Measuring Quality of Life in Deprescribing Trials: A Scoping Review

Running head: Quality of life and deprescribing

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Declarations

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Conflicts of interest

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Availability of data and material

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Author contributions

All authors meet the ICMJE authorship criteria and approve submission. The study was conceived by CL, WT, JP, SS, and FM. All authors contributed to design of the study. WT, AB, CL, HW, JAH, CX, SE, and FM collected data. All authors interpreted results. All authors contributed to drafting and critical revisions of the manuscript and approved the final submission.

Abstract

Background

Quality of life (QoL) is an important outcome to capture in clinical trials evaluating deprescribing interventions.

Objective

To conduct a scoping review to examine how QoL has been measured in deprescribing trials among older people and identify potentially relevant QoL scales, to better inform QoL measurement in future deprescribing trials.

Patients and Methods

We searched MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials, Google Scholar, Epistemonikos, ClinicalTrials.gov, and reference lists of eligible studies (from inception to October 2023). We included randomized and non-randomized comparative studies with a control group which evaluated deprescribing and polypharmacy reduction interventions in people ≥65 years of age and measured QoL as an outcome. We also included studies describing development and validation of QoL scales related to deprescribing, polypharmacy, or medication burden in adults ≥18 years of age. Two independent reviewers screened titles and abstracts, then full texts. Two independent reviewers extracted data from 25% of eligible studies in order to verify agreement, then a single reviewer extracted data from the remaining studies which a second reviewer cross-checked. We critically appraised scales based on the COSMIN checklist.

Results

We retrieved 7290 articles, of which 52 were eligible for inclusion, including 44 deprescribing trials and 8 scale development studies. From these studies, we found 21 scales which have been used in the context of deprescribing/polypharmacy (12 generic scales used in clinical trials and 9 medication-specific scales). Variations of the generic EQ-5D were the most used scales. The measurement properties of scales for capturing changes in QoL from deprescribing were uncertain. Medication-specific QoL scales have not been employed in deprescribing clinical trials and thus, their performance in this context is also not clear.

Conclusions

Several existing QoL scales have been applied to the context of deprescribing/polypharmacy clinical trials, and new scales specific to the problem have been proposed. If deprescribing does impact QoL, our findings suggest it is uncertain whether existing QoL scales can practically and reliably capture such a change or whether any scale is best. However, this review compares various aspects of the scales that researchers and clinicians can consider in decisions about measuring QoL in deprescribing trials, and in planning future research.

Protocol Registration

Open Science Framework: osf.io/aez6w

Key points

- Quality-of-life has increasingly been measured in deprescribing trials using a variety of scales, and several related scales have been developed relevant to polypharmacy and treatment burden

- This review describes and appraises the measurement properties and performance of available scales and provides insight for clinicians and researchers considering quality-of-life measurement in the context of deprescribing research.

1. Introduction

Polypharmacy has been defined as the prescription of numerous medications (often 5 or more), being on unnecessary medications, or medications where medication harms outweigh benefits.[1] Polypharmacy increases the risk of many negative health outcomes, including adverse drug events (ADEs) and hospitalizations.[2] Polypharmacy may also negatively impact functional status and ability to live according to goals and preferences, i.e., quality of life (QoL).[3] Deprescribing is the structured, supervised process of discontinuing or reducing medications that are unnecessary, where harms outweigh benefits, or medications do not align with a patient's care goals or health context.[4] Understanding the impact of deprescribing on QoL is one of the outcomes that is critical to demonstrating the value of deprescribing.[5–7] One way to understand impact on QoL is through controlled trials of deprescribing interventions. Historically, trials have not always captured QoL as a study outcome[8] though it is increasingly being measured.[9,10] Even when QoL is measured in deprescribing trials, changes or improvements have been difficult to demonstrate.[8,11] Further, collecting measures of QoL can be challenging, for example, requiring large sample sizes with long-follow ups, with participants potentially requiring surrogate responders or translations. This means that measuring QoL can be expensive, time-intensive, and is not always feasible.[12]

Despite its importance, and the known barriers, the optimal approach to measuring QoL in deprescribing trials has not been explored to date (e.g., which scale to use, timing of scale administration). A 2022 scoping review identified various medication-related QoL scales[13] , however, it did not address deprescribing trials specifically.[8,14,15] Therefore, to optimize and increase the measurement of QoL in deprescribing trials (and ultimately inform practice), we need to ensure we measure QoL efficiently and appropriately by adapting to the context of trial participants, especially older adults with chronic health problems taking multiple medications. The aim of this scoping review was to examine how QoL has been measured in deprescribing

research to date and describe the strengths and limitations of existing scales. This examination of current evidence can help inform measurement of QoL for future large-scale deprescribing controlled trials among older adults.

