69] Based on 6 SDOH categories (i.e., Economic Stability, Social and Community Context, Education, Neighborhood and Built Environment, Health and Health Care and Food) used to create a social index score and define 3 SDOH index clusters: low (0–52.8), medium (52.8–86.1), and high (86.1–100); higher score = worse social index (i.e., higher needs)	*N* = 99,217	• Median age: 71 years • Sex not reported • Black: 9.20%	Chronic disease (i.e., diabetes, hypertension, high cholesterol, and anticoagulation)	• *Refill request rate* (i.e., the amount of refill requests sent through text message after an initial refill reminder text was sent; refill request rate for overall study = 17.4%) [all patients were partially adherent or nonadherent (i.e., proportion of days covered/ PDC <80%)]	Refill requests were very highly inversely correlated ($r = -0.93$) with SDOH clusters (refill requests rates of 18.99%, 16.37%, and 12.84% for low, medium, and high SDOH groups, respectively)

Table 3. Continued

	Sample size	Sample characteristics	Disease condition	Adherence outcome	Association
Food insecurity[103] Assessed using the 10 adult-referenced items of the US Department of Agriculture's household-level 30-day food security scale [scores ≥3 = food insecure; 18.8% of respondents reported food insecurity]	*N* = 9,696	• Mean age (SE): 60.9 (0.2) years • Female: 61.2% • Black: 12.5%	Chronic illness (hypertension, arthritis, diabetes mellitus, cancer, asthma, chronic obstructive pulmonary disease, stroke, coronary heart disease, and presence of "psychiatric problem")	• *Self-report* (4 validated items adapted from the Medication Expenditure Panel Survey) [higher proportion = worse adherence; 23.4% reporting cost-related medication underuse]	After multivariable adjustment, food insecurity remained significantly associated with cost-related medication underuse (OR = 4.03; 95% CI 3.44–4.73; $P < 0.05$)
SDOH[104] *Perceived financial stress* • 6 items summed to create an overall score (higher score = greater stress) *Financial insecurity with healthcare* • 4 items measured on a summed scale (higher score = greater financial insecurity) *Food insecurity* • 4 items measured using a summed scale (higher score = greater food insecurity)	*N* = 4,158	• Age, mean (95% CI): 60.3 (59.7–60.9) years • Female: 50.4% • Black: 16.3%	Diabetes	• *Self-report* (3 items asking about engagement in cost-related nonadherence (CRN) behaviors over the past 12 months) [positive response to any item = CRN; 14% reported CRN in past 12 months]	In multivariate analyses, greater perceived financial stress (PR = 1.07; 95% CI 1.05–1.09), greater financial insecurity with healthcare (PR = 1.6; 95% CI 1.5–1.7), and greater food insecurity (PR = 1.3; 95% CI 1.2–1.4) were all associated with a greater likelihood of engaging in CRN behaviors over the past year
Neighborhood social environment[105] *Social affluence* • Derived from 5 variables (higher score = greater social affluence) *Neighborhood advantage* • Derived from 3 variables (higher score = greater neighborhood advantage) *Residential stability* • Derived from 2 variables (higher score = greater residential stability)	*N* = 179	• Age, mean (SD): 57.4 (9.5) years • Female: 67.6% • Black: 56.4%	Type 2 diabetes mellitus	• *Objective* (MEMS data) used to determine the proportion of medication MEMS cap openings in a given week relative to prescribed doses for the week [higher proportion = better adherence]	Compared with residents in neighborhoods with 1 or no high features present, residents in neighborhoods with high social affluence, high residential stability and high neighborhood advantage were more likely to have an adherent pattern compared with a nonadherent pattern (aOR = 8.48, 95% CI 1.71, 42.02; $P < 0.05$)
Neighborhood safety[106] Assessed via a single item asking "Do you feel safe in your neighborhood all of the time, most of the time, some of the time, or none of the time?" (less than "all the time" = unsafe neighborhood)	*N* = 3,401	• Age (safe vs. unsafe), mean (SE): 60.0 (0.6) vs. 59.3 (0.7) years • Female (safe vs. unsafe): 44.3% vs. 52.9% • Black (safe vs. unsafe): 7.7% vs. 11.7%	Type 2 diabetes mellitus	• *Self-report* (2 measures of treatment nonadherence): delayed filling prescription for any reason (safe vs. unsafe: 21.9% vs. 12.8%), delayed filling a prescription due to cost (safe vs. unsafe: 12.2% vs. 6.8)	A higher proportion of respondents living in unsafe neighborhoods reported delaying filling a prescription for any reason (aOR = 1.69, 95% CI 1.19, 2.40; $P = 0.004$) and delaying filling a prescription due to cost (aOR = 1.63, 95% CI 1.02, 2.62, $P = 0.043$) compared with those who reported feeling safe in their neighborhood

