

## RESEARCH PAPER

# Willingness of older people living with dementia and mild cognitive impairment and their caregivers to have medications deprescribed

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## Abstract

**Background:** people living with cognitive impairment commonly take multiple medications including potentially inappropriate medications (PIMs), which puts them at risk of medication related harms.

**Aims:** to explore willingness to have a medication deprescribed of older people living with cognitive impairment (dementia or mild cognitive impairment) and multiple chronic conditions and assess the relationship between willingness, patient characteristics and belief about medications.

**Methods:** cross-sectional study using results from the revised Patients' Attitudes Towards Deprescribing questionnaire (rPATDcog) collected as baseline data in the OPTIMIZE study, a pragmatic, cluster-randomised trial educating patients and clinicians about deprescribing. Eligible participants were 65+, diagnosed with dementia or mild cognitive impairment, and prescribed at least five-long-term medications.

**Results:** the questionnaire was mailed to 1,409 intervention patients and 553 (39%) were returned and included in analysis. Participants had a mean age of 80.1 (SD 7.4) and 52.4% were female. About 78.5% (431/549) of participants said that they would be willing to have one of their medications stopped if their doctor said it was possible. Willingness to deprescribe was negatively associated with getting stressed when changes are made and with previously having a bad experience with stopping a medication ( $P < 0.001$  for both).

**Conclusion:** most older people living with cognitive impairment are willing to deprescribe. Addressing previous bad experiences with stopping a medication and stress when changes are made to medications may be key points to discuss during deprescribing conversations.

**Keywords:** deprescribing, dementia, cognitive impairment, patient attitudes, potentially inappropriate medication use, older people

## Key Points

- Most people living with cognitive impairment are willing to stop one of their medications.
- Potential key points to include in deprescribing conversations and educational interventions include addressing stress when changes are made to medications, and identifying and discussing past negative experiences with deprescribing.
- Patient characteristics that are routinely collected (e.g. age and number of medications) may not be able to predict willingness to deprescribe; directly collecting attitudes, such as through use of the revised Patients' Attitudes Towards Deprescribing questionnaire (rPATDcog), could potentially be more effective than using demographics to target interventions and education (in research and practice).

## Background

Use of polypharmacy and potentially inappropriate medications (PIMs) is common in people living with dementia and can lead to increased risk of harms, such as adverse drug reactions, falls, hospitalization and mortality [1–5]. Optimising benefit and minimising risk of medication use requires both appropriate prescribing and appropriate deprescribing, i.e. discontinuation (or dose reduction) of medications where the harms outweigh the benefits in the individual [1, 6, 7]. The benefits and harms of medications can change over time in an individual, due to addition of new medications, development of new medical conditions and changes in care goals. In addition, older adults and people with dementia have altered pharmacokinetics and pharmacodynamics, which makes them more susceptible to adverse drug reactions [1, 8, 9].

Barriers to deprescribing have been described at all levels of the healthcare system, including at the physician and patient level [10, 11]. For example, physicians may feel that patients and/or their caregivers are resistant to deprescribing; whereas patients and their caregivers may be afraid of their condition returning and/or withdrawal reactions [12, 13].

Understanding patient attitudes towards deprescribing can inform development of interventions and conversations to optimise deprescribing in the context of shared decision-making as an essential part of good clinical care. The Patients' Attitudes Towards Deprescribing (PATD and revised version; rPATD) questionnaire was developed and validated to quantitatively capture how patients feel about their medications and potential deprescribing [14, 15]. A version of the rPATD, the rPATDcog, was developed and validated for people with cognitive impairment [16]. The rPATDcog has previously only been used in a single study ( $n=21$ , single site) [16] and only one other study ( $n=422$ , which used questions from the PATD and rPATD as it was prior to development of the rPATDcog) has focused on people living with dementia [17]. In addition, there is inconsistent evidence about whether participant characteristics are associated with willingness to have a medication deprescribed [18] and few studies have explored the association between willingness and other beliefs and attitudes [19]. Therefore, the aims of this study were to explore the attitudes of people living with cognitive impairment (dementia or mild

cognitive impairment, MCI) about their medications and willingness to have a medication deprescribed and assess the relationship between willingness, patient characteristics and belief about medications.

