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# **Does missing data matter in the revised Patients' Attitude Towards Deprescribing questionnaire? A systematic review and two case analyses**

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## **Abstract**

### **Background**

The revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire was developed to capture beliefs and perceptions of patients about deprescribing. In general, handling of missing data is underreported in survey studies. Underlying mechanisms related to missing data may impact the findings from survey studies.

### **Objectives**

The aim of this study was to assess the missing data in studies using the rPATD questionnaire through a systematic review and datasets from two studies.

### **Methods**

First, this review updated a systematic review on the rPATD (and other versions). We searched Medline via OVID, EMBASE, Scopus, Web of Science until 31<sup>st</sup> January 2023. Missing data reporting and methods to handle them were collected. Second, data from two deprescribing studies were analyzed using three methods of missing data handling: complete case analysis, personal mean substitution, and multiple imputation. We compared the scores from each domain and the associations of the domains with two questions from the rPATD to highlight how using different methods can influence the interpretation of study findings.

### **Results**

We identified 49 studies: 31 (63%) from this study and 18 (37%) from the original systematic review. The question or domain with the most missing data could be identified in 9 studies (18.4%). Missing data management was reported in 19 studies (38.8%). In one case analysis, the "Burden" domain was significantly associated with the question "*I would like to try stopping one of my medicines to see how I feel without it*" using complete case analysis

( $p=0.044$ ) or multiple imputation ( $p=0.038$ ), but not when using personal mean substitution ( $p=0.057$ ).

### **Conclusions**

Missing data and methods used to handle missing data were underreported in studies using the rPATD questionnaire. The methods should be chosen carefully as our analyses from two distinct studies suggest that they may impact the interpretation of the findings from the questionnaire.

**Keywords:** deprescribing; questionnaire; patient outcome assessment; missing data

**Abbreviations:** rPATD, revised-Patients' Attitude Toward Deprescribing

## 1. Introduction

Deprescribing is defined as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes”.<sup>1</sup> Deprescribing is a societal priority since polypharmacy and inappropriate medication use can result in significant side effects and drug interactions in an ageing population. Engaging patients in the deprescribing process and understanding their views is necessary to tailor intervention from a clinical or a research perspective. The revised Patients’ Attitudes Towards Deprescribing (rPATD) questionnaire was developed and validated in 2016.<sup>2</sup> It captures beliefs and perceptions of patients about deprescribing. To our knowledge, the rPATD is the most widely utilized questionnaire for measuring these outcomes. The rPATD fits the recommendations of minimum standards for patient-reported outcome measures in term of psychometric properties.<sup>3</sup>

Missing data is common in the field of patient-reported outcome measures and may lead to bias in the measure depending on the nature of the missing data if it is not considered. Missing data can be classified into three groups based on underlying reasons and mechanisms: missing completely at random, missing at random and missing not at random.<sup>4,5</sup> Missing completely at random occurs when missing data is unrelated to any study variable (*e.g.* broken pen making it impossible to fill in the boxes). Missing at random occurs when missing data is related to an observed variable (*e.g.* to explore a patient’s adherence to a medicine he/she does not have). Missing not at random occurs when missing data is related to the reason it is missing (*e.g.* drop-out of a clinical trial because the patient experiences side effects from the study drug).<sup>6</sup>

There are different ways to handle missing data in patient-reported outcome measures.<sup>7</sup> For instance, deletion methods such as complete case analysis removes all cases with at least one missing data. This method reduces the statistical power of analysis and may lead to selection bias if data are not missing completely at random.<sup>8</sup> Imputation of a missing value can be

performed using several methods. Personal mean score imputation substitutes the missing value with the mean of the other non-missing items of the subscale.<sup>9</sup> Multiple imputation replaces missing values with several options.<sup>4</sup> The appropriateness of these methods depends on the type and the proportion of missing data.<sup>10</sup>

In 2020, a systematic review and meta-analysis of the rPATD (and other versions) included 40 studies, however, the authors did not report the handling of missing data.<sup>11</sup> Several guidelines recommend how missing data and management should be addressed and reported, demonstrating the importance of selecting the most appropriate method.<sup>12,13</sup>

The aim of this study was to assess the handling of missing data in studies using the rPATD questionnaire through a systematic review and to assess the impact of missing data on rPATD results using datasets from two studies.

## **2. Methods**

This study included two steps. Firstly, we conducted a systematic review to describe the methods for handling missing data in studies that have used the rPATD questionnaire. Secondly, we showed how the methods for handling missing data can affect results using two examples from studies that previously used the rPATD questionnaire.

### 2.1 Systematic review

We followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) checklist.<sup>14</sup> This review updated a systematic review by Weir *et al.*<sup>11</sup>, following guidelines of the Cochrane handbook of systematic reviews.<sup>15</sup> While the previous systematic review included articles from 2016 to March 2020, we used the same search strategy to identify studies from March 2020 until 31<sup>st</sup> January 2023 (Appendix 1).

#### *2.1.1. Inclusion criteria*

Studies were eligible if they were original studies that included adults taking at least one medication. All study types and settings were included if the rPATD questionnaire or a translated version was used. No language or other exclusion criteria were applied. Duplicates were identified and excluded, and multiple reports of the same study were collated.

#### *2.1.2. Search*

We searched in Medline via OVID, EMBASE, Scopus, Web of Science from the end of the previous systematic review: 23 March 2020 to 31 January 2023. Two researchers (JNS and JPF) independently double screened the titles, abstracts and full texts. Any discrepancies were resolved by discussion. We added the results of this update to the included articles of the previous systematic review.

### *2.1.3. Outcomes*

We identified in each study the rate of missing data, the items or domains with the most missing data, and the methods used to handle missing data in the article or in supplementary files. The settings and who administered the questionnaire were also collected.

## *2.2. Cases analyses*

### *2.2.1. Data source*

To study the impact of different methods to handle missing data, we performed two case analyses using data from two studies: the DeprescriPP trial and the LESS study. Both studies had used the rPATD to assess patients' attitudes towards deprescribing.

