Outcome measures for interventions to reduce inappropriate chronic drugs: a narrative review

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STRUCTURED ABSTRACT

Background: Inappropriate prescribing is a highly important problem, given the growing aging multimorbid population with associated polypharmacy. An increasing number of studies have recently developed and tested interventions to withdraw inappropriate drugs, a process called deprescribing. However, we still lack complete information on the types and prevalence of measures used to assess the success of such interventions.

Objective: To categorize and synthesize the full spectrum of measures used in intervention studies focused on reducing inappropriate prescribing of chronic drugs in adults, in order to standardize measurements in future studies and help researchers design studies inclusive of the important measure types.

Design: We searched Ovid/MEDLINE to identify intervention studies focused on deprescribing chronic drugs in adults, published between 2010 and 2019.

Measurements: We extracted data on study characteristics, intervention components, and outcome measures. We categorized and synthesized the measures using a comprehensive and systematic framework, separating measures of intended and unintended consequences.

Results: Most (90/93) studies used measures of appropriate prescribing, such as drug cessation or dose reduction. The following measures were used infrequently across studies: patient-reported experience, preferences, and outcome (12 (13%), 2 (2%), and 25 (27%) studies, respectively); provider-reported experience (11 (12%) studies); patient-provider interaction (4 (4%) studies); and measures of unintended consequences (24 (26%) studies). Studies varied in the type and number of measures assessed, ranging from 1 to 20 different measures by study.

Conclusion: To ensure initiation, success, and long-term sustainability of deprescribing, it is important to assess the success of intervention studies using clinically relevant patient- and provider-centered measures. This categorized synthesis of outcome measures used in deprescribing studies may facilitate implementation of important measure types (e.g., patient reported measures, measures of unintended consequences) in future studies.

Key words: deprescribing; inappropriate medication; withdrawal; interventions; measures.

INTRODUCTION

Up to 30% of medical services are considered low-value, i.e., may result in more harm than benefit.[1-3] Inappropriate prescribing is increasingly seen among the growing older multimorbid population,[4,5] with up to one-third receiving inappropriate prescriptions.[6] In response, the Choosing Wisely initiative regularly publishes recommendations to minimize low-value prescribing.[1] While an increasing number of interventions focused on deprescribing inappropriate medications,[7] deprescribing chronic medications remains a complex process associated with barriers at both patient and provider levels,[8,9] particularly for medications, whose use was prompted by unpleasant symptoms. Fear of worsening symptoms may lead to resistance towards stopping these medications.[10] Further, clinicians lack time and resources for deprescribing, report low self-efficacy for stopping therapy, and feel uncertain about clinical consequences of deprescribing (e.g., stroke following antihypertensive drug reduction).[11] To ensure feasibility and sustainability of deprescribing, intervention studies should assess not only whether a medication was stopped or the dose reduced, but also patient-relevant clinical outcomes and patient and provider experience and preferences. The measures should capture both intended effects and unintended harms, a key priority identified by Choosing Wisely and patient advocates.[12,13] However, deprescribing intervention studies have highly variable outcome measures and rarely include clinical outcomes, as outlined in two reviews in older adults.[8,14] These reviews did not detail the types and frequency of use of the different measures, and only assessed controlled trials.[8,14] This global paucity of clinical outcomes and heterogeneity of measures may be explained by a lack of guidance. It is also more challenging to collect information on experience, preferences and clinical outcome measures, as this requires longer follow-up periods, prospective designs, and broader expertise.

We recently reviewed the literature to characterize measures employed in 117 interventions to reduce low-value care.[15] We found that measures focused largely on utilization and rarely addressed patient-centered outcomes or unintended consequences. The search strategy was not tailored to identify low-value prescribing of chronic medications and included only 44 studies focused on prescribing for

predominantly acute medications (two-thirds addressed acute antibiotic use). Given the unique challenges of stopping chronic medications, the measures to assess the impact of interventions may be notably different from those used in studies focused on stopping acute medications.

Based on this review, we suspected that outcome measures reported across deprescribing intervention studies for chronic medications would also lack coverage of important measure types.[15] Given the lack of prior reviews, and the need to standardize outcome measures for further studies,[16] we sought to provide the first review to: 1) identify measures used in recent studies evaluating the effect of interventions to reduce inappropriate prescribing of chronic medications in adults, including prescribing practices, clinical outcomes, cost/value, and patients' and providers' experience and interaction, and 2) categorize and synthesize these measures, using a comprehensive systematic framework, to provide deprescribing study designers with a list of candidate measures within each category.