2. Methods

Our scoping review was guided by the following question: How has QoL been measured in deprescribing research among older persons? We were particularly interested in older persons, as this population is at the highest risk of medication-related harm and is where deprescribing is most relevant.[16,17] We used scoping review methods because our aim was to investigate how research has been conducted (i.e., how QoL has been collected in past trials) and to identify gaps in research.[18–20] Reporting and conduct of our review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Scoping Review extension (PRISMA-ScR) checklist and Johanna Briggs Institute Manual for Evidence Synthesis.[21,22] The protocol was registered at Open Science Framework (osf.io/aez6w).[23]

2.1 Criteria for Inclusion and Exclusion of Studies

2.1.1 Type of studies

We included studies which evaluated a deprescribing or polypharmacy reduction intervention (we included polypharmacy management/medication optimization trials only if deprescribing was a major component of the intervention). Eligible studies were clinical trials, which could be either randomized controlled trials or controlled trials, provided they evaluated an intervention. The studies must have used generic QoL scales, medication-specific QoL scales, or scales that examined the effect of treatment burden on daily life. We also included studies that described the development and validation of a QoL scale relevant to deprescribing (i.e., scales developed specifically in the context of deprescribing, polypharmacy, or medication burden). There were no geographical limitations and no limitation on language of publication.

2.1.2 Population

Eligible studies were those conducted in older adults (either all participants ≥65 years old or mean/median age ≥65 years; we were flexible with this definition so we could include studies which broadly addressed older adults). The studies could be from any care setting such as primary care, hospital, long-term care, palliative care, and hospice. For scale development studies, we included scales developed in people ≥18 years of age. We allowed for a broader age range here as relevant scales may not necessarily be developed specifically in older adults.

2.1.3 Intervention

Eligible studies involved a deprescribing (stopping, tapering, dose reduction) intervention or polypharmacy reduction management intervention where deprescribing was a major component. This could include, but was not limited to, decision support tools, a medication review process, patient and/or provider education, or a multi-faceted intervention (i.e., combinations of approaches). There were no limitations on study design for scale development/validation studies. We excluded medication-specific withdrawal studies (e.g., trials that examine stopping versus continuation of a specific medication or medication class) as our focus was specifically on deprescribing or polypharmacy reduction interventions.[24] We also excluded trials that addressed polypharmacy if there was not a clearly described deprescribing component.

2.1.4 Outcome

Eligible studies measured and reported QoL or QoL-related concepts as an outcome using a scale. QoL could be measured using generic scales (e.g., EQ-5D-5L) or scales adapted or specifically designed for the context of deprescribing, polypharmacy reduction, or medication burden (e.g., the medication-related burden QoL scale[25]).

2.2 Search Methods

A medical librarian (DS) searched the following databases from inception to October 2023: Ovid MEDLINE, Ovid Embase, The Cochrane Central Register of Controlled Trials (CENTRAL, via Ovid), APA PsycINFO (via EBSCO), Google Scholar (via Harzing's Publish or Perish)[26], and ClinicalTrials.gov. We also searched Epistemonikos for related systematic reviews and hand searched the reference lists of reviews on medication-related QoL.[13] We searched the reference lists of eligible studies to find additional studies. We present the database searches in Online Resource 1. Search terms included both subject headings and keywords and were tested against known articles meeting eligibility criteria (e.g., RCTs which measured quality of life, and known scales related to treatment burden)

2.3 Study selection

Screening for eligible studies was conducted using Covidence, a web-based systematic review platform. Following the search and removal of duplicate studies, each title and abstract was screened for eligibility by at least two independent reviewers (WT, CL, AB, HW, JH, FM). The full text version of relevant articles identified in title and abstract was then assessed by two of the reviewers (WT, CL, AB, HW, JH, FM) to identify a final set of eligible studies. Disagreements were resolved by a third reviewer who was not involved in the original decision.

2.4 Data Extraction and Synthesis

Data was extracted from included studies into a piloted, structured data form in Microsoft Excel. A total of 25% of eligible studies were extracted in duplicate. A third reviewer compared the extracted results for consistency and resolved discrepancies. Given the high level of consistency, the remaining articles were extracted by a single reviewer and checked by a second reviewer. For deprescribing trials, we extracted the author, year of publication, country of origin, aims, methods, characteristics of participants, intervention and comparator, QoL scale used, whether the scale was generic or medication-focused, and QoL results. We also identified whether

interventions led to a reduction in medication use or inappropriate medication use compared to control, and summarized QoL results in this subgroup.

For both the deprescribing trials and studies describing development and validation of relevant QoL scales, we extracted data about the scales themselves. This involved reviewing relevant development and validation studies for the eligible scales identified by a supplemental search. Once we identified eligible scales from our search, we conducted non-systematic, post-hoc supplementary searches to obtain further information about scales for the data extraction step. For medication-focused scale development and validation studies, one author (WT) screened all of the Google Scholar citations ("Cited By") for each eligible original scale development study to identify further data about the scales. For generic scales, one author (WT) searched MEDLINE with the name of the scale and the keywords "deprescribing OR polypharmacy" to identify potentially relevant development or validation studies. The search was limited for practical purposes given we had already carried out a systematic search for the main study question. We considered a study relevant if it validated an existing generic scale specifically in the context of polypharmacy or deprescribing. This approach to identifying additional derivation and validation studies was done post-hoc.

Each eligible scale was critically appraised by a single author (one of WT, CL, FM) using two separate processes based on the COSMIN checklist. For medication-specific development studies, we performed our own critical appraisal using a modified version of the COSMIN checklist (Online Resource 2), which assesses the methodological quality of studies on measurement properties of patient-reported outcome measures.[27] For generic scales, we used the COSMIN critical appraisal results from an existing systematic review on measuring QoL in older adults, which examined three aspects of scale quality: validity, reliability, responsiveness.[28] We

chose to use this existing systematic review's critical appraisal results for pragmatic reasons, balancing team workload and capacity.