Abbreviations: aOR, adjusted odds ratio; BIAT, Brief Implicit Association Test; BP, blood pressure; CI, confidence interval; CRN, cost related nonadherence; CVD, cardiovascular disease; K-Wood-MAS-4, 4-item Krousel-Wood Adherence Scale; MEMS, Medication Event Monitoring System; MMAS, Morisky Medication Adherence Scale; PDC, proportion of days covered; PEPPI, Perceived Efficacy in Patient–Physician Interactions; PR, prevalence ratio; SD, standard deviation; SDOH, social determinants of health; SC-IAT, Single Category Implicit Association Test; SE, standard error; TP, time preferences; US, United States; ZPTI, Zimbardo Time Perspective Inventory.

[a]Outcomes in the analysis based on 128 participants with complete data; the exception is the "Systolic BP, doctor's visit" outcome which is based on 89 participants.

[b]This single item measure was noted to be highly correlated with objective measures of adherence.[102]

significant improvements among stroke survivors in objectively measured adherence (using a Medication Events Monitoring System (MEMS) measure) and self-reported Medication Adherence Report Scale (MARS) total adherence change scores in the intervention group compared with the control group, following an intervention designed to address both *automatic* and *reflective* aspects of adherent behavior.[49] These results provide further evidence for the utility of addressing both *reflective* (*explicit*) and *automatic* (*implicit*) aspects of behavior to increase medication adherence.[49]

Building on this research, we recently reported on the associations of implicit determinants of self-reported and objectively measured medication adherence in older insured adults with hypertension.[67] We captured complete pharmacy refill data on 85 community-dwelling older commercially insured adults (44.7% women; 20.0% Black) and found that more positive implicit attitudes and more positive explicit attitudes were associated with reduced odds of objective low PDC adherence (adjusted odds ratio = 0.12, 95% CI 0.02, 0.80; $P = 0.029$ and adjusted odds ratio = 0.87, 95% CI 0.78, 0.98; $P = 0.022$, respectively). Further, more positive explicit attitudes toward antihypertensive medications were associated with lower (better) *self-reported* adherence scores ($\beta = -0.04$, 95% CI −0.07, 0.00; $P = 0.026$) on the K-Wood-MAS-4.[8,50] Implicit attitudes were not associated with K-Wood-MAS-4 adherence ($\beta = -0.05$, 95% CI −0.57, 0.47; $P = 0.843$). Explicit and implicit attitude scores were uncorrelated ($r = 0.07$; $P = 0.533$), signaling that these adherence measures provide different data about adherence in older adults. Of note, in fully adjusted hierarchical logistic regression models (including traditional risk factors), we found that the addition of implicit and explicit attitudes significantly increased the proportion of variance explained in PDC adherence to 35.9%. For K-Wood-MAS-4, only the addition of the explicit attitudes significantly increased the proportion of variance explained to 24.4%. These results support prior research regarding the role of subconscious processes underlying medication nonadherence in older adults, the benefits of objective and self-report adherence tools in understanding adherence behavior, and the potential for targeting patient implicit and explicit attitudes toward medications to improve adherence.[67]

Time preferences

Given the asymptomatic nature of hypertension, the disease itself is not particularly relevant in the daily lives of most people (Table 3).[89] Therefore, the taking of daily medications to manage the disease to prevent a future adverse event may be an indicator of the patient's time preferences (e.g., immediate or delayed gratification). Time preferences have been conceptualized as a potential motivator of medication adherence, influencing how individuals' past experiences inform present decision-making and future goal setting.[90] With hypertension, the "benefits" of controlled BP are primarily associated with *future* lower probability of heart attack, stroke, and kidney disease. However, the immediate "risks" such as side effects of medications (e.g., fatigue, sexual dysfunction, and frequent urination),[44,45] costs and inconvenience of taking medications,[31] stigma associated with the diagnosis and the treatment,[64] or subconscious concern that taking medications daily will increase stress and interfere with other priorities,[86] can act as barriers to adherence. Some studies assessing medication adherence in chronic diseases (e.g., heart failure[91]; hypertension and diabetes[90]) have found that time preferences are significantly associated with real-world health behavior. More recent work on how people value rewards as a function of time (i.e., how they make intertemporal choice) examined behaviors specific to hypertension control: more present-oriented individuals (i.e., immediate gratification/"high discounting" individuals) were less likely to check their BP regularly, less likely to alter their diet to help control their hypertension, and less likely to follow their physician's advice.[71] Chapman *et al.* reported that responses to monetary time preference scenario were not significantly correlated with adherence measures assessed via self-report, pill count, or BP in a sample of 195 older adults with hypertension (mean age 79.2 years).[92] However, in a younger sample (mean age 62.9 years; 91% with self-reported hypertension), Sansbury *et al.* reported a direct effect of future time perspective on medication adherence: an increase by a single unit in future time perspective (0–5 scale) was associated with a 0.32 SD increase in adherence to medication ($P < 0.05$).[90] Although further work is needed in larger and more diverse samples to understand the specific role of time preferences in health behaviors among older adults with hypertension, the emerging evidence linking time preferences and adherence behavior signals an important opportunity for innovative interventions. Because the benefits of treating hypertension are focused on the future, interventions and monitoring strategies that use time perspective to tailor counseling interventions designed to overturn nonadherent behaviors should be developed and evaluated in clinical trials.