METHODS

Search strategy

We performed a literature search in Ovid/MEDLINE search from January 1, 2010, to October 13, 2019 to identify original studies of any design reporting outcome measures of interventions to reduce inappropriate prescribing of chronic drugs in adults (**Supplementary Text S1**). A separate search strategy was used for benzodiazepine-related drugs, without the term "appropriate prescribing" given that most use is considered inappropriate. The search was restricted to Ovid/MEDLINE, as we welt that this source alone would be sufficient to identify articles that would allow us to capture the full spectrum of available measures. Inclusion criteria were: adult population; original study (i.e., not a review or meta-analysis); intervention to reduce the use of a least one chronic inappropriate drug. We included both quantitative and qualitative studies. We excluded studies that focused on: 1) only new drug prescriptions (e.g., new prescription of proton pump inhibitor during hospitalization) or only on short-term or acute drugs (e.g., antibiotic for urinary tract infection); we didn't use a clear cut-off to define a

drug as non-chronic, as it varied depending on the drug class; 2) reducing polypharmacy in general without assessing prescribing appropriateness; 3) deprescribing as part of a global intervention not focused on reducing inappropriate prescribing; 4) inappropriate prescribing assessed globally as potentially inappropriate prescription, potential prescribing omission, inappropriate dosage or drug interactions. We focused on interventions to deprescribe chronic drugs, because the specific challenges and barriers are likely to be different than those for prescribing acute drugs or new drugs.

Measure definition and categorization

A measure was defined as any assessment of prescribing practice, clinical outcome, cost/value, or experience following the deprescribing intervention. We classified the measures used in the studies into several categories, adapted from a framework previously developed by our research team **(Supplementary Table S1)**:[15] 1) measure specification (count, scale, proportion); 2) measure type (appropriateness, utilization/ordering, intermediate outcome, outcome, patient-reported outcome (PROM), patient-reported experience (PREM), patient preferences, provider-reported experience, patient-provider interaction, cost-related); 3) measure reporting type (patient, provider, medical/pharmacy record, validated scale/questionnaire, non-validated scale/questionnaire, blinded assessment); 4) measure of unintended consequence (including substitution of an alternative low-value drug, underuse of the drug being intervened upon, underuse of related services, PREM, provider-reported experience, patient-provider interaction, patient selection, care location shift, harmful outcome, reimbursement), which were classified as "definite" if the study specifically reported it as such in the methods section, or "possible" if it was inferred by the reviewer. Appropriateness and utilization/ordering measures were further classified into subcategories: cessation, dose reduction, new prescription, switch for another drug. Utilization/ordering measures included prescribing measures not assessing the appropriateness of the drug.

Data extraction

The first author (CEA) performed the literature search and used a standardized form to extract relevant data. Data on study characteristics included first author name, publication year, design, setting, participants (with specific inclusion criteria such as older age, multimorbidity, polypharmacy), number and class(es) of drug(s), and intervention aim, target (patient or provider), description and type (e.g., education, feedback, drug review). Data on measures included information required for categorization.

Data analyses

Separate articles referring to the same study were grouped for analysis. Similar measures across these articles were also merged. We present study characteristics as frequencies/percentage of studies (number of studies with characteristic relative to total number of studies), and measures as frequencies/percentage of measures (number of measures of a specific type relative to total number of measures) and percentage of studies, respectively. We summarized all measures used in the studies, grouping similar measures (e.g., drug cessation, intervention acceptance) used across different studies, to provide a synthesized reference list of potential measures to consider in future deprescribing studies.

RESULTS

Studies included

From the 4,190 articles identified in Ovid/MEDLINE, 4,041 were excluded upon review of the title and/or abstract (**Figure 1**). Of the remaining 149 articles, 44 were excluded upon review of the full-text, resulting in 105 articles included in the review. Eight studies published their results through two to four separate articles, so that the total of 105 articles represents 93 unique studies. A complete list of the 105 articles is provided in **Supplementary Text S2**.

Study population, setting, design and drug classes

Most of the 93 studies (n=60, 65%) focused on older patients. Fifty-one (55%) studies were conducted in the outpatient setting, 27 (29%) in long-term care, 19 (20%) in the inpatient setting, and 8 (9%) in the pharmacy (**Table 1**). A control group was used in 42 (45%) studies, of which half employed randomization. The most frequent drug classes studied were sedative-hypnotics (in 64 (69%) studies) and antipsychotics (in 43 (46%) studies). Forty-two (45%) studies involved a single drug class. Study characteristics are detailed in **Supplementary Table S2**.