## Methods

This paper presents the results of the rPATDcog questionnaire, administered as part of the OPTIMIZE study. The OPTIMIZE study investigated the effectiveness of a patient (and care partners if present)- and clinician-focused educational deprescribing intervention (occurred from April 2019 to March 2020; [20–22]). The rPATDcog was sent to intervention participants as part of the intervention along with an educational brochure. The full methods and main results have been previously published [20–22]. The study was approved by the Kaiser Permanente Colorado and Johns Hopkins University institutional review boards, individual consent was waived (pragmatic design and all medications change decisions were conducted by the patients' primary care providers).

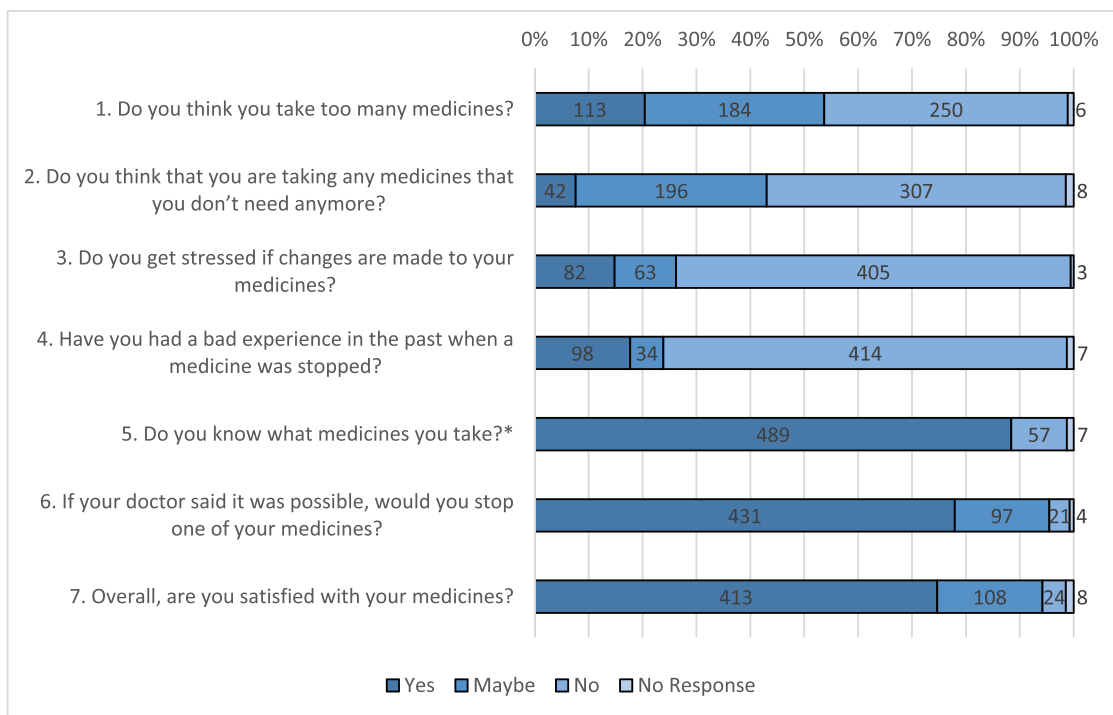
## Setting and participants

The OPTIMIZE study was conducted in 18 primary care practices (9 intervention and 9 control) in the Kaiser Permanente Colorado not-for-profit integrated healthcare delivery system (Colorado, United States). To be included, patients had to be aged  $\geq 65$  years, have Alzheimer disease and related dementias (ADRD) or MCI, have 1+ additional chronic conditions and be on 5+ long-term medications. They also had to have an appointment during the intervention period scheduled 7+ days in advance (so that the intervention material, including the questionnaire, could be mailed out prior to their appointment). Patients in long-term care or hospice at baseline were excluded. Only intervention patients were sent the rPATDcog. Patients were included in this analysis if they returned the rPATDcog with at least one of the questions completed.