3. Results

A PRISMA flow diagram is shown in Figure 1. Our search retrieved 7290 titles and abstracts after de-duplication. We reviewed 296 full text articles and identified 10 potentially relevant articles through citation searching from full text articles. A total of 52 studies met eligibility criteria, including 44 deprescribing trials and 8 scale development studies.

Characteristics of eligible studies are in Table 1. The mean/median age of participants in trials ranged from 68 to 88 years of age. The interventions in the trials were heterogeneous, and included computerized decision support, multidisciplinary medication reviews, tools, education, and training, among others. In deprescribing trials, the generic QoL scales EQ-5D-5L (13/44; 30% of studies) and -3L (11/44; 25% of studies) were the most common QoL scales—a further 9 out of 44 (20%) studies used the "EQ-5D" without specifying which version (Figure 2). In 14 out of 44 (32%) studies, EQ-VAS was reported. Follow-up ranged from 4 weeks to 24 months.

In 4 out of 44 studies (9%), deprescribing led to a statistically significant improvement in QoL when compared to the control. Of the 4 studies that showed a difference, one study used the generic scale 15D to measure QoL, two studies used EQ-5D-3L, one study used EQ-VAS. There was no statistically significant difference in QoL in 38 out of 44 studies (86%), and mixed results in 2 out of 41 studies (4.9%) (e.g., multiple QoL scales used and/or different timepoints with conflicting results). Two studies measured QoL as a primary outcome and both found deprescribing did not affect QoL. In other studies, QoL was not measured as a primary outcome.

Among the 40 studies which measured medication use outcomes, deprescribing interventions led to a reduction in medication use or potentially inappropriate medication use in 27 (68%). In this

subgroup of 27 studies, deprescribing interventions led to a statistically significant improvement in QoL in 3 (11%).

In scale development studies, the mean/median age of participants ranged from 51 to 71 years of age. Scale development studies included people with multiple chronic conditions and/or people taking multiple medications. Scales were developed using different methods, including interviews, literature reviews, and authors conducted validity and/or psychometric testing on scales.

Across all eligible studies, we identified 21 scales (12 generic scales and 9 medication-specific scales) which have been used or developed to evaluate QoL (or aspects related to QoL) in the context of deprescribing/polypharmacy reduction. Details of scales and quality assessment results are in Table 2. Of 9 medication-specific scales, three scales specifically assessed medication-related QoL. The other six scales were primarily aimed at assessing treatment burden but captured aspects related to QoL in the context of deprescribing and polypharmacy management and were thus included. For 9 medication-specific scales the number of items ranged from 10 to 60 and the time to complete was reported for one scale. For 12 generic scales the number of items ranged from 1 to 36, and the time to complete ranged from <5 minutes to 15 minutes for the 10 scales that reported time to complete. Our COSMIN-based quality assessment found varying quality among the scales (Figure 3). Most of the generic scales had their measurement properties validated in older adults (Figure 3); however, the EQ-5D-5L and -3L were the only generic scales we identified which have been examined in the context of polypharmacy and deprescribing specifically. For generic scales, EQ-5D-5L and EQ-5D-3L were found to have “excellent” validity and reliability among older adults and “good” responsiveness. The generic scales 15D and ICECAP-O were both rated as having “good” validity, “good” reliability, and “good” responsiveness among older adults. In contrast, the QoL-AD scale was

rated as having “fair” validity, “poor” reliability, and “unclear” responsiveness. For medication-specific scales, we examined 10 aspects of quality. For medication-specific scales, the PROMPT-QoL and MTBQ were both rated as “excellent” in 8 out of 10 aspects while the brief PETS and TBQ were rated as “excellent” in 7 out of 10 aspects, the LMQ-3 was rated as “excellent” in 6 out of 10, and the MRQoL in 3 out of 10. The medication-specific scale MRB-QoL was rated as “excellent” for 2 out of 10 aspects.

4. Discussion

4.1 Summary of findings

Our scoping review identified 21 scales that have been either used in deprescribing trials or developed to examine QoL-related concepts relevant to deprescribing. These included generic QoL scales, medication-specific QoL scales, and scales that examined the effect of treatment burden on daily life. The EQ-5D versions were the most commonly used scales in these trials. The scales varied in terms of quality, number of items, time to complete, concepts measured, and specificity to deprescribing.

4.2 Considerations for measuring QoL in deprescribing trials

4.2.1 Generic QoL scales in the context of deprescribing

Bhaduri et al. examined the psychometric properties of the EQ-5D-5L and -3L in persons aged ≥70 years with polypharmacy within the OPERAM trial,[10] and concluded both were similarly valid, and responsive to participant changes in function as measured by the Barthel index.[15] Only 62% of intervention participants had a medication stopped in this trial. Further, the Barthel Index specifically examines activities of daily living and not all aspects of QoL. Thus, the responsiveness to any changes in QoL that occur from deprescribing is still not clear from this analysis. A 2022 systematic review[29] of EQ-5D-5L and EQ-5D-3L in persons ≥75 years old (not specific to deprescribing or medication optimization studies) questioned the responsiveness of these scales to detect clinical changes over time, suggesting that the responsiveness of the -5L is unclear and that the -3L is "hardly able to adequately detect clinical changes over time" while also noting possible ceiling effects. The 2022 systematic review also highlighted how these issues are common among other generic QoL scales in older adults, citing the SF-36 and SF-12 as further examples. Authors further noted inconsistent results around the validity or reliability of the EQ-5D-3L and -5L. This is in contrast with Siette et al. whose 2021 systematic review

concluded that the EQ-5D-3L and -5L had excellent validity and reliability and good responsiveness according to COSMIN criteria.[28] Thus, even though the generic EQ-5D scales have been widely used in deprescribing research to date, their ability to detect changes in QoL from deprescribing is uncertain due to inconsistent evidence. Since other generic scales have not been tested in the context of deprescribing or polypharmacy research, their performance and responsiveness in this field is also uncertain. Further evaluation of responsiveness and performance under deprescribing circumstances would be helpful.