Intervention characteristics

The interventions were most often multifaceted and targeted a patient (in 44 (47%) studies) and/or a provider (in 85 (91%) studies). The most frequent intervention types were a review of drug appropriateness and indication in 40 (43%) studies, followed by education at the patient or provider level in 29 (31%) and 31 (33%) studies, respectively. The intervention types used in each study are detailed in **Supplementary Table S2**.

Outcome measures characteristics within studies

Across the 93 studies, we identified 511 outcome measures. We present frequencies of each measure type in **Table 2**. Complete drug cessation was the most frequently assessed measure, in 79 (85%) studies. Thirty-two (34%) studies used at least one patient-reported measure, including PROMs, PREMs, and patient preferences. One fourth of the studies (n=24) reported using at least one measure of unintended consequences (e.g., withdrawal symptoms or use of restraints for agitation). Non-patient reported outcome measures (e.g., hospitalizations), including intermediate outcomes (e.g., uptake of deprescribing intervention by the prescribing physician), were used in 46 (49%) studies. Provider-reported experience, patient-provider interaction, and cost-related measures were rarely used. **Table 3** provides a synthesized and categorized list of all measures used across the studies, with some examples. The frequencies and types of measures used in each study are listed in **Supplementary Table S3**.

Outcome measures source within studies

We present frequencies of each measure source (i.e., patient-reported, provider-reported, medical/pharmacy record, validated/non-validated scale or questionnaire, blinded assessment) in **Table 2**. Medical or pharmacy records were the most frequent sources used for measures (86 (93%) studies). Blinded measures assessment was performed in only 11 (12%) studies (50% of the randomized trials).

Appropriateness and utilization/ordering measures

Thirty-four (37%) studies used both appropriateness and utilization/ordering measures (i.e., without assessing appropriateness of prescribing), while 56 studies (60%) measured only appropriateness, and a single study (1%) only utilization/ordering. Appropriateness and utilization measures included cessation, dose reduction, new prescription, and switch for another drug, either alone or in combination. For example, Ailabouni et al. evaluated the number of drugs prescribed (utilization/ordering measure) and the Drug Burden Index (appropriateness measure), while Brodaty et al. assessed cessation of inappropriate antipsychotics (appropriateness measure) and prescription rate of other psychotropic drugs (utilization/ordering measure).[17,18] Studies assessing several drug classes most often reported these measures for all classes combined and for each class separately. For example, Ammerman et al. assessed discontinuation rate of any potentially inappropriate medication evaluated, as well as discontinuation rate of anticholinergics, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, peripheral alpha blockers, benzodiazepines, antihistamines, and antipsychotics separately.[19]

Patient-reported measures

Twenty-five studies (27%) used PROMs, while only 12 (13%) and 2 (2%) studies assessed PREMs and patient preferences, respectively. PROMs mostly included quality of life or perceived health status, as well as drug-specific outcomes, such as sleep quality, drug dependence, cognition, sedative side effects or withdrawal/anxiety/depression symptoms for sedative-hypnotics, or gastrointestinal symptoms for proton pump inhibitors. PREMs most often evaluated a patient's experience with the intervention (e.g.,

satisfaction with educational material) or of the tapering process (e.g., reasons for tapering difficulties). Patient preferences measures included reasons for refusing deprescribing or preferences for the intervention.

Provider-reported experience and patient-provider interaction measures

Eleven (12%) studies evaluated provider-reported experience measures, including experience, satisfaction or acceptance of the intervention, as well as self-efficacy for deprescribing. Only 4 (4%) studies used patient-provider interaction measures, reporting the number of counseling occasions, personal interactions, discussion documentation, and drug review with the patient.

Non-patient reported intermediate outcome and outcome measures

Thirty-three (35%) and 19 (20%) studies included a non-patient-reported outcome or intermediate outcome measure, respectively. Intermediate outcome measures often related to acceptance rate of deprescribing recommendations. Outcome measures included healthcare services utilization (hospitalization, length of stay, ambulatory visits) and mortality. Additionally, outcome measures often included outcomes related to specific drugs (e.g., falls or confusion for sedative-hypnotics, neuropsychiatric symptoms or use of a seclusion room for antipsychotics, incidence of cardiovascular events for antihypertensive and lipid-lowering drugs).