## Measures and data collection

This manuscript uses the rPATDcog results and baseline demographic information collected in the OPTIMIZE study intervention group. The rPATDcog has seven questions, plus

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**Figure 1.** Participant responses to rPATDcog questions. \*Among persons who responded 'no' to knowing what medications they take, 46(81%) reported having a list of their medications.

question #5 about knowledge of their medicines has a sub-question (Figure 1). It is a shortened and adapted version of the rPATD to make it suitable for people with cognitive impairment. The response options are 'Yes', 'Maybe' and 'No' [16].

A hard copy of the rPATDcog was mailed to participants and they were instructed to complete the questionnaire and return it to the study team using the included pre-paid return envelope. No reminders or financial incentives were provided. If the patient was eligible for the intervention twice during the study period, and they had not returned the rPATDcog the first time, then a second copy of the questionnaire was sent to them along with the intervention materials. Participants were instructed that they could fill it out on their own, or have someone such as family member (i.e. caregiver) fill it out. Participant demographics and clinical characteristics were collected from the Kaiser Permanente Colorado Virtual Data Warehouse, which includes data on health plan enrolment, demographics, census data, health-care utilisation, diagnoses and pharmacy dispensing [23–25]. Long-term medication use was defined as any prescribed medication for which the patient had at least a 28-day supply. Identification of PIM use was based on a modified 2015 Beers list of drugs to avoid in cognitive impairment [26] with opioids added [20].

### Analysis

Results of the rPATDcog were described as the proportion who said yes, maybe or no to each question. Participant

characteristics were compared between survey responders and non-responders as well as by responses to the rPATDcog question on willingness to deprescribe (question #6). Characteristics were described using proportions for categorical variables and means and standard deviations for continuous and count variables. Significant differences between groups used chi-square tests for categorical variables, *t*-tests for age and Kruskal–Wallis tests for other continuous or count variables. Kendall Tau correlations were used to explore the relationship between rPATDcog questions.

We also examined whether the number of medications and proportion of participants on one or more PIMs, differed by response (yes, maybe or no) to the rPATDcog question items, based on Kruskal–Wallis and chi-square tests, respectively.

Missing data (rPATDcog responses and participant characteristics; see Table 1 and Figure 1) were excluded from analysis. All analyses were unadjusted, and a *P* value of <0.05 was considered significant. Analyses were completed using SAS® Studio Software version 3.8 (SAS Institute Inc., Cary, North Carolina).

## Results

### Participants

The OPTIMIZE intervention group participants (*n* = 1,431) were sent the rPATDcog questionnaire. Twenty-two of these were not able to be delivered, resulting in 1,409 who potentially received the questionnaire. Of these, 39.2%

**Table 1.** Characteristics of rPATDcog responders and non-responders

Variable		Responder <i>N</i> = 553 (%)	Non-responder <i>N</i> = 856 (%)	<i>P</i> value <sup>a</sup>
Age	Mean	80.1	79.8	0.47
	SD	7.4	7.6	
Gender	Female	290(52.4)	502(58.6)	0.02
	Male	263(47.6)	354(41.4)	
Race and ethnicity	Hispanic	31(5.6)	87(10.2)	0.02
	Non-Hispanic White	454(82.1)	633(74.0)	
	Non-Hispanic Black	37(6.7)	77(9.0)	
	Non-Hispanic Indian	2(0.4)	6(0.7)	
	Non-Hispanic Asian	8(1.5)	18(2.1)	
	Other	15(2.7)	27(3.2)	
ADRD versus MCI only	Unknown	6(1.1)	8(0.9)	0.004
	MCI only	145(26.2)	168(19.6)	
	ADRD	408(73.8)	688(80.4)	
Long-term medications	Mean (SD)	7.0(2.2)	6.9(2.1)	0.16
Chronic conditions	Mean (SD)	8.3(3.0)	8.6(3.3)	0.12
On 1+ PIMs	Yes	153 (27.7)	277(32.4)	0.06
	No	400(72.3)	579(67.6)	
Length of enrolment in health plan (years)	Mean (SD)	19.7(8.1)	18.9(8.4)	0.09
Neighbourhood deprivation index <sup>b</sup>	Mean (SD)	-0.6(0.6)	-0.6(0.6)	0.50
Median family income for their zip code <sup>c</sup> (USD)	Mean (SD)	99,801(34,076)	98,951(35,890)	0.41