First, we used data from the DeprescriPP trial conducted in France, in which questionnaires containing the rPATD questions were sent to 2306 primary care patients aged  $\geq 65$  years who had been using proton pump inhibitors (PPI) for  $\geq 1$  year in November 2020. Participants were asked to return the completed questionnaires by postal mail. The DeprescriPP trial has not yet been published.<sup>16</sup>

Second, we used data from the Swiss LESS study in which questionnaires containing rPATD questions were administered to 306 patients aged  $\geq 70$  years, having  $\geq 3$  chronic conditions, and taking  $\geq 5$  chronic medications, after these patients had been recruited by their general practitioners. Questionnaires were completed in the general practitioner's waiting room or at home from May 2018 to February 2019. The LESS Study has already been published.<sup>17</sup>

### *2.2.2. Assessment of patients' attitudes towards deprescribing*

The rPATD contains 22 items: 20 questions covering four domains (five items for each domain): i) belief in appropriateness of the medication use ("Appropriateness"), ii) perceived



burden of medication taking (“Burden”), iii) concerns about stopping (“Concerns about stopping”), and iv) level of involvement in medication management (“Involvement”), and two global questions “Overall, I am satisfied with my current medicines” and “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” (Appendix 2). Each item in the burden, concerns about stopping and involvement domains is noted on a 5-point Likert scale from 1 to 5 (“strongly disagree” to “strongly agree”). Items from the appropriateness domain were reverse scored because of negatively worded items.<sup>2</sup> Domain scores were calculated with the mean of the five items. Higher scores in each domain indicated a greater perceived burden, appropriateness, concerns about stopping and involvement in medication management.

### 2.2.3. Statistical analysis

We applied an algorithm developed by Mirzaei *et al.* to provide a guidance on possible methods for handling missing data.<sup>7</sup> We evaluated the missing data in the two datasets from the DeprescriPP and LESS studies. The algorithm considers the missing data as negligible if they represent less than 5% of the dataset. Performing a Little’s Test of Missingness is recommended if missing data occurred between 5 and 40% to determine whether the data could be classified as missing completely at random. A significant p-value <0.05 means that the data are not missing completely at random.<sup>18</sup> Then, data can be classified as missing at random if an observed variable is structurally related to the missing data. Otherwise, data is classified as missing not at random. We described the mean score at the domain-level using three different methods: pair-wise deletion, personal mean score imputation, and multiple imputation (mi-two way, as described by Van Ginkel *et al.*).<sup>19</sup> To illustrate the impact of the three different methods, we dichotomized the global question “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” in a binary outcome with agree for those

who responded agree or strongly agree and disagree for those who responded disagree for those who responded strongly disagree, disagree or unsure. We performed a multiple logistic regression to analyze the association between the global question and the four domains to compare the three different methods. A sensitivity analysis was performed using the question “*I would like to try stopping one of my medicines to see how I feel without it*” (item 2 of the Appropriateness domain). This question has been used in previous studies for sensitivity analyses and as the primary outcome because it may capture the patient's willingness to deprescribe separately from the influence of the doctor and seems less susceptible to the ceiling effect.<sup>20,21</sup> We dichotomized this question in a binary outcome with agree for those who responded strongly agree, agree or unsure and disagree for those who responded strongly disagree or disagree. We performed a multiple logistic regression to analyze the association between this specific item and the four domains to compare the three different methods. We calculated odd ratios (OR) and 95% confidence interval. A p-value <0.05 was considered statistically significant. Microsoft Excel 2019 (Microsoft Corporation) was used for data management and statistical analysis were performed using Stata 17.0 (StataCorp, College Station, TX, USA).

#### *2.2.4. Ethics approval*

The DeprescriPP trial has been approved by the Ethics Committee of the *Collège National des Généralistes Enseignants* (#08062011).<sup>16</sup> Ethical approval for the LESS study was obtained from the Ethics Committee of the Canton of Bern, Switzerland (Ref. 2017–02188).<sup>17</sup>

### **3. Results**

#### *3.1. Systematic review*

We identified 49 studies: 18 (36.7%) from the original systematic review and 31 (63.3%) from the present update (Figure 1). The design, methods, number of participating patients, and other characteristics of included studies are presented in Table 1. Sample sizes ranged from 18 to 1981 participants with a total of 14,898 participants. Study designs were the following: cross-sectional surveys (32, 65.3%), surveys nested in a longitudinal study (10, 20.4%) and development, validation, and cross-cultural adaptation studies (7, 14.3%). How the questionnaire was administered was described in 38 studies (77.6%) including self-administered (n=16, 42.1%), researcher-administered (n=15, 39.5%), self-administered with help available (n=7, 18.4%).

Missing data management was reported in 19 studies (38.8%). The methods used for handling missing data were complete case analysis (n=12, 63.2%), pair-wise deletion (*i.e.*, analysis when data of interest was available, n=3, 15.8%), other methods (n=4, 21.1%: two studies excluded questionnaires from the analysis if more than 50% of items were missing and two excluded the domain if at least 40% of items were missing).

The methods used for handling missing data were reported in seven studies (43.8%) when the rPATD was self-administered. For the other administration mode, methods were reported in six studies (27.3%). In nine studies (18.4%), the question or domain with the most missing data could be identified. Namely, the question “I spend a lot of money on my medicine” (n=4, 44.4%) and the “Burden” domain (n=3, 33.3%) were most often reported missing.

#### *3.2 Case analyses*

##### *3.2.1. Results from the DeprescriPP dataset (France)<sup>16</sup>*

In total, 1151 (49.9%) questionnaires were received. There were 769 (66.8%) complete rPATD questionnaires. The item with the lowest percentage of missing data was “I think one or more of my medicines may not be working” (91, 7.9%) and the domain with the lowest percentage of missing data was “Involvement” (173, 15.0%). The item with the highest percentage of missing data was “I have had a bad experience when stopping a medicine before” (170, 14.8%) and the most incomplete domain (i.e., with at least one missing item) was “Concerns about stopping” (232, 20.2%). Data were not classified as missing completely at random given Little’s Test of Missingness was significant ( $p=0.019$ ). Missing were classified as missing not at random, as unrelated to another observed variable. The scores of each domain appeared similar regardless of deletion methods or substitution methods (Table 2).