Cost-related measures

Ten (11%) studies assessed effects on costs. The majority of these measured drug costs, while three (3%) evaluated the cost of the intervention (e.g., provision of educational material) and two measured the cost of healthcare services utilization. Only two (2%) studies used a value measure, specifically assessing cost-utility of the intervention.

Qualitative measures

While all studies used quantitative measures, only 18 (19%) also performed a qualitative assessment. Qualitative measures included patient and provider experience, acceptance or satisfaction with the intervention assessed qualitatively (e.g., by interview), key messages remembered by providers, reasons for not deprescribing or for restarting a deprescribed drug, feasibility of the intervention, patient perception of deprescribed drugs, physician impression of deprescribing rounds, communication preferences, or decisions during discussions between patients and providers.

Measures of unintended consequences

Twenty-four (26%) studies reported at least one measure of unintended consequences, which represented 10% (n=52/511) of all measures. Among them, 21 were clearly mentioned as such in the methods, and thus classified as "definite," while 31 were considered as unintended consequences by the reviewer and classified as "possible." Unintended consequences included changes in symptoms or withdrawal related to drug tapering, use of restraints or substitute drugs, changes in laboratory parameters, as well as adverse events during deprescribing, such as hospitalization, falls, death or cardiovascular events. Of the 52 measures, outcome measures documenting unintended consequences were the most frequent (n=21, 40%), followed by PROMs (n=15, 29%), utilization/ordering measures (n=10, 19%), appropriateness measures (n=5, 10%) and provider-reported experience measures (n=1, 2%).

DISCUSSION

In this review of 93 deprescribing studies, we found that almost all authors used an appropriateness measure assessing change in prescribing, most frequently drug cessation, to examine the impact of their interventions. Less often they simply used a measure of utilization or ordering, without taking into account appropriateness of medication indication and/or dosage. Less than half of the studies examined

non patient-reported outcomes, such as mortality or utilization of healthcare services. Patient-provider interaction, provider-reported experience, and cost-related measures were used infrequently and only 26% of the studies evaluated unintended consequences of deprescribing.

Outcome measures were uncommon and inconsistently used across all studies. Not surprisingly, any specific measure employed was usually related to the type of intervention. For example, studies on sedative-hypnotic drugs evaluated the incidence of falls or the use of other psychotropic drugs, while studies on proton pump inhibitors assessed rebound dyspeptic symptoms or the use of a rescue drug such as a H2 blocker. Interventions with a strong focus on the patients were more likely to assess patient-reported measures, although these were present in less than one third of the studies, and measures of patient experience and preferences were particularly rare.

The literature suggests that deprescribing is more likely to be successful when individual patient context, preferences, and goals are considered,[20-22] particularly when patients may have withdrawal symptoms , such as for psychotropic drugs or proton pump inhibitors,[23,24] and thus education and active participation for self-management is required.

Although a strong focus on patient involvement is important, deprescribing remains most often initiated, directed, and sometimes required by providers, who may face multiple barriers,[11] so studies should also assess the experience of the providers with the interventions. However, only a minority of authors employed provider-reported experience measures, while four studies assessed patient-provider interactions, including shared-decision making. For example, Carr et al. assessed the number of conversations around benzodiazepine cessation, and found that patients with more conversations had higher rates of deprescribing.[25] Deprescribing chronic drugs may lead patients to fear or even experience withdrawal symptoms. Thus, it is important that providers understand how the patients experience potential harms and benefits of reducing the drugs, and discuss and implement deprescribing in a shared-decision-making process, a key facilitator to deprescribing.[26] Future studies should more consistently assess provider experience and patient-provider interactions. Tools such as CollaboRATE

or the revised Patients' Attitudes Towards Deprescribing questionnaire could be used for this purpose.[27,28]

Specific barriers and facilitators for deprescribing were largely assessed by qualitative studies, mostly by interviewing or surveying patients or providers, while qualitative methods were rarely used in intervention deprescribing studies (only 18 of the 93 (19%) studies included in this review).[21,29-33] Qualitative research requires particular expertise and resources that differ from purely quantitative methods,[34] but allows a broader assessment of barriers and facilitators, as well as patient- and provider-reported experiences than quantitative measurement alone, so that it should be integrated in deprescribing intervention studies.[35]