ADRD: Alzheimer disease and related dementias; MCI: mild cognitive impairment; PIMS: potentially inappropriate medications; SD: standard deviation; USD: US dollar. <sup>a</sup>*P* values from Chi-square tests for categorical variables, *T*-test for age and Kruskal–Wallis tests for remaining continuous and count variables. <sup>b</sup>Five from responder and eight from non-responder missing neighbourhood deprivation index (NDI). NDI is a standardised *z*-score that summarises multiple indicators including education, income and employment into a score where higher values indicate lower SES. The possible range of NDI scores is -3 to 3. Higher values mean more neighbourhood economic disadvantage, lower values mean more neighbourhood economic advantages. The minimum NDI in responders was -1.8, and the maximum was 1.5. <sup>c</sup>One from responder and seven from non-responder missing data for Median Family Income. Income represents census zip code level, not individual. The 2016–2020 Median Family Income of Colorado was \$75,231. The minimum Median Family Income by zip code of responders was \$25,671 and maximum was \$250,001.

(553/1,409) were returned, all which had at least one question completed; 515 (93.1%) answered all seven main rPATDcog questions.

Survey responders (participants) had a mean age of 80.1 (SD 7.4) and 52.4% were female. Participants took a mean of 7.0 long-term medications (SD 2.2) for a mean of 8.3 (SD 3.0) chronic medical conditions and 27.7% were on one or more PIM(s).

Non-responders were similar to responders in age, number of long-term medications, number of chronic conditions, proportion on 1+ PIMs, length of enrolment in health plan and measures of socioeconomic status (Table 1). There was a statistically significant difference between rPATDcog responders and non-responders in relation to gender, with males more likely to respond compared with females ( $P=0.02$ ), fewer Hispanic people responding than non-Hispanic people ( $P=0.02$ ), people with ADRD less likely to respond and people with MCI more likely to respond ( $P=0.004$ ).

### Attitudes of older people living with cognitive impairment towards their medications and deprescribing

Responses to the rPATDcog are shown in Figure 1. About 78.5% (431/549) of participants said that they would be willing to have one of their medications stopped if their doctor said it was possible, with a further 17.7% responding 'maybe' to this question. In this cohort, there was a

high overall satisfaction with their medications (75.8%, 413/545). About 20.7% (113/547) of responders thought that they are taking too many medications and 7.7% of responders (42/545) think that they are taking a medication that they do not need any more. Concerns about deprescribing were expressed by 26.3% (145/550) who found changes potentially stressful and 24.2% (132/546) who reported having, or possibly having, a previous bad experience when a medication was stopped.

### Associations between beliefs and attitudes captured in the rPATDcog

Over half of the possible correlations between the rPATD questions were statistically significant (Table 2). Being willing to have a medication deprescribed was positively associated with feeling like they are taking too many medications and believing that they are taking one or more medications that they no longer need. It was also negatively associated with getting stressed when changes are made and with previously having a bad experience with stopping a medication. The questions with the greatest correlation were feeling like they are taking too many medications with feeling like they are taking a medication that they no longer need.

### Associations between participants' characteristics and willingness to deprescribe

Responses to the question 'If your doctor said it would be possible, would you stop one of your medicines'