High level of agreement in the “Involvement” and low levels in the “Appropriateness” and “Concerns about stopping” domain were significantly associated with agreement to the global question “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines”, with the same strengths of association, irrespective of the three methods used to handle missing data (Table 3). Regarding the sensitivity analysis, the four domains were significantly associated with the question “I would like to try stopping one of my medicines to see how I feel without it”, irrespective of the three methods used to handle missing data (Table 4).

### *3.2.2. Results from the LESS dataset (Switzerland)<sup>17</sup>*

In total, 306 rPATD questionnaires were completed by participants. There were 268 (87.6%) complete questionnaires. The items with the lowest percentage of missing data were “I have a good understanding of the reasons I was prescribed each of my medicines” and “Overall, I am satisfied with my current medicines” (1, 0.3%) and the domain with the lowest percentage of missing data was “Appropriateness” (9, 2.9%). The items with the highest percentage of

missing data were “I spend a lot of money on my medicines” (8, 2.6%), “I would be reluctant to stop a medicine that I had been taking for a long time” (8, 2.6%), and “I have had a bad experience when stopping a medicine before” (8, 2.6%) and the most incomplete domain was “Concerns about stopping” (17, 5.6%). Following the algorithm from Mirzaei *et al.* <sup>7</sup>, missing data were considered negligible. The scores of each domain appeared similar regardless of deletion methods or substitution methods (Table 5).

Low levels of agreement in the “Appropriateness” and “Concerns about stopping” domains were significantly associated with the global question “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines”, with the same strength of association, irrespective of the three methods used to handle missing data (Table 6).

Regarding the sensitivity analysis, the domains “Appropriateness” and “Involvement” were significantly associated with the question “I would like to try stopping one of my medicines to see how I feel without it”, irrespective of the three methods used to handle missing data (Table 7). The domain “Burden” was significantly associated with this question by using complete case analysis ( $p=0.044$ ) or multiple imputation ( $p=0.038$ ), but not by using personal mean substitution ( $p=0.057$ ).

#### 4. Discussion

The rPATD has been used in 49 studies since its development and validation in 2016, with a two-fold increase in the past three years alone. Missing data and methods for handling them were rarely reported. Our case analyses revealed that methods for handling missing data had a significant impact on rPATD findings, although it was not major.

Despite the existence of guidelines for reporting survey studies, researchers often overlook reporting how they have dealt with missing data, and lack consideration for the implications of handling missing data in their analyses.<sup>12,22</sup> Our systematic review suggest that the same can be said for researchers using the rPATD, since only four out of ten reported how they managed missing data. Our findings suggest that this may relate to the study design and how the questionnaire was administered. Less than half of the studies included in our systematic review self-administered the rPATD, although it was designed this way,<sup>2</sup> and the remaining studies were administered by a researcher or with help available. We found that methods for handling missing data were more often reported when the rPATD was self-administered. A researcher or clinician administering the questionnaire may reduce the amount of missing data but may influence the interpretation of items. It may also lead to social desirability bias with participants reporting more desirable attitudes and less undesirable ones.<sup>23</sup>

Complete case analysis was the most common method to handle missing data. Similarly, a systematic review of questionnaires by Eekhout *et al.* in 2010 found complete case analysis to be the most common method used in 262 studies published in epidemiology journals.<sup>24</sup> However, complete case analysis can only be used when data is missing completely at random to avoid bias.<sup>25</sup> Also, complete case analysis can lead to a reduction in the sample size and a loss of power depending on the level of missingness.

In our case analyses, the different methods for handling missing data did not significantly modify the findings of the primary analysis. For the DeprescriPP study, this can be explained

by having a sample large enough to maintain sufficient statistical power. For the LESS study, there were few missing data which may have been due to recruitment strategy by general practitioners and the fact that the questionnaire could potentially have been administered in the waiting room (*versus* postal survey for the DeprescriPP trial).<sup>17</sup> However, the sensitivity analysis highlighted a minor difference between the three methods for handling missing data in the LESS study. The item “*I would like to try stopping one of my medicines to see how I feel without it*” was significantly associated with the domain “Burden” using complete case analysis and multiple imputation methods but not with person mean substitution method. This illustrated that methods for handling missing data may impact findings in some scenarios and thus, should be reported carefully.

This study comes with several limitations. First, we conveniently selected two deprescribing studies for our case analyses because the co-authors had access to the data. Nevertheless, these data permitted to perform secondary analyses, which adequately showed the effects of different methods used for handling missing data.

Second, we chose to perform our analyses on original data from two questionnaire studies. These two studies permitted to evaluate missing data in the questionnaire under different study designs, settings and administration modes. However, our findings may not be generalizable beyond the primary care setting, and we excluded the following administration modes: online or researcher-administered. A simulation study with several scenarios of missingness rates may be needed to further explore the differences between the methods of missing data for the rPATD questionnaire, similarly to a previous study on quality of life questionnaires.<sup>26</sup>

## **Conclusions**

In this study, we conducted a focused update of the systematic review on studies using the rPATD questionnaire. Additionally, we explored different methods to handle missing data using datasets from two distinct studies to assess their impact on their results. Our findings suggest that administration modes of questionnaire, missing data and methods used to handle missing data should be systematically reported to improve the quality of survey studies, as they may affect rPATD survey results. In some scenarios, the methods used to handle missing data may have an impact on the interpretation of the results on patients' willingness to have medications deprescribed.



## **Registration and protocol**

The update of this systematic review was not registered. The protocol of the original systematic review was registered in PROSPERO (CRD42020150007).

## **Ethics**

The DeprescriPP trial has been approved by the Ethics Committee of the Collège National des Généralistes Enseignants (#08062011). Ethical approval for the LESS study was obtained from the Ethics Committee of the Canton of Bern, Switzerland (Ref. 2017–02188).

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## **Competing interests**

The authors declare that they have no competing interests.

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## **Availability of data and materials**

Data and materials are available upon request of the corresponding author.