Withdrawing medications is recommended when harms outweigh benefits.[7] However, deprescribing may result in withdrawal symptoms (e.g., sweating or irritability for benzodiazepines), return of the medical condition (e.g., heartburn for proton pump inhibitors), increased use of healthcare services, or incidence of a new condition precluded after a preventive medication is reduced (e.g., stroke for antihypertensive medications).[36] It is therefore important to carefully monitor the patients during and after the deprescribing process, and to measure potentially unintended consequences, such as more frequent than expected new or recurrent symptoms, or higher healthcare services utilization.[13] Our review suggests an important gap in this context, since only 27% and 35% of the authors assessed patient-reported and other outcome measures, respectively, and one fourth assessed unintended consequences of the interventions. Finally, since some of these outcomes are infrequent or may occur only after a relatively long follow-up period, it is important to design the studies for these outcomes if important clinically. In our review, only one fourth of the interventions were randomized, with blinded measure assessment in only half of the randomized trials.

We found very little overlap in the number and types of outcome measures used across the studies. Research on deprescribing will have little cumulative impact on patient care without a standardized outcome set that covers the important types relevant to deprescribing. The lack of consistency in outcome measures reported may be related to a lack of exemplars in the literature on which to base the

design of deprescribing intervention studies and the relatively recent interest in the topic. There were indeed some initial attempts to develop outcome sets in the context of deprescribing, but these focused on older patients with polypharmacy and on medication appropriateness more broadly.[37,38] Thus, the results may not be generalizable to other populations or to specific medications. For example, in those studies, PROMs included cognitive functioning, patient perception of medication burden, and pain relief. Those outcome measures may be particularly pertinent for older multimorbid patients with polypharmacy, but less relevant for younger patients trying to stop proton-pump inhibitors, for example. Outcome sets for older adults also have a strong focus on medication-related outcomes, such as therapy duplication, complexity or adherence, all of which are related to polypharmacy. We did not limit our work to older or multimorbid patients with polypharmacy and used a framework to develop a broader but nonetheless synthesized set of measures for each category. This framework may serve any deprescribing intervention study and help to ensure that relevant measures across the whole spectrum, including patient- and provider-centered and unintended consequences measures, are included.

We found little consistency not only in the number and types of measures considered, but also in the designs and intervention types of the studies. All these issues are important to ensure the success of deprescribing interventions. The following criteria may serve as exemplars for future researchers: 1) high evidence-based design (randomized controlled trial); 2) intervention component targeting not only the providers, but also patients; 3) broad set of measures to assess the success and acceptability of deprescribing, with both qualitative and quantitative assessment; and 4) follow-up period long enough to evaluate sustainability of deprescribing, which may provide information on scalability. The OPTI-SCRIPT Study (articles numbers 2-5 in **Supplementary Table S2** and **Supplementary Table S3**),[39-42] a cluster randomized controlled trial conducted in an outpatient general care setting to deprescribe multiple potentially inappropriate drugs, is such an exemplar. The feasible intervention targeted providers (web-based algorithm, education, drug review) and patients (educational leaflets), and the authors assessed not only prescribing practices, but also clinical outcome, patient-reported experience and outcomes, provider-reported experience, and patient-provider interaction, using a mixed-method

process. In addition, patients were followed-up for 12 months and cost-utility and cost-effectiveness were evaluated.

There are several limitations to this review. First, we did not grade the quality of the studies, because we focused on outcome measures and not on the effectiveness of the interventions themselves. Nonetheless, it is noteworthy that a minority of the studies were randomized and only 45% included a control group. Second, we searched only Ovid/MEDLINE. However, this search identified a large number of articles, and extending the search to other databases (e.g., EMBASE) did not significantly increase the number of relevant articles. Third, we did not review unpublished or ongoing studies, and it is possible, although unlikely, that ongoing studies are using a larger spectrum of measures. Our study also has several strengths. First, we used a broad search strategy, including specific search terms to capture interventions targeting the most frequent inappropriate drugs. This strategy was developed with a medical librarian and tested for identification of the most relevant articles. Second, we used a comprehensive and systematic categorization framework to capture a broad range of measures, including both intended and unintended consequences of the interventions. Finally, we synthesized and categorized the measures to help designers of future deprescribing intervention studies have access to the full spectrum of available measures.