**Table 2.** Correlations between attitudes and beliefs captured by the rPATDcog questions

rPATDcog questions	Q1.	Q2.	Q3.	Q4.	Q5.	Q6.
Q1. Do you think you take too many medicines?	—					
Q2. Do you think that you are taking any medicines that you don't need anymore?	0.56 <sup>a</sup>	—				
Q3. Do you get stressed if changes are made to your medicines?	0.15 <sup>a</sup>	0.12 <sup>b</sup>	—			
Q4. Have you had a bad experience in the past when a medicine was stopped?	0.04	0.01	0.27 <sup>a</sup>	—		
Q5. Do you know what medicines you take?	-0.06	-0.05	-0.06	-0.002	—	
Q6. If your doctor said it was possible, would you stop one of your medicines?	0.18 <sup>a</sup>	0.20 <sup>a</sup>	-0.15 <sup>a</sup>	-0.10 <sup>b</sup>	-0.005	—
Q7. Overall, are you satisfied with your medicines?	-0.36 <sup>a</sup>	-0.33 <sup>a</sup>	-0.10 <sup>b</sup>	-0.05	0.02	-0.09 <sup>b</sup>

<sup>a</sup>Kendal-Tau correlation *P* value <0.001. <sup>b</sup>Kendal-Tau correlation *P* value >0.001 and <0.05.

generally did not differ by measured participant characteristics, with one exception (Supplementary Appendix S1). Patients with more chronic conditions expressed greater willingness to deprescribe than patients with fewer conditions (mean conditions = 8.5 if responding 'yes' versus 6.9 if responding 'no', *P* = 0.009). There was no difference in willingness based on whether the survey was completed by the patient or their caregiver.

**Associations between medication use and beliefs and attitudes towards medications and deprescribing**

Two rPATDcog questions were significantly associated with number of long-term medications (Table 3). There was a difference in number of medications taken by those who responded 'yes' (7.6), 'maybe' (7.2) and 'no' (6.7) to taking too many medications (*P* < 0.001). Number of medications was also different depending on whether participants had previously had a bad experience when stopping a medication (Yes: 8.0, Maybe: 7.9, No: 6.8, *P* < 0.001). Similarly, a higher proportion of those on one or more PIMs, compared with no PIMs, reported having a bad experience when stopping a medication in the past (29.5% versus 13.6%; *P* < 0.001, Table 4). In addition, a higher proportion of people on 1 or more PIMs reported being stressed when changes are made to their medications (22.6% versus 11.7%; *P* = 0.01).

Neither number of medications nor use of one of more PIMs were associated with reported willingness to have a medication deprescribed in this population.

**Discussion**

We found that approximately three-quarters of older people living with cognitive impairment (ADRD or MCI) and their caregivers from the OPTIMIZE intervention arm were willing to have one of their medications stopped if their doctor said it was possible. This is the largest study to-date which has explored how people living with dementia

and cognitive impairment feel about deprescribing. This is important because this population has a high prevalence of potentially inappropriate medication use and are likely to benefit from deprescribing because of higher risks of adverse drug events [1, 8, 9].

The high level of willingness to have a medication deprescribed in our study (78.5%) is similar to in other populations. A recent systematic review and meta-analysis of results of the PATD and its variations found that 84% (95% confidence interval, CI 81–88%) of participants were willing to have a medication deprescribed, with a range of 49–98% in the 40 included studies [18]. The only previously published study that used the rPATDcog found that 81% (17/21) of people with cognitive impairment would be happy to stop one of their medications if their doctor said it was possible [16]. In a recently published cross-sectional analysis of people living with dementia in the United States (which used questions from the PATD and rPATD), 87% were willing to stop one or more of their medications [17]. However, people living with cognitive impairment may have different attitudes about deprescribing than people without cognitive impairment. In previous studies that included people with and without dementia, less severe cognitive impairment was associated with greater belief that their medications were appropriate [27], and people with probable dementia (compared with those without dementia) were less likely to want to reduce the number of medications they were taking [28].