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## 6. Figures

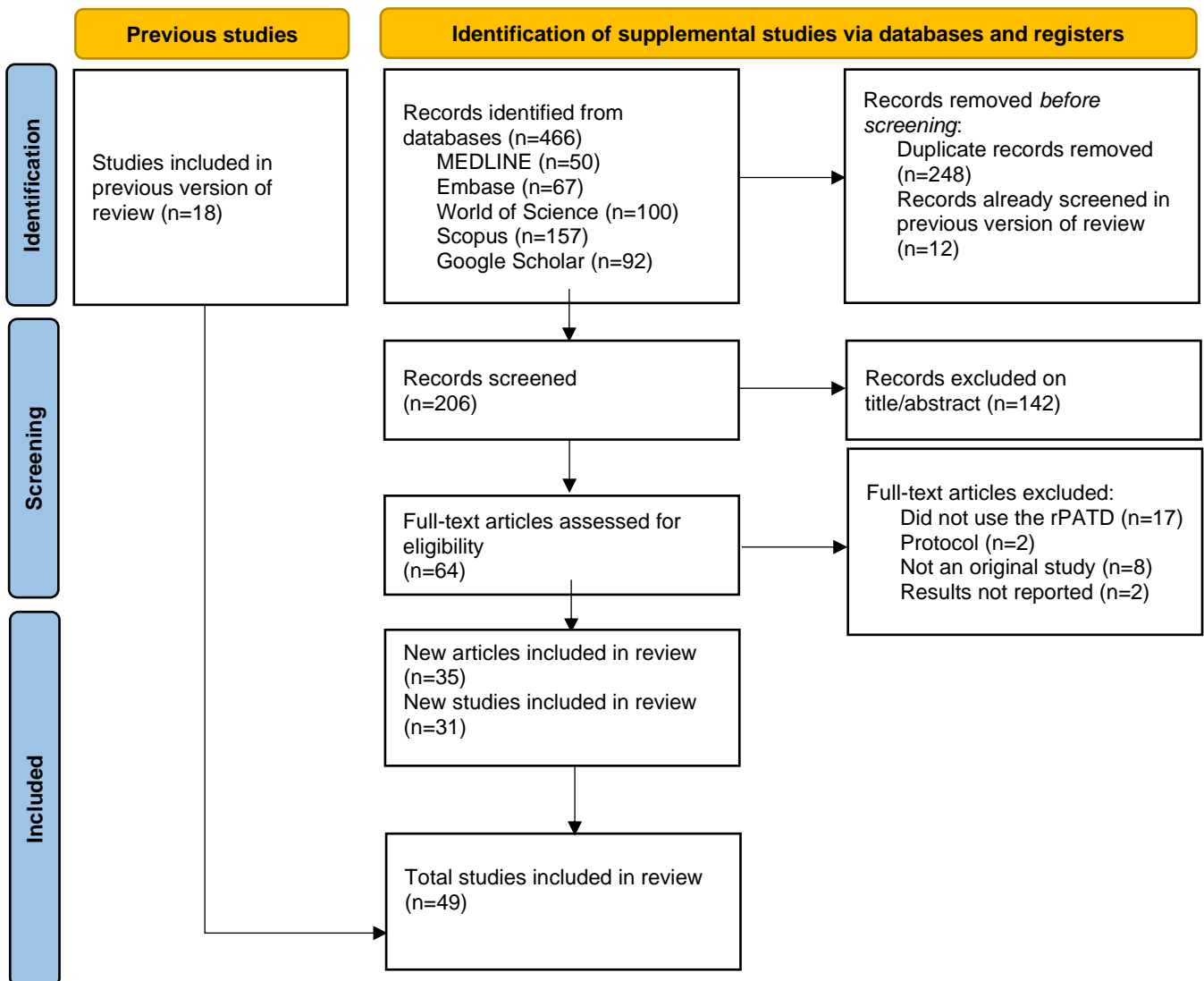


Figure 1: PRISMA flow-chart diagram for the updated systematic review

rPATD: revised Patients' Attitudes Towards Deprescribing

## 7. Tables

**Table 1.** Study characteristics, questionnaire administration and missing data handling

| Source<br>Year<br>Country   | Sample size,<br>Study design                        | Study population   | Questionnaire<br>administration,<br>Setting   | Translated<br>Language | Questionnaire<br>modification<br>how   | Reporting of missing<br>data management   | Item/domain with the<br>highest missing data<br>(proportion)*   |
|---|---|--|---|------------------------|--|---|---|
| Achterhof <i>et al.</i> , 2020,<br>Switzerland <sup>27</sup><br>Rozsnyai <i>et al.</i> 2020,<br>Switzerland <sup>17</sup> | 306, cross-sectional<br>survey                      | Primary care patients<br>≥ 70 years, ≥ 3<br>chronic diseases, ≥ 5<br>long-term<br>medications  | Anonymously self-reported and<br>handed back to<br>practice nurse in GP<br>offices or at home                                     | Yes<br>German          | “12 questions<br>were added to<br>the<br>questionnaire to<br>cover topics<br>important to<br>patients in a<br>primary care<br>setting” | Pair-wise deletion<br>Patients excluded if<br>missing data on global<br>question “willingness to<br>stop if the doctor said it<br>was possible” | Items: “I spend a lot of<br>money on my medicines”,<br>“I have had a bad<br>experience when stopping<br>a medicine before”, “I<br>would be reluctant to stop<br>a medicine that I had been<br>taking for a long time”<br>(2.3%) |
| Alshammari<br><i>et al.</i> , 2021,<br>Saudi Arabia <sup>28</sup>   | 138, cross-sectional<br>survey                      | Hospitalized patients,<br>≥ 60 years, ≥ 3<br>chronic diseases, ≥ 5<br>long-term<br>medications | Interview-based or<br>self-administered<br>questionnaire  | Yes<br>Arabic          | No   | Complete case analysis<br>“24 were not able to<br>complete the<br>questionnaire”  | NA  |
| Bucsa <i>et al.</i> ,<br>2022,<br>Romania <sup>29</sup>   | 219, cross-sectional<br>survey                      | ≥ 65 years, ≥ 1<br>chronic disease, ≥ 1<br>long-term medication                                | NA, Internal<br>medicine<br>departments in<br>university hospital   | Yes,<br>Romanian       | No   | NA  | NA  |
| Bužančić <i>et al.</i> , 2021,<br>Croatia <sup>30</sup>   | 315, cross-sectional<br>survey                      | ≥ 40 years, ≥ 1 long-term<br>medication  | Handed out to<br>participants.<br>Completed at home<br>or at community<br>pharmacies, with or<br>without pharmacist<br>assistance | Yes,<br>Croatian       | No   | NA  | NA  |
| Cardwell <i>et al.</i> ,2019,<br>Ireland <sup>31</sup>  | 200, survey<br>within a non-<br>randomized<br>study | ≥ 65 years, ≥ 10<br>medications  | Self-administered<br>with help available,<br>community setting  | No                     | No   | NA  | Domain “Burden” (19%)   |