In conclusion, this review confirmed our hypotheses that the success of deprescribing is most consistently evaluated by drug cessation or dose reduction, while patient- and provider-reported experience, preferences and outcomes, as well as measures of unintended consequences, are infrequently considered. To ensure success and sustainability of deprescribing, it is important that intervention studies include measures that are more clinically meaningful and centered on patients and providers. To allow assessment of rare outcomes and in-depth evaluation of patient and provider preferences and experience, we suggest using a mixed-methods approach, combining a randomized controlled design with qualitative and implementation assessments. Finally, to facilitate incorporation of a broad spectrum of measures into those future studies, the synthesis and categorization of the available measures and identified gaps offers a first reference list of measures that can be useful for any

deprescribing study. Further validation of these measures by patients and providers concerned by inappropriate prescribing will ensure that measures relevant to the stakeholders are included in the process of deprescribing.

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Conflicts of Interest

The authors declare that they do not have a conflict of interest.

Author Contributions

CEA, EAK and TH designed the study. CEA conducted the literature review, extracted the data, performed the analyses, interpreted the results and wrote the manuscript. MLK developed the abstraction database for data abstraction. EAK and TH contributed to interpretation of the data. EAK, TH, MLK and JM revised the manuscript critically for important intellectual content. All authors agreed for submission of the final version of the manuscript.

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Table 1. Study characteristics (N=93)

Study characteristics	Number (%) of studies
Setting and patient characteristics	
Inpatient	19 (20)
Long-term care	27 (29)
Outpatient	51 (55)
Pharmacy	8 (9)
Other (emergency department, rehabilitative care, home care)	24 (26)
Older patients only	60 (65)
Methods	
Randomized study	21 (23)
Control group	42 (45)
Quantitative assessment	93 (100)
Qualitative assessment	18 (19)
Number of drug class(es) targeted by the interventions	
1	42 (45)
2	13 (14)
3	6 (6)
≥4	32 (34)
Classes of drugs targeted by the interventions	
Sedative-hypnotics	64 (69)
Antipsychotics	43 (46)
Antidepressants	36 (39)
Opioids	33 (36)
Anticholinergics	33 (36)
Proton pump inhibitors	35 (38)
Other drug class	35 (38)
Intervention type	
Targeting patient	44 (47)
Education	29 (31)
Drug substitution	8 (9)
Other	26 (28)
Targeting provider	85 (91)
Feedback / report card	9 (10)
Education	31 (33)
Guideline	20 (22)
Drug checklist	18 (19)
Drug review	40 (43)
Other clinical decision support	15 (16)
Pay for performance	1 (1)
Other	45 (48)

Total numbers for each characteristic are higher than the total number of studies, because some studies included more than one of these characteristics.

Table 2. Types and sources of measures

	Number (%) of measures	Number (%) of studies with ≥1 of the measure category / subcategory / source
Measure Type		
1. Appropriateness*	211 (51)	90 (97)
Cessation	171 (33)	79 (85)
Dose reduction	68 (13)	30 (32)
Switch for another drug	16 (3)	5 (5)
New prescription	14 (3)	3 (3)
Other	7 (1)	1 (1)
2. Utilization/ordering*	52 (10)	35 (38)
Cessation	16 (3)	10 (11)
Dose reduction	11 (4)	5 (5)
Switch for another drug	23 (5)	17 (18)
New prescription	21 (4)	13 (14)
Other	5 (1)	2 (2)
3. Intermediate outcome**	27 (5)	19 (20)
4. Outcome**	94 (18)	33 (35)
5. Patient-reported outcome	62 (12)	25 (27)
6. Patient-reported experience	15 (3)	12 (13)
7. Patient preferences	4 (1)	2 (2)
8. Provider-reported experience	16 (3)	11 (12)
9. Patient-provider interaction	4 (1)	4 (4)
10. Value (outcome/cost)	3 (1)	2 (2)
11. Cost	12 (2)	10 (11)
12. Other	11 (2)	10 (11)
Measure of unintended consequences	52 (10)	24 (26)
Definite unintended consequence	21 (4)	9 (10)
Possible unintended consequence	31 (6)	19 (20)
Measure source		
Patient-reported	117 (23)	33 (36)
Provider-reported	75 (15)	36 (39)
Medical / pharmacy record	349 (68)	86 (93)
Validated scale / questionnaire	66 (13)	25 (27)
Non-validated scale / questionnaire	30 (6)	16 (17)
Blinded assessment	92 (18)	11 (12)

*An appropriateness or utilization/ordering measure can be a combination of the subcategories, explaining that adding the subcategories results in more measures than the overall category.
**Not patient reported
Total number of measures: 511. Total number of unique studies: 93.