Similar to previous studies [18], we found very few characteristics associated with reported willingness to deprescribe. In our study, only number of chronic conditions was associated, with those with more chronic conditions being more willing to deprescribe. Previous studies have had mixed results regarding number of chronic conditions; with two finding a similar positive association [28, 29], and another two did not [30, 31]. Identifying people by characteristics (such as age and number of medications), who are most likely to be willing to have a medication deprescribed could allow interventions to be targeted where there is the greatest chance of effecting change; or, conversely, to identify populations

**Table 3.** Association between responses to the rPATDcog and number of medications

	N	Survey item response category						Kruskal–Wallis <i>P</i> value
		Yes		Maybe		No		
		Mean	SD	Mean	SD	Mean	SD	
1. Do you think you take too many medicines?	547	7.6	2.2	7.2	2.4	6.7	1.9	<0.001
2. Do you think that you are taking any medications that you don't need anymore?	545	7.1	1.8	7.3	2.3	6.9	2.1	0.09
3. Do you get stressed if changes are made to your medicines?	550	7.7	2.7	7.1	2.3	6.9	2.0	0.06
4. Have you had a bad experience in the past when a medicine was stopped?	546	8.0	2.6	7.9	2.9	6.8	1.9	<0.001
5. Do you know what medicines you take?	546	7.0	2.1	NA	NA	7.2	2.3	0.63
6. If your doctor said it was possible, would you stop one of your medicines?	549	7.0	2.1	7.4	2.6	7.0	2.1	0.79
7. Overall, are you satisfied with your medicines?	545	7.0	2.1	7.2	2.2	7.9	2.5	0.14

**Table 4.** Association between responses to the rPATDcog and use of one or more PIMs

	No PIMs		1+ PIMs		Chi sq <i>P</i> value
	N	%	N	%	
1. Do you think you take too many medicines?	72	19.5	34	23.3	<i>P</i> = 0.31
Yes					
Maybe	126	34.1	41	28.1	
No	171	46.3	71	48.6	
2. Do you think that you are taking any medications that you don't need anymore?	30	8.1	9	6.2	<i>P</i> = 0.46
Yes					
Maybe	134	36.3	48	32.9	
No	205	55.6	89	61.0	
3. Do you get stressed if changes are made to your medicines?	43	11.7	33	22.6	<i>P</i> = 0.01
Yes					
Maybe	39	10.6	19	13.0	
No	287	77.8	94	64.4	
4. Have you had a bad experience in the past when a medicine was stopped?	50	13.6	43	29.5	<i>P</i> < 0.001
Yes					
Maybe	21	5.7	13	8.9	
No	298	80.8	90	61.6	
5. Do you know what medicines you take?	331	89.7	130	89.0	<i>P</i> = 0.72
Yes					
No	38	10.3	16	11.0	
6. If your doctor said it was possible, would you stop one of your medicines?	297	80.5	110	75.3	<i>P</i> = 0.20
Yes					
Maybe	60	16.3	28	19.2	
No	12	3.3	8	5.5	
7. Overall, are you satisfied with your medicines?	280	75.9	111	76.0	<i>P</i> = 0.74
Yes					
Maybe	74	20.1	27	18.5	
No	15	4.1	8	5.5	



who have low willingness, who could be a good target for educational interventions. However, the limited associations found in ours and other studies suggests that willingness to deprescribe may be difficult (or potentially impossible) to predict based on routinely collected characteristics, such as age and number of medications, and that more novel predictors may be needed. Directly collecting attitudes, such as through use of the rPATDcog, could be a promising way to target interventions and education (in research and practice). This is similar to the field of medication non-adherence, where external patient characteristics have been found to be poor predictors and beliefs are better predictors of non-adherence [32, 33].

This study also resulted in new information about the association between medication use and attitudes. The association of number of medications with feeling like they are taking too many medications may be a result of the external characteristic (medication use) influencing the belief. That is, the beliefs of patients who feel that they are on too many medicines are valid, which illustrates the importance of listening to the concerns of patients. We also found that participants who had a greater number of medications and those on 1+ PIMs were more likely to have had a previous bad experience when stopping a medication. We posit that these experiences/attitudes could have impeded deprescribing, therefore leading to being on more medications and not stopping inappropriate medications. This shows the need for support from healthcare professionals throughout the deprescribing process (i.e. support and monitoring) to optimise future willingness to deprescribe. Further research is needed into how beliefs about medications are formed and how they may influence medication use to inform deprescribing in practice. Increased patient awareness of medications, in particular that the benefits and harms can change over time could also support deprescribing efforts.