4.2.2. Deprescribing intervention effectiveness

In most trials (91%) identified, no difference in QoL was detected after deprescribing interventions, which is something that has been noted in evidence syntheses of the effects of deprescribing interventions to date.[8] It remains unclear whether this is due to insufficient sensitivity of existing scales to detect differences in QoL or some other issue. Lack of impact on QoL may not be related to intervention effectiveness. We found that even in the subgroup of trials where deprescribing interventions were effective in reducing medication use, most trials (89%) still did not show impact on QoL. Further, we identified two trials with QoL as a primary outcome, and both found no difference in QoL after a deprescribing intervention.[30,31] Most trials have not been adequately powered to detect QoL differences.

4.2.3 Use of medication-specific scales in trials

The medication-specific scales we identified tended to address issues related to treatment burden specifically (that is, they were not specifically designed to address polypharmacy nor deprescribing but the related concept of treatment burden). While not all scales directly captured QoL, they did capture how medications affected daily life, and were thus included. The use of these medication-specific scales in the context of deprescribing have also not been widely explored. Jennings et al. examined use of the medication-specific MRQoL in community-

dwelling older adults with polypharmacy and found that the scale did not correlate with the number of daily medications or potentially inappropriate medications.[32] Thus, these authors surmised that usefulness and feasibility of using the MRQoL was doubtful. We found that the time to complete most of the medication-specific scales was not clearly reported in development/validation studies. Some of these scales had a large number of questions, thus the practicality of using many of the medication-specific scales in a clinical trial remains doubtful.

4.2.4 Factors to consider when assessing the impact of deprescribing on quality of life

Any impact of deprescribing on QoL may depend on the medication(s) being deprescribed as part of an intervention as well as the individual patient (e.g., number of chronic conditions, concomitant medications). For example, deprescribing a multivitamin or preventive medication that is well-tolerated may have no effect on perceived QoL. Subtle changes in cognition from deprescribing anticholinergics may also not appear on generic QoL scales such as EQ-5D scales. Patients may also not link specific medications or pill burden to their QoL. While polypharmacy itself appears to be negatively associated with QoL, it is unclear whether this is due to the total number of medications or due to specific medications in a person's regimen (for example, those causing side effects).[33,34] Simply reducing the number of pills someone takes alone may not necessarily drive a change in QoL. Inability to detect differences in QoL after deprescribing may also reflect patients' diverse values and preferences, or medical complexity. Patients have divergent views on polypharmacy, with some finding medications beneficial and necessary, and others preferring to be on fewer medications.[35] Deprescribing may be viewed as "taking something away" and thus may result in different and unique perceptions from patients compared to starting treatment.[36] If patients are tolerating medications and are not concerned about polypharmacy, they may not perceive any benefit to being on fewer medications. However, patients with high medication burden who suffer from side effects may experience a large impact on QoL following deprescribing (such cases are commonly encountered clinically in

geriatric settings[37]). The fact that clinical trials tend to report an average effect could dilute recognition of a potential benefit that may be seen among persons who prefer being on fewer medications or who experience actual adverse effects. Reducing the number of medications someone takes without affecting QoL has been suggested as a positive outcome alone[12]; however, the extent to which patients themselves believe this has not been examined to our knowledge.

4.2.5. Timing of scale administration

The timing of scale administration (e.g., follow-up period in trials) in relation to when a medication was deprescribed may also be important, something which has been examined in oncology research[38,39] but not in the context of deprescribing or polypharmacy. The duration of follow-up, and timing of QoL measurement, varied in trials we identified. The relationship between a medication change and a possible QoL improvement may depend on the individual medication and patient circumstance. A scale may be administered months after a medication change is made, making it difficult to capture any effect of deprescribing. For some medication changes, such as a long benzodiazepine taper, any QoL improvement may not be seen for several months after deprescribing and if follow-up occurs shortly after deprescribing such improvements may not be measured. Ideally any QoL changes would be sustained long-term and could be captured months after deprescribing. However, in medically complex older adults, health status can change frequently and suddenly. Thus, it may be challenging to clearly relate a medication change to a change in QoL over a longer period of follow-up. Further, conducting a long follow up may not be feasible.

4.3 Limitations

We conducted a comprehensive search strategy to identify QoL scales relevant to deprescribing interventions, including grey literature search and a search of clinical trials databases. In

balancing comprehensiveness and pragmatism, our review may have excluded relevant QoL scales. Further, for practical reasons (time, capacity), only one reviewer critically appraised studies. We identified many studies at the full text stage which aimed to address polypharmacy but did not have a clear deprescribing component. We elected to exclude these studies as they may not have necessarily examined QoL changes which occurred because of stopping or reducing medications. We aimed to assess the effect of the deprescribing process or deprescribing interventions on QoL as opposed to the effect of deprescribing individual medications. However, as discussed above we recognize the QoL may be more associated to individual medications/conditions than others. Thus, we may have excluded potentially relevant QoL scales by limiting our search only to studies which examine deprescribing interventions/processes.