Table 3. Summary of measures used in the studies for each category and subcategory

1. Appropriateness (a), 2. utilization/ordering (b)
Cessation: a) number of patients with inappropriate drug ceased; b) mean number of prescriptions
Dose reduction: number of patients with: a) ≥50% dose reduction of inappropriate drug; b) change in drug dose
New prescription: a) number of new inappropriate drugs; b) number of drugs restarted (appropriateness not assessed)
Switch for another drug: a) switches for alternative drug because of withdrawal; b) number with antidepressant as alternative
3. Intermediate outcome
Number of: deprescribing recommendations / drug alerts requiring an intervention
Proportion of: deprescribing recommendations accepted by patients / providers
Proportion of: patients with tapering plan developed / withdrawal attempt / receiving a deprescribing intervention
Reasons for: rejecting recommendation / not achieving deprescribing
4. Outcome
Healthcare services utilization (e.g., length of stay, hospitalization, outpatient visit)
Drug side effects / withdrawal signs (e.g., delirium, aggressive behavior, insomnia)
Adverse effects of drug cessation (e.g., hyperglycemia, fall, CVD event, seclusion room, physical restraints, death)
5. Patient-reported outcome
QoL / well-being / health status (EQ-5D-3L, 15D-HRQoL, Well-Being Questionnaire, 36-item Short Form Survey)
Functional status / activities of daily living (Groningen Activity Restriction Scale)
Withdrawal symptoms / drug side effects (SDS, BWSQ, Udvalg for Kliniske Undersogelser side effect rating scale)
Sleep quality / satisfaction (Pittsburgh Sleep Quality Index, Oviedo Sleep Questionnaire)
Gastrointestinal symptoms (Gastrointestinal Symptom Rating Scale, Gastroesophageal Reflux Disease Impact Scale)
Cognitive function (MoCA, MMSE, PAS-CIS; InterRAI-Long Term Care Facilities)
Psychopathology (Brief Symptoms Inventory, Hospital Anxiety and Depression Scale, Geriatric Depression Scale, CES-D)
Beliefs about drugs (Beliefs about Medicines Questionnaires) / Self-efficacy (Medication Reduction Self-efficacy Scale)
6. Patient-reported experience
Experience / satisfaction with the intervention (e.g., tapering process, implication in drug review, educational material)
Difficulties during the intervention / reasons for deprescribing failure (e.g., fears because of prior failed attempts, withdrawal)
7. Patient preferences
Proportion of patients who agreed / refused deprescribing; reason(s) for refusing
Preferences for the intervention
8. Provider-reported experience
Self-efficacy to deprescribe / develop a deprescribing plan / implement a deprescribing plan
Satisfaction / experience / perception / difficulties / feasibility / acceptance / adoption / key messages of the intervention
Preferences for communication between providers (e.g., face-to-face, messages through electronic record)

Most useful part of the intervention (e.g., reminder message, tool, patient handout)
9. Patient-provider interaction
Personal interactions / discussions between patients and providers regarding deprescribing
Number of counseling occasions provided to each patient by the pharmacist / physician
Drug review with the patient
10. and 11. Cost-related
10. *Value (outcome/cost)*: cost-utility (costs/QALYs) / cost-effectiveness (costs/number of potentially inappropriate drugs)
11. *Costs*: costs of: drugs / intervention (implementation, material (e.g., patient education brochure)) / healthcare services use
Unintended consequences
Switch for: substitute drug / additional drug / drug restarted for symptom control
Withdrawal signs or symptoms / worsening of symptoms treated by the deprescribed drug
Other adverse effects of deprescribing (e.g., hyperglycemia, CV events, QoL, death, fall)
Healthcare resource utilization (e.g., length of stay, hospitalization, outpatient visits)

Abbreviations: BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; CES-D, Centre for Epidemiological Studies Depression Scale; CV, cardiovascular; EQ-5D-3L, EuroQol five-dimensional three-level questionnaire; 15D-HRQoL, 15-dimensional health-related quality of life instrument; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; QALY, quality-adjusted life year; QoL, quality of life; PAS-CIS; Psychogeriatric Assessment Scales – Cognitive Impairment Scale; SDS, Severity of Dependence Scale.

Legend: Given that appropriateness and utilization/ordering measures are rather obvious and were ubiquitously used across studies, we only provide one example for each of their subcategories. For the other categories / subcategories, we synthesize all measures used across studies and provide examples of validated scales in brackets. Some measures are relevant for specific drugs only.