SDOH—structural

Given that adherence to antihypertensive medications is a complex health behavior and may be affected not only by the individual but also in the context of his/her community, attention has turned to determinants of health that go beyond the *individual-level* SDOH to include community-level *structural* SDOH that can predispose people, including older women and men, to ill health and unhealthy behaviors (Table 3).[69,70,93–95] SDOH have been defined as the "conditions in the places where people live, learn, work and play that affect a wide array of health and quality of life risks and outcomes" (https://www.cdc.gov/socialdeterminants/index.htm, Accessed 20 October 2020).

Several of the individual SDOH are captured by traditional barriers such as age, sex, race, educational attainment, insurance status, social support, and income level and have been linked to adherence behavior. Importantly, however, these individual SDOH encompass far more than demographic characteristics, further reflecting those wider structures and forces that give rise to and reinforce social hierarchies and divisions, and shape the opportunities, social position, and lived experiences of individuals.[73] Race and sex differences in adherence have been identified, with higher rates of low medication adherence among Blacks vs. Whites and mixed evidence of differences across sex.[9,32,33] However, data on efficacy and sustainability of interventions by sex and race are limited, making interpretation of findings challenging and limiting assessments of generalizability.[96] Sex and race differences in social, patient, healthcare system, and disease and treatment barriers to medication adherence, among older hypertensive adults, have also been identified, heightening the call for tailored interventions that address person-specific barriers to medication adherence among older adults.[32,33,96] Although the potential importance of addressing SDOH to improve medication adherence and address health disparities has been recognized,[70] there is limited research studying the specific approaches in which SDOH pathways interact to affect adherence, particularly among older adults.[69] In a cross-sectional study assessing the impact of individual SDOH on prescription refill requests by Medicare patients using a conversational artificial intelligence text messaging solution, Brar Prayaga *et al.* found that Spanish vs. English speakers and older vs. younger patients had significantly lower refill request rates.[69]

Although less is currently known about structural SDOH, opportunities exist to investigate the role of structural SDOH and medication adherence with expanded access to data, identification of appropriate methodological frameworks, and elucidation of the associations between structural SDOH and objective vs. subjective adherence measures. In a study investigating the role of structural SDOH on antihypertensive medication adherence, Donneyong *et al.* reported an average low antihypertensive medication nonadherence rate (PDC <80%) of 25% (SD of 18.8%) in 3,000 US counties; the rate of low adherence was directly associated with poverty/food insecurity ($\beta = 0.31$, $P < 0.001$) and weak social supports ($\beta = 0.27$, $P < 0.001$) and inversely associated with healthy built environment ($\beta = -0.10$, $P = 0.02$).[95] Of note, these 3 constructs reportedly explained 30% of the variance in county-level antihypertensive medication adherence ($R^2 = 0.30$). Further work is needed regarding the relationship between individual and structural SDOH and medication adherence (objective and subjective measures), and the strategies to improve both.

Conceptual model

Building on prior published conceptual frameworks[72,86] and recent evidence, we propose an expanded conceptual framework of factors influencing medication implementation adherence and subsequent BP control, clinical outcomes, and healthcare utilization among older adults with hypertension (Figure 2). The updated model incorporates *implicit* (i.e., *subconscious*)[78] and *explicit* (i.e., *conscious*)[83] attitudes toward antihypertensive medications, in addition to *time preferences*, and *structural SDOH* as emerging determinants that influence and may explain additional variation in, medication-taking behavior. The importance of both objective adherence measures (reflecting incidental adherence behavior) and subjective adherence measures (reflecting deliberative adherence behavior) that capture medication-taking across the adherence cascade (Figure 1) is highlighted. It is also noted that several factors contributing to poor adherence to prescribed medications may lead to increased use of complementary and alternative medicine, which may further contribute to low medication adherence.