|  |  |  |  |              |   |   |    |
|--|--|--|--|--------------|---|---|----|
| Cardwell et al., 2020, Ireland <sup>32</sup>     | 96, survey within a non-randomized study | Primary care patients ≥ 65 years, ≥ 10 repeat medicines                                | NA, General practices  | No           | No  | NA  | NA |
| Cateau et al., 2023, Switzerland <sup>33</sup>   | 73, cross-sectional survey               | Nursing home residents   | NA, nursing home   | Yes, French  | No  | NA  | NA |
| de Juan Roldán et al., 2022, Spain <sup>34</sup> | 60, cross-cultural adaptation            | ≥ 18 years ≥ 5 medications (duration ≥ 6 months)                                       | Self-complete, 3 urbans primary care health centers  | Yes, Spanish | No  | Complete case analysis “Questionnaires with more than 2 blank items would be excluded”      | NA |
| Edelman 2019, Netherlands <sup>35,36</sup>       | 179, cross-sectional survey              | Men ≥ 30 years with lower urinary tract symptoms, taking an alpha-blocker              | NA, NA   | Yes, Dutch   | Yes, Modified questions to create alpha-blocker-specific rPATD factors                              | NA  | NA |
| Gaurang et al., 2021, India <sup>37</sup>        | 156, cross-sectional survey              | Patients ≥ 18 years with chronic diseases, ≥ 1 regular medication and their caregivers | Interviewer assisted in a tertiary health care facility  | Yes, Tamil   | No  | Complete case analysis “28 questionnaires were incomplete and were excluded from the study” | NA |
| Gilpin et al. 2022, United Kingdom <sup>38</sup> | 150, cross-sectional survey              | Hospitalized patients ≥ 65 years, ≥ 1 medication                                       | Completed on the acute admission. Nurse identified appropriate participants. Self-administered, hospital setting | No           | No  | NA  | NA |
| Gnjidic 2019, Australia <sup>39</sup>            | 42, survey in a feasibility study        | ≥ 65 years, taking a benzodiazepine  | Self-administered, hospital setting  | No           | 5 benzodiazepine-specific questions were added  | NA  | NA |
| Growdon et al. 2022, United-States <sup>40</sup> | 422, survey in a cohort study            | ≥ 65 years with possible or probable dementia  | Participants or their proxy respondents undergo annual interviews  | No           | Yes, “selected prompts were: (1) “You feel that you may be taking one or more medicines that you no | NA  | NA |

|  |                                  |  |   |                         | longer need”<br>(belief about<br>necessity of<br>one's<br>medications);<br>(2) “If your<br>doctor said it<br>was possible,<br>you would be<br>willing to stop<br>one or more of<br>your regular<br>medications”<br>(willingness to<br>deprescribe);<br>and (3) “What<br>is the maximum<br>number of pills<br>you would be<br>comfortable<br>taking daily?”” |    |    |
|--|----------------------------------|--|---|-------------------------|---|----|----|
| Hanna et al. 2023,<br>Lebanese <sup>41</sup>       | 262, cross-sectional survey      | Ambulatory adults ≥ 65 years ≥ 1 chronic medication        | Face-to-face interviews   | Yes, Arabic             | No  | NA | NA |
| Ikeji 2019,<br>USA <sup>42,43</sup>                | 19, cross-sectional survey       | ≥ 65 years, taking a PPI                                   | NA, outpatient clinic   | No                      | Modified to focus on proton pump inhibitors   | NA | NA |
| Jungo et al. 2021,<br>Switzerland <sup>44,45</sup> | 323, survey within a cluster-RCT | ≥ 65 years, ≥ 3 chronic disease, ≥ 5 long-term medications | Baseline phone-call of the RCT  | Yes, German             | No  | NA | NA |
| Kua 2020,<br>Singapore <sup>46</sup>               | 615, cross-sectional survey      | ≥ 65 years, ≥ 1 medication and caregivers                  | Self-administered, hospitals, community pharmacies and primary care clinics | No                      | No  | NA | NA |
| Kua 2019,<br>Malaysia <sup>47,48</sup>             | 502, cross-sectional survey      | ≥ 60 years, ≥ 1 medication and caregivers                  | Self-administered, community  | Yes, Mandarin and Malay | No  | NA | NA |

|   |   |   |   |             |      |  |  |
|---|---|---|---|-------------|------|--|--|
| Khasawneh et al. 2022, Jordan <sup>49</sup>       | 719, cross-sectional survey                             | Adults with chronic diseases  | pharmacies and primary care clinics<br>Online questionnaire, posted to social media portals | Y, Arabic   | NA   | NA   | NA   |
| Lee et al. 2022, South Korea <sup>50</sup>        | 500, cross-sectional survey                             | ≥ 65 years, ≥ 6 long-term medications   | Online survey, e-mail to the panel  | Y, Korean   | No   | NA   | NA   |
| Lukacena et al. 2022, United-States <sup>51</sup> | 103, cross-sectional survey                             | ≥ 18 years, ≥ 3 chronic medications   | NA, At the pharmacies on iPads  | N           | No   | Pair-wise deletion<br>“For the regression analysis, those with missing values on key characteristics were excluded”  | NA   |
| Lundby et al. 2021, Denmark <sup>52</sup>         | 300, cross-sectional survey                             | Geriatric inpatients, geriatric outpatients, and nursing home residents with Orientation-Memory-Concentration score of ≥8 | Researcher-administered, in geriatric wards or nursing homes                                | Y, Danish   | No   | Others<br>“Individuals with two or more missing items within the same rPATD factor did not receive a total score.”   | Item: “I feel that I may be taking one or more medicines that I no longer need” (5%) |
| Lundby 2020, Denmark <sup>53,54</sup>             | 162, validation study and cross-sectional survey        | Nursing home residents with Orientation-Memory-Concentration score of ≥8  | Researcher - administered, in nursing homes   | Yes, Danish | No   | Others<br>“If two or more items were missing within a given rPATD factor, the factor was discarded for that patient, that is, no total score was calculated for the factor.” | Item: “I spend a lot of money on my medicines” (7%)                                  |
| Major 2019, Australia <sup>55</sup>               | 66, cross-sectional survey within an intervention study | Average 12 medications  | Self-administered, during pharmacist home visit   | No          | Q7 ? | NA   | NA   |
| Martinez 2020, USA <sup>56</sup>                  | 30, pre-post intervention study                         | Women ≥ 45 years, insomnia symptoms   | Self-administered, community setting  | No          | No   | Complete case analysis<br>“Only participants who completed all components  | NA   |