We conducted quality assessment of identified scales to further contextualize our findings. We used a modified version of the COSMIN criteria to appraise scales rather than the full version. Thus, our quality assessment may have missed important factors related to measurement properties of the existing scales. However, our modified version prioritized criteria judged to be most relevant to deprescribing.

4.4 Future directions

QoL has been recognized as an important outcome to capture in deprescribing trials.[5,6] Our review can be used by researchers and clinicians to consider how to measure QoL when planning their deprescribing trials. Future work in this area could investigate the myriad uncertainties that exist. This may include investigating whether generic or medication-specific QoL scales are most appropriate or whether QoL assessment may be tailored to individual medication(s) being deprescribed with an intervention. Given that many medication-specific QoL scales have not been tested in deprescribing trials, future trials may consider implementing some of these scales.

Finally, our findings will also inform future performance testing or modification of existing scales, or development of new scales to measure QoL in deprescribing research.

5. Conclusion

We identified 21 QoL scales that have been used or developed in deprescribing-related research. If deprescribing has any impact on QoL, our findings suggest that it is not currently clear whether existing QoL scale would be able to capture such a change nor whether any particular scale is better suited for this purpose. However, by mapping the properties of existing scales, our findings can help researchers and clinicians planning and conducting deprescribing trials, and provide insight for future deprescribing research.

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Tables and Figures

Fig 1. PRISMA flow diagram

Table 1. Characteristics of included studies (N=44 intervention studies and 8 scale development studies).

Intervention studies								
Study	**Design (n)**	**Setting**	**Age (SD or IQR)[a]**	**Key Participant Characteristics**	**Intervention**	**Reduction in medications?[b]**	**Scale and effect on QoL**	**Follow-up[c]**
Anderson 2020[40]	RCT (n=150)	Community	74 (11)-77 (12)	≥ 5 medications	GP training, patient-GP consultation, and pharmacist medication review	✓	EQ-5D-5L, EQ VAS ✗	4-6 months
Ashizawa 2022[41]	Pros Obs (n=1260)	LTC	86 (8)	--	Team-based medication optimisation	✓	EQ-5D-5L ✗	12 months
Balsom 2020[42]	RCT (n=45)	LTC	84 (NR)	--	Medication review by pharmacist	✓	RAI-MDS scores ✗	6 months
Beer 2011[43]	RCT (n=44)	Multiple	80 (11)	≥ 1 negative symptom ascribable to the drug	Systematic deprescribing intervention based on list of target drugs	NR	SF-36, EQ-VAS ✗	NR
Bladh 2011[44]	RCT (n=386)	Hospital	81 (15)-82 (11)	--	Computer-assisted medication review with report sent to patient and GP	✓	EQ-5D, EQ-VAS ✗	6 months
Blum 2021[10]	RCT (n=2008)	Hospital	79 (10)	≥ 5 long-term medications	CDSS-supported medication optimisation by pharmacist and physician	✗	EQ-5D ✗ EQ-VAS ✓	12 months
Bryant 2011[45]	RCT (n=498)	Community	75-76 (NR)	≥ 5 medications	Pharmacist medication review and meeting with GP	✓	SF-36 ✗	6 months
Callegari 2022[46]	RCT (n=217)	LTC	83 (8)-85 (9)	Excluded if medication review within 3 months prior to start	Physician education and physician medication review using NorGeP-NH	✗	QUALID ✗	12 weeks
Campins 2017[47]	RCT (n=503)	Community	79 (6)	≥ 8 medications	Clinical pharmacist recommendations based on GP-GP algorithm and STOPP/START	✓	EQ-5D[d] ✗	6 months
Cateau 2021[48]	RCT (n=62)	LTC	84 (10)-87 (11)	≥ 5 medications	Pharmacist medication review followed by plan developed by multidisciplinary team	✗	EQ-5D-5L ✗	4 months
Curtin 2020[49]	RCT (n=130)	Hospital	84 (6)-86 (6)	Advanced frailty, ≥5 medications	STOPPFrail guided deprescribing plan communicated to physician	✓	QUALIDEM, ICECAP-O ✗	3 months
DelCura-Gonzalez 2022[50]	RCT (n=593)	Community	70 (3)	≥ 5 medications	GP training	✓	EQ-5D-5L, EQ-VAS ✗	12 months
Etherton-Beer 2023[51]	RCT (n=303)	LTC	85 (8)	≥1 medication	Structured deprescribing protocol applied by pharmacists, GP agreement	✓	EQ-5D-5L ✗	12 months
Frankenthal 2014[52]	RCT (n=359)	LTC	83 (9)	≥ 1 medication	Pharmacist medication review using STOPP/START	✓	SF-12 ✗	12 months
Gillespie 2017[53]	RCT (n=196)	Community	76 (5)-77 (5)	≥ 1 inappropriate prescription by a pharmacist	Academic detailing and web-based algorithm for medication review	✓	EQ-5D-3L ✗	12 months