### Strengths and limitations

The strengths of this study are its large sample size, use of a validated questionnaire and the robust participant characteristic data.

However, this study has several limitations. The rPATDcog questionnaire was sent out to intervention participants, who at the same time, received the deprescribing educational brochure. Given that our findings on proportion willing to deprescribe were similar to previous studies, this may have had a minimal effect on our findings.

We had a response rate of ~40%, which is similar to most posted survey studies in older adults [34]. We were able to compare the characteristics of responders to non-responders to inform generalisability. On most measured characteristics, responders were similar to non-responders. We found female versus male and people with ADRD versus MCI were less likely to respond, as were people of Hispanic race/ethnicity. Although we found a statistical difference, the numerical differences in these characteristics between responders and non-responders are small and therefore may not have a great

influence on the generalizability of our findings. Participants were from a single healthcare provider in the United States and attitudes may be different in other healthcare systems, in and outside of the United States. Future studies with the rPATDcog may benefit from an in-person approach to completion of the questionnaire to maximise response rate and involvement of people with severe cognitive impairment.

We were not able to explore associations with characteristics such as frailty, type and severity of dementia and level of independence; future research into this may be valuable. Another limitation is that the rPATDcog is susceptible to response bias (self-administered questionnaire); however, as participants were instructed to send the questionnaire to the researchers, rather than directly to their Primary Care Provider, the impact of this may have been minimal. Finally, we allowed for a care partner to complete the questionnaire on behalf of their loved one (to maximise number of responses), and this might have influenced the findings (although we found no difference in willingness to deprescribe when the survey was completed by a care partner versus the person with cognitive impairment).

### Implications for practice and research

Prescribers have reported concerns about initiating a conversation about deprescribing for fear of damaging the relationship with the patient, particularly with people living with cognitive impairment as it could be misinterpreted that the person was no longer worth treating [1, 8]. Despite a high level of satisfaction with their medicines, most older people with cognitive impairment are open to conversations about deprescribing. However, further research is needed about how reported willingness to deprescribe on a survey translates into actual medication deprescribing.

Results of the rPATDcog may be used to inform deprescribing discussions, leading to more meaningful shared decision-making [35–37]. Our findings provide insight into key points to be included in educational interventions and one-on-one conversations. For example, we found that those who reported getting stressed when changes are made, and those who previously had a bad reaction when stopping were less likely to be willing to deprescribe. In our population ~1 in 5 reported possibly having a previous bad experience with stopping a medication.

Further quantitative and qualitative research is required into how people living with cognitive impairment feel about deprescribing, particularly in relation to how their beliefs and attitudes align or misalign with that of their care partner. This can then inform how clinicians can navigate difficult discussions with dyads of people living with dementia and their care partners.

### Conclusion

We found that most older people living with cognitive impairment and their caregivers were willing to deprescribe.

Addressing previous bad experiences with stopping a medication and stress when changes are made to medications may be key points to discuss during deprescribing conversations.

**Supplementary Data:** Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**Declaration of Conflicts of Interest:** Dr Reeve reported receiving grants from the National Institutes of Health (sub-award to Dr Reeve's institution) during the conduct of the study and royalties from UpToDate for writing a chapter on deprescribing. Drs Bayliss, Gleason, Green, Maciejewski, Sheehan and Boyd; and Shetterly, Sawyer, Norton and Maiyani reported receiving grants from the National Institute on Aging during the conduct of the study. Dr Bayliss also received grants from the Agency for Healthcare Research and Quality. Dr Green reported receiving grants from the National Institute on Aging Impact Collaboratory during the conduct of the study. Dr Maciejewski reported receiving Veterans Affairs Health Services Research and Development funding and owning Amgen stock due to his spouse's employment. Dr Boyd reported receiving royalties from UpToDate for writing a chapter on multimorbidity and honoraria from Dynamed for reviewing a chapter on falls outside the submitted work. No other disclosures were reported.

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The sponsor had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

**Data Availability Statement:** Source data (derived from Electronic Health Records) comply with human subjects protection and HIPAA standards and as such are not publicly available.

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