|  |                                  |  |  |                 |  |  |  |    |
|--|----------------------------------|--|--|-----------------|--|--|--|----|
|  |                                  | and sleep aids usage<br>≥ 3 months   |  |                 |  |  | of the rPATD at baseline<br>and post-intervention were<br>included in this analysis.”                  |    |
| McCarthy et al. 2022, Ireland <sup>57</sup>    | 229, survey within a cluster-RCT | ≥65 years and prescribed ≥15 repeat medicines                                    | Postal questionnaires, at home               | No              | No   |  | NA   | NA |
| Navid et al. 2021, United-States <sup>58</sup> | 134, retrospective cohort study. | Heart failure with preserved ejection fraction                                   | First clinical encounter in the program      | No              | No   |  | Complete case analysis<br>“Given low degree of missingness, we conducted a complete case analysis”     | NA |
| Ng 2019, Malaysia <sup>59</sup>                | 18, cross-sectional survey       | ≥ 18 years diagnosed with Parkinson disease                                      | NA, at a public health talk                  | NA              | NA   |  | NA   | NA |
| Nusair 2020, Jordany <sup>60</sup>             | 358, validation study and survey | ≥ 18 years, ≥ 5 medications  | NA, NA                                       | Yes, Arabic     | No   |  | NA   | NA |
| Nusair et al. 2022, Jordan <sup>61</sup>       | 501, cross-sectional survey      | ≥18 years, ≥ 5 medications, and do not require a caregiver or assistance at home | Interviewed by a clinical pharmacist         | Yes, Arabic     | No   |  | NA   | NA |
| Oktora et al. 2023, Indonesia <sup>62</sup>    | 196, cross-sectional survey      | ≥60 years with type 2 diabetes   | Research assistants, in primary care centers | Yes, Indonesian | Yes, “name of the specific medicines prescribed”   |  | “Complete case analyses were performed”  | NA |
| Omar 2019, Malaysia <sup>63</sup>              | 189, cross-sectional survey      | ≥ 65 years, ≥ 1 medication   | NA, NA                                       | Yes, Malay      | No   |  | Complete case analysis<br>“Those who did not complete the questionnaire were excluded from the study.” | NA |
| Paque 2019, Belgium <sup>64</sup>              | 296, cross-sectional survey      | ≥ 65 years with limited life-expectancy and caregivers                           | Researcher-administered, in nursing home     | Yes, Dutch      | Yes, addition of an item on patients’ willingness to speak to their general practitioner |  | NA   | NA |

|  |   |   |   |                 |   |  |  |
|--|---|---|---|-----------------|---|--|--|
| Pereira et al. 2020, Portugal <sup>65</sup>    | 25, cross-sectional survey                                | ≥ 65 years taking at least 1 medication   | NA  | Yes, Portuguese | about their medications<br>No   | NA   | NA   |
| Pereira et al. 2022, Portugal <sup>66-69</sup> | 192, cross-cultural adaptation and cross-sectional survey | ≥ 65 years and taking at least 1 regular medication                                   | Self-administered or “interview administered by the researcher to some of the participants upon solicitation” | Yes, Portuguese | No  | Pair-wise deletion<br>“Missing values were deleted pairwise”   | Items: “I feel that I am taking a large number of medicines”, “I spend a lot of money on my medicines”, “I would like to try stopping one of my medicines to see how I feel without it”, and “I have had a bad experience when stopping a medicine before” (1.6%)<br>Item: “I spend a lot of money on my medicines” (8%) |
| Rakheja et al. 2022, Canada <sup>70</sup>      | 110, cross-sectional survey                               | ≥ 65 years and ≥ 1 prescribed medication for the past 3 months                        | Self-administered, in community pharmacies and centers  | Yes, French     | No  | NA   |  |
| Reeve 2018, Australia <sup>71</sup>            | 21, development and pilot study                           | ≥ 18 years, ≥ 1 medication, with a diagnosis of mild cognitive impairment or dementia | Researcher-administered, NA   | No              | Yes, rPATDcog   | Others<br>“Returned questionnaires (by mail or submitted online) had to have at least 50% of the questions completed to be included in the analysis” |  |
| Reeve 2019, Australia <sup>72,73</sup>         | 386, validation study cross-sectional survey              | ≥ 65 years, ≥ 1 medication, and caregivers  | Self-administered, at home  | No              | No  | Others<br>“Exclusion from analysis (<50% of questions answered)”   | Domain “Burden” (12.4%)  |
| Reeve 2018, United-States <sup>74</sup>        | 1981, cross-sectional survey                              | ≥ 65 years  | Self-administered, at home  | No              | Yes, 8 items from rPATD and 2 items from PATD, and 4-point Likert-scale | NA   | NA   |