Grischott 2022[54]	RCT (n=609)	Hospital	78 (NR)	≥ 5 medications	Medication review and customized letters to GPs	✗	EQ-5D-3L, EQ-VAS ✗	6 months
Jodar-Sanchez 2015[55]	RCT (n=1403)	Community	75 (7)	≥ 5 drugs medications	Pharmacist training	✓	EQ-5D-3L ✓	6 months
Kornholt 2022[30]	RCT (n=408)	Outpatient	81 (7)	≥9 medications	Clinical pharmacologist medication review communicated to patients, physicians	✓	EQ-5D-5L, EQ-VAS ✗[f]	13 months
Lenaghan 2007[56]	RCT (n=136)	Community	84-85 (NR)	≥ 4 medications	Pharmacist medication review and meetings with pharmacist and GP	✓	EQ-5D, EQ-VAS ✗	6 months
Lin 2018[57]	RCT (n=178)	Outpatient	78 (6)	> 6 medications, ≥3 chronic diseases	Physician-pharmacist medication review	NR	EQ-5D-3L, EQ-VAS ?	12 months
Liou 2021[58]	RCT (n=100)	LTC	86 (4)-87 (6)	≥ 5 medications	Pharmaceutical care services	✓	EQ-5D-3L, EQ-VAS ✗	18 months
Mahlknecht 2021[59]	RCT (n=579)	Community	81 (7)	≥ 8 medications	Multidisciplinary medication review	✗	EQ-5D-5L, EQ-VAS ✗	24 months
Mangin 2023[60]	RCT (n=37)	Community	79 (4)-80 (6)	≥5 medications	TaperMD decision support tool	✗	EQ-5D-5L ✗ SF-36 ✗	6 months
McCarthy 2022[61]	RCT (n=404)	Community	76 (7)	≥15 medications	GP training	✓	EQ-5D-5L ✗	6 months
McDonald 2022[9]	RCT (n=6693)	Hospital	78 (13)	≥5 medications	Individualized deprescribing reports to physicians	✓	EQ-5D-5L ✗	30 days
Moga 2017[62]	RCT (n=50)	Unknown	78 (7)	≥1 anticholinergic drug	Physician-pharmacist MTM	✓	SF-36 ✗	8 weeks
Muth 2016[63]	RCT (n=230)	Community	75 (6)-76 (7)	≥ 5 medications	Patient interview, computer-assisted medication review by GP	✗	EQ-5D[d] ✗	12 weeks
Muth 2018[64]	RCT (n=505)	Community	72 (7)	Taking ≥5 medications	CDSS-assisted medication review by GP	✗	EQ-5D[d] ✗	9 months
Olsson 2012[31]	RCT (n=150)	Hospital	83 (5)	Ready for discharge, ≥ 5 medications	Prescription review letter send to GP and patient	✗	EQ-5D-3L, EQ-VAS ✗[f]	12 months
O'Mahony 2020[65]	RCT (n=1,537)	Hospital	78 (12)	Admitted under the care of specialist departments other than geriatric medicine	Software-guided reports to physicians on ways to optimize medications	✗	EQ-5D-3L ✗	12 weeks
Pitkala 2014[66]	RCT (n=227)	LTC	83 (7)	≥1 medication and life expectancy > 6 months	Nurse training	✓	15D ✓	12 months
Polinder 2016[67]	RCT (n=612)	Community	76 (7)	Visited the ED due to a fall, use ≥ 1 FRIDs, MMSE score of at least 21	Research physician assessment of FRIDs with collaboration with physician and nurse	NR	EQ-5D, SF-12 ?	12 months
Potter 2016[68]	RCT (n=95)	LTC	84 (7)	--	Individualized medication review by a GP	✓	QOLAD, EQ-5D[d] ✗	12 months
Rieckert 2020[69]	RCT (n=3904)	Community	82 (4)	≥ 8 medications	Electronic decision support tool by GPs	✓	SF- 12 ✗	24 months
Romskaug 2021[70]	RCT (n=174)	Community	83 (7)	Taking ≥7 medications	Geriatric assessment, consultation between geriatrician and GP	✓	15D ✗	24 weeks
Roughead 2022[71]	RCT (n=282)	LTC	87 (NR)	≥4 medications or ≥1 anticholinergic or sedative medicine	Pharmacist training and medication review	NR	EQ-5D-5L ✗	12 months
Sakakibara 2015[72]	Pros Obs (n=50)	Community	84 (8)-88 (8)	Dementia	Pharmacist review of medications	✓	EQ-5D[d] ✗	6 months

Syafhan 2021[73]	RCT (n=356)	Community	68 (13)	Hospital admission or 2+ ER visits in last year, ≥6 medications	Clinical pharmacist medication optimisation	✓	EQ-5D-5L, VAS ✗	6 months
VanderLinden 2017[74]	RCT (n=214)	Hospital	85 (5)	≥10 medications	Medication reconciliation, medication review	✓	EQ-5D-3L ✓	3 months
Van Der Meer 2018[75]	RCT (n=157)	Community	76 (7)	≥5 medications, ≥ 1 psycholeptic/ psychoanaleptic drug	Community pharmacist medication review and collaboration with physicians	✗	EQ-5D-3L ✗	3 months
Verdoorn 2019[76]	RCT (n=629)	Community	78 (8) – 80 (7)	≥ 7 long-term medications	Community pharmacist medication review and meeting with GP	✓	EQ-5D-5L, EQ-VAS ✗	6 months
Williams 2004[77]	RCT (n=144)	Outpatient	73 (6)-74 (6)	≥5 medications	Pharmacist medication review guided by MAI and multidisciplinary meeting	✗	SF-36 ✗	6 weeks
Wouters 2017[78]	RCT (n=426)	LTC	83 (9)-84 (10)	Life expectancy > 4 weeks	Multidisciplinary medication review	✓	EQ-5D-3L ✗	12 months
Zechmann 2020[79]	RCT (n=334)	Community	76 (9)	≥ 5 long-term medications	GP deprescribing algorithm and training	✗	Five-point Likert-scale, VAS, EQ-5D-3L ✗	12 months