LEGENDS FOR FIGURES

Figure 1. Flow-chart of search result

DESCRPTIVE TITLE OF SUPPLEMENTAL MATERIAL

Search strategy, list of articles and details on studies and measures

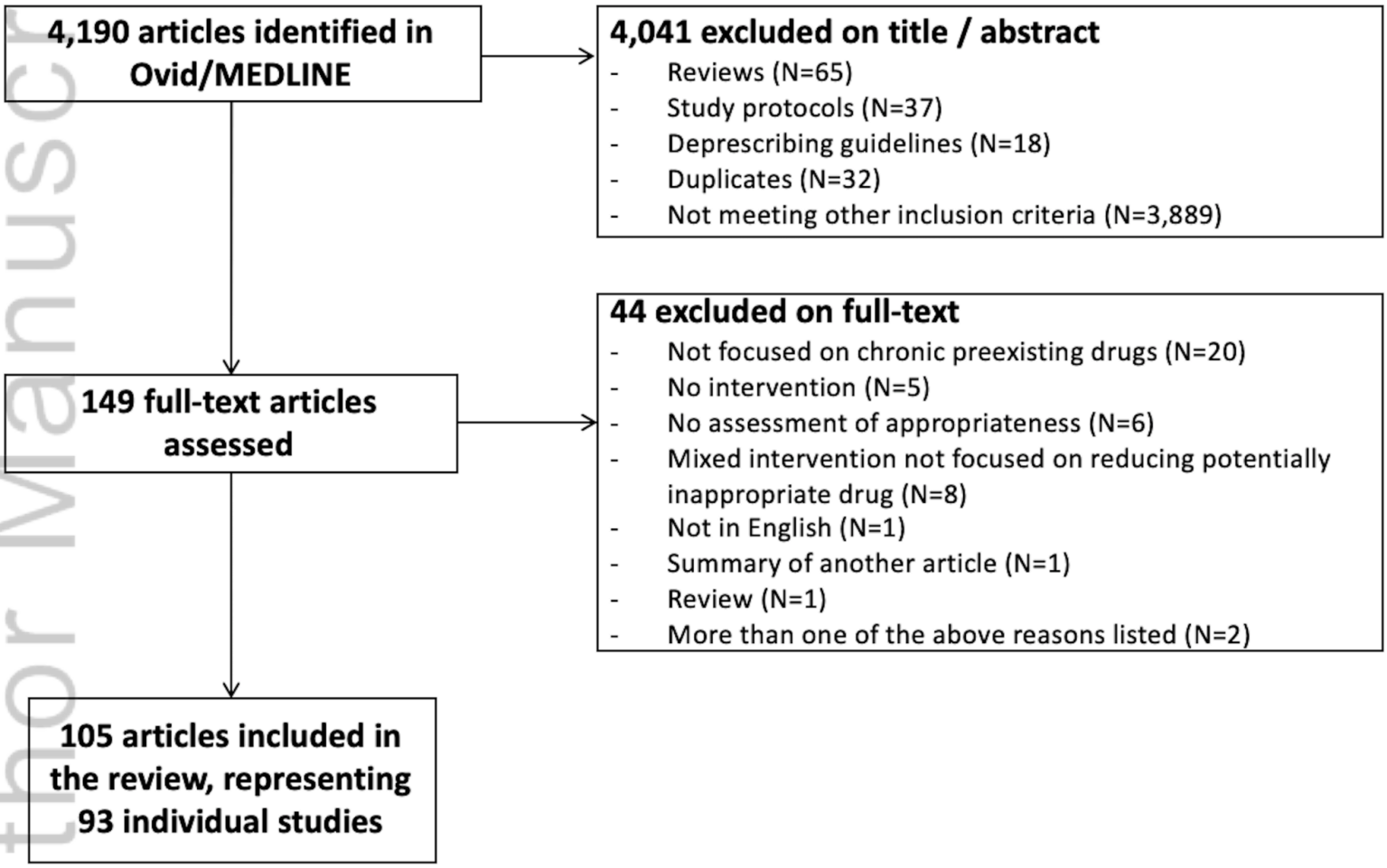
Supplementary Text S1. Search strategy

Supplementary Text S2. Complete list of articles

Supplementary Table S1. Measure categorization and assessment

Supplementary Table S2. Detailed study characteristics

Supplementary Table S3. Summary of measures for each study



JGS_16697_Figure 1 - Deprescribing measures.png