|  |                                  |   |   |              |  |  |   |
|--|----------------------------------|---|---|--------------|--|--|---|
| Reeve et al. 2023, United-States <sup>75</sup><br>Maiyani et al. 2022, United-States <sup>76</sup> | 553, survey within a cluster-RCT | ≥ 65 years, Alzheimer disease and related dementias or mild cognitive impairment, ≥ 1 additional chronic condition, ≥ 5 long-term medications | Self-administered or with help of a caregiver, at home                                      | No           | (deleted “unsure”)<br>Yes, rPATDcog  | Complete case analysis<br>“Missing data were excluded from analysis”   | Items: “I feel that I may be taking one or more medicines that I no longer need” and “Overall, I am satisfied with my current medicines” (1.1%) |
| Roux et al. 2022, France <sup>77</sup>   | 367, Cross-sectional survey      | Community-dwelling or nursing home older adults ≥ 65 years taking ≥ 1 prescribed medications  | Administered by researchers or healthcare professionals , NA                                | Yes, French  | No   | Complete case analysis<br>Score for “Individuals without missing data for all the questions in the corresponding factor” | Domain “Burden” (6.8%)  |
| Roux et al. 2021, France <sup>78</sup>   | 320, Cross-cultural adaptation   | ≥ 65 years ≥ 1 chronic medication (i.e. use ≥ 3 months) and lived in the community or in institutions   | Self-administered with a researcher present, NA   | Yes, French  | No   | Complete case analysis<br>“Questionnaires with at least one missing data were excluded from analyses.”                   | NA  |
| Saka et al. 2022, Nigeria <sup>79</sup>  | 350, Cross-sectional survey      | Ambulatory patients ≥ 65 years, ≥ 5 chronic medications   | Interviewer-administration, Medical outpatient units of two secondary healthcare facilities | Yes, Yoruba  | No   | Complete case analysis<br>“Nine copies (2.3%) were excluded due to missing data”   | NA  |
| Scott 2019, United-Kingdom <sup>20</sup>   | 75, cross-sectional survey       | ≥ 70 years, ≥ 5 medications and caregivers  | Self-administered with help available, at hospital  | No           | Yes, change in 1 item from the “Burden” domain regarding cost of medicines | NA   | NA  |
| Serrano Giménez et al. 2020, Spain <sup>80</sup>   | 42, survey within a cohort study | Patient living with HIV on highly active antiretroviral therapy ≥ 65 years  | Self-reported, follow-up by the Pharmaceutical Care Consultation                            | Yes, Spanish | No   | NA   | NA  |

|   |                              |  |  |              |  |   |    |
|---|------------------------------|--|--|--------------|--|---|----|
| Shrestha et al. 2021, Australia <sup>81</sup> | 385, Cross-sectional survey  | Ambulatory patients $\geq 65$ years, $\geq 1$ regular medication | of Viral Diseases from the Hospital Pharmacy Service.<br>Face-to-face interview, hospitals | Yes, Nepali  | No   | NA  | NA |
| Tan et al. 2022, China <sup>82</sup>          | 1897, Cross-sectional survey | Residents $\geq 65$ years  | Face-to-face interviews, community health centers  | Yes, Chinese | No   | Complete case analysis<br>“We excluded participants with any missing item of the rPATD questionnaire” | NA |
| Tegegn 2018, Ethiopia <sup>83</sup>           | 316, cross-sectional survey  | $\geq 65$ years, $\geq 1$ medication                             | Researcher-administered  | Yes, Amharic | Yes, 4-point Likert-scale (deleted “unsure”) | NA  | NA |

\*reported in the text or based on table of results.

GP: general practitioner; HIV: human immunodeficiency virus; NA: not available; RCT: randomized controlled trial

**Table 2.** Scores of the rPATD domains using “complete domain analysis”, “personal mean score imputation” and “multiple imputation” methods on the DeprescriPP dataset (n=1151)

| <b>Methods of handling missing data</b> | <b>Cases n (%)</b> | <b>rPATD domain mean score</b> | <b>Standard deviation</b> |
|---|--------------------|--------------------------------|---------------------------|
| <b>Complete domain analysis</b>         |                    |                                |                           |
| Burden                                  | 942 (81.8)         | 2.51                           | 1.06                      |
| Appropriateness                         | 952 (82.7)         | 3.87                           | 0.97                      |
| Concerns about stopping                 | 919 (79.8)         | 2.89                           | 0.95                      |
| Involvement                             | 978 (85.0)         | 4.36                           | 0.67                      |
| <b>Personal mean score imputation</b>   |                    |                                |                           |
| Burden                                  | 1067 (92.7)        | 2.54                           | 1.06                      |
| Appropriateness                         | 1062 (92.3)        | 3.86                           | 0.99                      |
| Concerns about stopping                 | 1027 (89.2)        | 2.90                           | 0.95                      |
| Involvement                             | 1046 (90.9)        | 4.34                           | 0.69                      |
| <b>Multiple imputation</b>              |                    |                                |                           |
| Burden                                  | 1113 (96.7)        | 2.56                           | 1.09                      |
| Appropriateness                         | 1105 (96.0)        | 3.83                           | 1.01                      |
| Concerns about stopping                 | 1059 (92.0)        | 2.93                           | 0.99                      |
| Involvement                             | 1067 (92.7)        | 4.34                           | 0.71                      |



**Table 3.** Association of “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” response\* with the four rPATD domains using three different methods on the DeprescriPP dataset.

| Methods of handling missing data      | Crude odds ratio [95% confidence interval] | p-value      |
|---------------------------------------|--|--------------|
| <b>Complete case analysis</b>         |  |              |
| Burden                                | 1.02 [0.83-1.26]                           | 0.847        |
| Appropriateness                       | 0.55 [0.43-0.72]                           | <b>0.000</b> |
| Concerns about stopping               | 0.47 [0.38-0.59]                           | <b>0.000</b> |
| Involvement                           | 1.95 [1.49-2.54]                           | <b>0.000</b> |
| <b>Personal mean score imputation</b> |  |              |
| Burden                                | 0.99 [0.82-1.19]                           | 0.890        |
| Appropriateness                       | 0.54 [0.44-0.67]                           | <b>0.000</b> |
| Concerns about stopping               | 0.49 [0.41-0.59]                           | <b>0.000</b> |
| Involvement                           | 1.83 [1.46-2.28]                           | <b>0.000</b> |
| <b>Multiple imputation</b>            |  |              |
| Burden                                | 0.99 [0.83-1.19]                           | 0.936        |
| Appropriateness                       | 0.53 [0.43-0.66]                           | <b>0.000</b> |
| Concerns about stopping               | 0.50 [0.42-0.60]                           | <b>0.000</b> |
| Involvement                           | 1.86 [1.50-2.33]                           | <b>0.000</b> |

\* “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” was coded 0 (unsure, disagree, strongly disagree) or 1 (agree, strongly agree).