Scale development studies						
Study	**Design (n)**	**Setting**	**Age (SD or IQR)[a]**	**Key Participant Characteristics**	**Development methods**	**Scale**
Duncan 2018[80]	n=1546	Community	71 (12)	≥3 long-term conditions 73% in pilot > 70 years 55% development study >70 years	Developed from existing PROMs and treatment burden framework, feedback from the patients; cognitive interviews; reliability and validity testing	Multimorbidity treatment burden questionnaire (MTBQ)[c]
Eton 2017[81]	n=332	Community	66 (11)	≥ 2 chronic conditions	Qualitative interviews and cognitive testing, pilot, factor analysis plus reliability and construct validity testing	Patient experience with treatment and self-management (PETS) [c]
Eton 2020[82]	n=400	Multiple	58 (13)	≥2 diagnosed chronic medical conditions	Patient interviews, healthcare provider surveys, pilot testing, validation testing	PETS brief [c]
Katusiime 2018[83]	Interviews (n=11), Stage I (n=729), II (n=336), and III (n=30)	Community	NR	1 to 12 regular medicines	Cognitive interviews, psychometric testing, validity testing	Living with medicines questionnaire (LMQ-3) [c]
Mohammed 2018[84]	n=367	Community	64 (21)	≥ 3 medications on regular basis, and have ≥1 medical condition	Meta-synthesis, survey and exploratory factor analysis plus internal consistency analysis	Medication-related burden quality of life (MRB-QoL)
Sakthong 2015[85]	Round-1 (n=120, Round-2 (n=60)	Outpatient	NR	Taking ≥1 medication for at least three months continuously	Concept review, cognitive interviews, and initial psychometric evaluation	Patient-reported outcomes measure of pharmaceutical therapy for quality of life (PROMPT-QoL)

Tran 2014[86]	n=610	NR	52 (12)	≥ 1 condition that had required ongoing health care for ≥ 6 months	Literature review, pretest to assess the relevance of items, clarity, and wording and assess validity and reliability by a test–retest of TBQ adapted into English	Treatment burden questionnaire (TBQ)[d]
Tseng 2016[87]	n=219	Outpatient	NR	≥ 5 medications	Interviews; validity and reliability testing	Medication-related quality of life (MRQoL)

GP = general practitioner; IQR = interquartile range; LTC = long-term care; MAI = medication appropriateness index; MTM = medication therapy management; NR = not reported; PROM = patient reported outcome measure; RCT = randomized controlled trial; SD = standard deviation

[a] mean or median age in years

[b] there was a statistically significant reduction in the number of medications or potentially inappropriate medications for the intervention group compared to comparator

[c] last follow-up where quality of life measured

[d] not specified whether EQ-5D-5L or -3L

[e] not quality of life scale specifically but directly capture impact of medications on daily life

[f] quality of life was primary outcome

✓ statistically significant improvement in quality-of-life scale between intervention and control

✗ no statistically significant improvement in quality-of-life scale between intervention and control

? mixed or unclear results on statistically significant difference in quality-of-life scale between intervention and control

Table 2. Quality of life scales identified.

Scale	Population developed in	Number of items (time to complete)	Response scale	Aspects covered
			Generic scales[b]	
15D	General population (adults)	15 (5 to 10 mins)	1 (best) to 5 (worst); scaled to a total score of 0 to 1	Mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, sexual activity
EQ-5D-5L	General population (adults)[a]	5 + VAS (<5 mins)	1 to 5 converted to a value from 0 to 1; plus 100-point VAS	Mobility, Self-Care, Usual Activities, Pain or Discomfort, Anxiety or Depression
EQ-5D-3L	General population (adults)[a]	5 + VAS (<5 mins)	1 to 3, converted to a value from 0 to 1; plus 100-point VAS	Mobility, Self-Care, Usual Activities, Pain or Discomfort, Anxiety or Depression
VAS scale from 0 to 100	General population (adults)[a]	1 (<5 mins)	0 (worst health) to 100 (best health)	Overall health
QOL-AD	Adults living with dementia	13-15 (10 to 15 mins)	Poor (1) to excellent (4); total is the sum of all items	Physical health, energy, mood, living situation, memory, family, marriage, friends, ability to do chores, fun, money, life as a whole
DQI	18-75 years with dementia	6 (unclear)	No problems, some problems, severe problems	Physical health, self-care, social functioning, mood, memory, orientation
SF-36	General population (adults)	36 (10 mins)	Varies; calculating an overall score not recommended	Physical function, impact of physical health on usual role, bodily pain, general health, vitality, social functioning, impact of emotional health on usual roles, and mental health
SF-12	General population (adults)	12 (5 mins)	Varies; calculating an overall score not recommended	Same as SF-36
5-point Likert scale	Unclear	1 (unclear)	-2 (worst possible health) to +2 (best possible health)	Overall health
ICECAP-O	Older adults	5 (5 to 10 mins)	Varies by item	Love and friendship, thinking about the future, doing things that make you feel valued, enjoyment and pleasure, independence