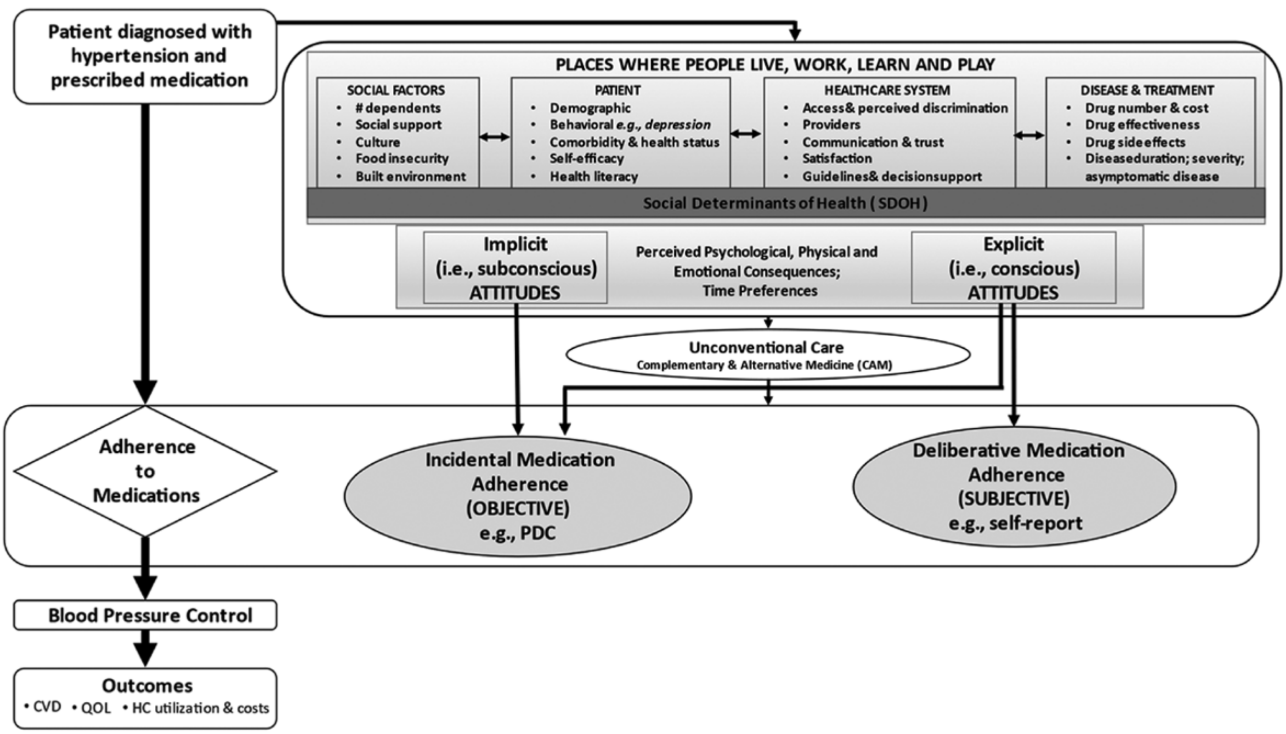

Figure 2. Conceptual model of implementation adherence. Abbreviations: CVD, cardiovascular disease; HC, healthcare; PDC, proportion of days covered; QOL, quality of life. (Adapted from refs. [72,86].)

PERSPECTIVES AND FUTURE DIRECTIONS

The expanded conceptual model presented here provides a framework for addressing low adherence in older adults with hypertension that goes beyond the traditional risk factors. This framework can guide design, implementation, and assessment of innovative interventions targeting improvement in medication adherence that include emerging determinants that explain additional variation in medication-taking behavior. A focus on behavior change in older adults has the potential to "move the needle" toward healthy aging, especially given the evidence that older people can be strongly motivated to change behavior, and can even be more successful than their younger counterparts in making changes permanent.[97,98] Further research is needed to validate tools and ensure access to data to evaluate these novel determinants and their impact on objective and subjective adherence measures in diverse women and men. To advance the field, planning and assessment of adherence interventions should include rigorous experimental designs, sufficient sample sizes to explore sex and race differences, objective and subjective measures of adherence and clinical outcomes, use of established theoretical frameworks, determination of mechanisms underlying behavior change, and structured interventions that allow for sufficient follow-up and are reproducible in clinical and research settings.[99] Such efforts will provide much needed information on efficacy and effectiveness of adherence interventions and lead to sustained improvement in medication adherence and clinical outcomes for older women and men with hypertension.

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DISCLOSURE

The authors declared no conflict of interest.

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