**Table 4.** Association of “I would like to try stopping one of my medicines to see how I feel without it” response\* with the four rPATD domains using three different methods on the DeprescrIPP dataset

| Methods of handling missing data      | Crude odds ratio [95% confidence interval] | p-value      |
|---------------------------------------|--|--------------|
| <b>Complete case analysis</b>         |  |              |
| Burden                                | 1.71 [1.26-2.33]                           | <b>0.001</b> |
| Appropriateness                       | 14.7 [9.50-22.90]                          | <b>0.000</b> |
| Concerns about stopping               | 2.02 [1.49-2.73]                           | <b>0.000</b> |
| Involvement                           | 0.47 [0.32-0.69]                           | <b>0.000</b> |
| <b>Personal mean score imputation</b> |  |              |
| Burden                                | 1.53 [1.17-2.00]                           | <b>0.002</b> |
| Appropriateness                       | 14.90 [10.16-21.85]                        | <b>0.000</b> |
| Concerns about stopping               | 1.83 [1.41-2.36]                           | <b>0.000</b> |
| Involvement                           | 0.49 [0.35-0.69]                           | <b>0.000</b> |
| <b>Multiple imputation</b>            |  |              |
| Burden                                | 1.46 [1.13-1.90]                           | <b>0.004</b> |
| Appropriateness                       | 15.43 [10.61-22.43]                        | <b>0.000</b> |
| Concerns about stopping               | 1.73 [1.35-2.21]                           | <b>0.000</b> |
| Involvement                           | 0.50 [0.36-0.70]                           | <b>0.000</b> |

\* “I would like to try stopping one of my medicines to see how I feel without it” was coded 0 (disagree, strongly disagree) or 1 (unsure, agree, strongly agree).

**Table 5.** Scores of the rPATD domains using “complete domain analysis”, “personal mean score imputation” and “multiple imputation” methods on the on the LESS dataset (n=306)

| <b>Methods of handling missing data</b> | <b>Cases<br/>n (%)</b> | <b>Mean score</b> | <b>Standard deviation</b> |
|---|------------------------|-------------------|---------------------------|
| <b>Complete domain analysis</b>         |                        |                   |                           |
| Burden                                  | 292 (95.4)             | 2.55              | 1.00                      |
| Appropriateness                         | 297 (97.1)             | 3.76              | 0.92                      |
| Concerns about stopping                 | 289 (94.4)             | 2.37              | 0.83                      |
| Involvement                             | 294 (96.1)             | 4.61              | 0.51                      |
| <b>Personal mean score imputation</b>   |                        |                   |                           |
| Burden                                  | 303 (99.0)             | 2.55              | 1.00                      |
| Appropriateness                         | 304 (99.3)             | 3.75              | 0.93                      |
| Concerns about stopping                 | 303 (99.0)             | 2.40              | 0.87                      |
| Involvement                             | 305 (99.7)             | 4.60              | 0.51                      |
| <b>Multiple imputation</b>              |                        |                   |                           |
| Burden                                  | 306 (100.0)            | 2.55              | 1.00                      |
| Appropriateness                         | 305 (99.7)             | 3.75              | 0.93                      |
| Concerns about stopping                 | 306 (100.0)            | 2.40              | 0.87                      |
| Involvement                             | 306 (100.0)            | 4.60              | 0.51                      |

**Table 6.** Association of “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” response\* with the four rPATD domains using three different methods on the LESS dataset

| Methods of handling missing data      | Crude odds ratio [95% confidence interval] | p-value      |
|---------------------------------------|--|--------------|
| <b>Complete case analysis</b>         |  |              |
| Burden                                | 1.05 [0.69-1.60]                           | 0.826        |
| Appropriateness                       | 0.60 [0.37-0.97]                           | <b>0.036</b> |
| Concerns about stopping               | 0.45 [0.31-0.66]                           | <b>0.000</b> |
| Involvement                           | 1.41 [0.75-2.64]                           | 0.290        |
| <b>Personal mean score imputation</b> |  |              |
| Burden                                | 1.07 [0.72-1.60]                           | 0.729        |
| Appropriateness                       | 0.59 [0.37-0.93]                           | <b>0.023</b> |
| Concerns about stopping               | 0.44 [0.31-0.63]                           | <b>0.000</b> |
| Involvement                           | 1.40 [0.79-2.51]                           | 0.252        |
| <b>Multiple imputation</b>            |  |              |
| Burden                                | 1.03 [0.70-1.53]                           | 0.864        |
| Appropriateness                       | 0.56 [0.36-0.89]                           | <b>0.013</b> |
| Concerns about stopping               | 0.45 [0.32-0.64]                           | <b>0.000</b> |
| Involvement                           | 1.40 [0.78-2.50]                           | 0.255        |

\* “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” was coded 0 (unsure, disagree, strongly disagree) or 1 (agree, strongly agree).

**Table 7.** Association of “I would like to try stopping one of my medicines to see how I feel without it” response\* with the four rPATD domains using three different methods on the LESS dataset

| Methods of handling missing data      | Crude odds ratio [95% confidence interval] | p-value      |
|---------------------------------------|--|--------------|
| <b>Complete case analysis</b>         |  |              |
| Burden                                | 1.68 [1.01-2.79]                           | <b>0.044</b> |
| Appropriateness                       | 24.8 [10.73-57.17]                         | <b>0.000</b> |
| Concerns about stopping               | 1.54 [0.95-2.49]                           | 0.080        |
| Involvement                           | 0.37 [0.17-0.79]                           | <b>0.011</b> |
| <b>Personal mean score imputation</b> |  |              |
| Burden                                | 1.59 [0.99-2.57]                           | 0.057        |
| Appropriateness                       | 23.91 [10.79-53.00]                        | <b>0.000</b> |
| Concerns about stopping               | 1.49 [0.96-2.29]                           | 0.074        |
| Involvement                           | 0.38 [0.19-0.76]                           | <b>0.006</b> |
| <b>Multiple imputation</b>            |  |              |
| Burden                                | 1.63 [1.03-2.59]                           | <b>0.038</b> |
| Appropriateness                       | 24.15 [11.11-52.52]                        | <b>0.000</b> |
| Concerns about stopping               | 1.52 [0.99-2.33]                           | 0.053        |
| Involvement                           | 0.39 [0.19-0.78]                           | <b>0.008</b> |

\* “I would like to try stopping one of my medicines to see how I feel without it” was coded 0 (disagree, strongly disagree) or 1 (unsure, agree, strongly agree).