QUALIDEM	Adults living with dementia	40 (10 mins)	Never, Seldom, Sometimes, Often (score varies according to item; subscales are totalled)	Care relationship, positive affect, negative affect, restless tense behaviour, positive self image, social relationships, social isolation, feeling at home, occupation
QUALID	Adults with late-stage dementia (completed by proxy)	11 (5 mins)	Varies; 5 options per question, total score ranges from 11-55 (higher scores = lower QoL)	Items addressed: smiles, appears sad, cries, facial expressions of discomfort, physical comfort, statements that suggest discontent, irritable or aggressive, enjoys eating, enjoys being touched, enjoys interacting with others, appears emotionally calm and comfortable
			Medication-specific scales	
Patient Experience with Treatment (PETS)[c]	Adults with multiple chronic conditions[a]	48 (unclear)	Response options vary by question; scores transformed to 0-100	Medical information, medications, medical appointments, monitoring health, interpersonal challenges, expenses, difficulty with healthcare, role/social activity limitations, physical/mental exhaustion
Patient Experience with Treatment (PETS) 2.0[c]	Adults with multiple chronic conditions[a]	60 (unclear)	Response options vary by question; scores transformed to 0-100	Medical information, medications, medical appointments, monitoring health, interpersonal challenges, expenses, difficulty with healthcare, role/social activity limitations, physical/mental exhaustion, diet, exercise, medical equipment
Patient Experience with Treatment (PETS) brief[c]	Adults with multiple chronic conditions[a]	32 (unclear)	Varies; scores transformed to 0-100 scale where higher scores suggest higher treatment burden	Medical information, medications, medical appointments, monitoring health, interpersonal challenges, expenses, difficulty with healthcare, role/social activity limitations, physical/mental exhaustion
Patient-reported outcomes measure of pharmaceutical therapy for QoL (PROMPT-QoL)	Adults taking any medications for >3 months[a]	43 (3 to 35 mins)	5-point Likert scale; scores range from 0 to 100 with higher scores suggesting better QoL	Attitude toward medication, and disease information, effectiveness, side-effects, psychological impacts of medication use, convenience, accessibility, therapeutic relationships, overall quality of life
Living with medicines questionnaire (LMQ-3)[c]	Adult patients with long-term polypharmacy[a]	41 (unclear)	5-point scale from strongly agree to strongly disagree; scores range from 41 to 205	Interference with daily life, relationships, effectiveness, general concern about medicines, side effects, practical difficulties, cost, lack of autonomy/control of medicine use
Medication related burden QoL tool (MRB-QoL)	Adults taking ≥3 medications on a regular basis[a]	31 (unclear)	5-point Likert scale from 1: strongly agree to 5: strongly disagree; total scores range from 0 to 100	Routine and regimen complexity, psychological burden, functional and role limitation, therapeutic relationship, social burden

Multimorbidity treatment burden questionnaire (MTBQ)[c]	Adults with 3 or more chronic conditions[a]	10 (3 optional questions) (unclear)	5-point scale ranging from "not difficult" to "extremely difficult"; overall score from 0 to 100 (higher scores = higher burden)	Taking medications, remembering to take medications, collecting medication, monitoring, arranging appointments, seeing lots of health professionals, attending appointments, obtaining information, making lifestyle changes, relying on family and friends
Treatment burden questionnaire (TBQ)[c]	Adults with at least one chronic condition	13 (15 for English version) (unclear)	Each item has a scale from 0 to 10 ranging from "no burden" to "considerable burden"	Inconvenience, frequency of medication, medication reminders, instructions, lab tests, self-monitoring, doctors visits, arranging appointments, paperwork, diet, physical exercise, social relationships
Medication-related QoL scale (MRQoL)	Adults with polypharmacy	14 (2 mins)	6-point Likert scale ranging from "none of the time" to "all of the time"	Role limitations due to medication, self-control, vitality

DQI = dementia quality of life instrument; ICECAP-O = ICEpop CAPability measure for Older people; QoL = quality-of-life; QoL-AD = quality of life in Alzheimer's disease scale; QUALID = quality of life in late stage dementia; VAS = visual analogue scale

[a] scale developed, evaluated, or validated in the context of polypharmacy or deprescribing

[b] For generic scales, we used data from Siette 2020[28]

[c] not specifically designed to measure quality of life directly but capture impact of mediations on daily life

Fig 2. Quality of life scales reported in deprescribing trials[a]

Abbreviations: VAS = visual analogue scale
a Some trials employed multiple quality of life scales
b EQ-5D not specified as -3L or -5L

Fig 3. Critical appraisal of identified quality of life scales using modified COSMIN checklist.

Appraisal of generic scales based on existing systematic review[28] which applied COSMIN checklist to 15D, EQ-5D-5L, EQ-5D-3L, QOL-AD, DQI, SF-36, SF-12, ICECAP-O, QUALIDEM, and QUALID. Appraisal of medication-specific scales was conducted using a modified version of the COSMIN checklist (see Supplementary Table S2) based on publications in Table 2.

For the QUALIDEM scale validity has been rated as poor to excellent in different studies and for the QUALID scale, validity and reliability have been rated as poor to fair in different studies.[28]