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Deprescribing of antidepressants: development and application of indicators of high-risk and overprescribing

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List of abbreviations

WHO	World Health Organization
ICD	International Statistical Classification of Diseases and Related Health Problems
DSM	Diagnostic and Statistical Manual of Mental Disorders
APA	American Psychiatric Association
GP	General practitioners
UK	United Kingdom
POKAL	Predictors and outcomes in primary depression care
U.S.	United States
ADR	Adverse drug reaction
SSRI	Selective serotonin-reuptake inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitors
TCA	Tricyclic antidepressant
MAOI	Monoamine oxidase inhibitors
NASSA	Noradrenergic and specific serotonergic antidepressants
NDRI	Norepinephrine-Dopamine Reuptake inhibitors
CVD	Cardiovascular disease
CI	Confidence interval
NSAID	Nonsteroidal anti-inflammatory drug
RAM	RAND/UCLA Appropriateness Method
NHS	National Health Service
BNF	British National Formulary
PDI	Potential deprescribing indications
OR	Odds ratio
sRR	Standardized relative risk
PIM	Potentially inappropriate medication
STOPP/START	Screening Tool of Older Person’s Prescriptions/ Screening Tool to Alert doctors to Right Treatment
GDNG	Gesundheitsdatennutzungsgesetz
FDZ	Forschungsdatenzentrum
EMPOWER	Eliminating Medications Through Patient Ownership of End Results
PARTNER	Patient-centred Deprescribing of Psychotropic, Sedative and Anticholinergic Medication in Elderly Patients With Polypharmacy

List of publications

This cumulative thesis consists of the following publications:

1. **Brisnik V**, Vukas J, Jung-Sievers C, Lukaschek K, Alexander GC, Thiem U, et al. Deprescribing of antidepressants: development of indicators of high-risk and overprescribing using the RAND/UCLA Appropriateness Method. BMC Med. 2024;22(1):193.

DOI: 10.1186/s12916-024-03397-w

2. **Brisnik V**, Rottenkolber M, Vukas J, Schechner M, Lukaschek K, Jung-Sievers C, et al. Potential deprescribing indications for antidepressants between 2012 and 2019: repeated cross-sectional analysis in two Scottish health boards. BMC Medicine. 2024;22(1):378.

DOI: 10.1186/s12916-024-03584-9

Contributions of the Ph.D. candidate

My contribution to publication I

As a first author of paper I, I was involved in the specification of research questions under the supervision of my doctoral supervisor Prof. Dr. Tobias Dreischulte. I was responsible for conducting all the steps of the expert consensus process which included the following: recruitment of the expert panel, literature review, writing the evidence report, specification of candidate indicators to be subjected to the consensus process, analysis of expert ratings, preparing the expert panel meetings, co-moderating the expert panel meetings, and preparing the final list of indicators (final results).

I have written the first draft of the manuscript, incorporated co-authors' comments, finalized the manuscript based on reviewers' comments, and prepared the response letters to address reviewer comments during the peer review process.

My contribution to publication II

As a first author of paper II, I was involved in the specification of research questions under the supervision of my doctoral supervisor Prof. Dr. Tobias Dreischulte. For the repeated cross-sectional analysis of administrative claims data, I operationalized all indicators developed in paper I by linking administrative codes to relevant medications and comorbidities, including the definition of proxies for data items not directly measurable in the data source used (e.g., medication proxies for chronic medical conditions). I was responsible for preparing and managing the data (data cleaning) and I performed the statistical analyses using the SPSS statistical package and was involved in all stages of the interpretation of the data.

I have also written the first draft of the manuscript, incorporated co-authors' comments, finalized the manuscript based on reviewers' comments, and prepared the response letters to address reviewer comments during the peer review process.

Introductory summary

1. General introduction

1.1 Depression, multimorbidity and polypharmacy in primary care

Depression

Depression is a common mental health disorder with a chronic and recurrent pattern (1). Depression commonly manifests as a state of markedly depressed mood, diminished interest or pleasure in daily activities, loss of energy or fatigue, changes in appetite and sleeping patterns or impaired concentration over a prolonged period of time (2).

Prevalence and epidemiology

Depression has a global impact, with the World Health Organization (WHO) reporting that in 2023 approximately 5% of all adults worldwide were experiencing the disorder (3). This translates to approximately 280 million people with significant functional impairment and diminished quality of life (3). While lifetime prevalence fluctuates notably between countries and genders (4, 5), it is estimated that the lifetime risk of developing depression is around 11-18%, meaning that a significant portion of humanity will experience depression at some point in their lives (6-8). In Germany, the 12-month prevalence of unipolar depression is reported at almost 8.0% and it is rising (9-11). An observational study in Germany using ambulatory claims data found, that the prevalence of treated depressive disorders increased from 12.5% to 15.7% between 2009 and 2017 (+26%) (12). In light of the WHO's projection that depression will become the leading global disease burden by 2030 (6), timely diagnosis and appropriate treatment of depression remain crucial.

Diagnosis and severity

In Germany, unipolar depression is generally classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD) of the WHO (both 10th and 11th version considered), while internationally the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association (APA) is also used (2). Based on the number of symptoms (combination of primary and additional) and their duration (have to be present for at least 2 weeks), depression can be categorized into three levels of severity according to ICD-10: mild, moderate, and severe (13). This classification forms the basis for treatment recommendations. Antidepressants are generally not recommended as an initial treatment for mild depressive episodes (defined by the presence of at least 4 symptoms in total, i.e., presence of at least 2 main symptoms (e.g., depressed mood or loss of interest in daily activities) and 1 or more additional symptoms (e.g., sleep disorder)). However, for moderate (i.e., at least 6 in total, but presence of at least 2 main symptoms and

3 or more additional symptoms) and severe depressive episodes (i.e., presence of all 3 main symptoms with at least 5 additional symptoms), antidepressants are recommended in combination with psychotherapy (2). According to the ICD-11, which will replace the ICD-10, not only the number of symptoms but also their intensity and the degree of functional impairment will be taken into account for the severity classification (14).

Challenges in primary care setting

For patients with depressive disorders, primary care providers are often the first point of contact and the central provider of outpatient care (1, 15, 16). A recent observational study in Germany showed that more than half (54.1%) of patients with depression were treated by general practitioners (GPs)(15), with even higher proportions reported internationally, for instance in Australia and United Kingdom (UK) (17, 18). GPs are often responsible for the initial diagnosis of depression, but they also frequently manage the condition, especially for patients with mild to moderate symptoms of depression (1).

Primary care providers also play a crucial role in managing coexisting physical comorbidities (1), which may interfere with the diagnosis and therapeutic management of depression, particularly in patients with multiple chronic conditions. Multimorbidity, defined as the coexistence of two or more chronic conditions, is a phenomenon that increases with age and can further complicate the clinical picture of depression (19). Patients with multimorbidity may not explicitly report their depressed mood (20), and somatic symptoms might either be obscuring or be misinterpreted as symptoms of depression (affecting diagnostics) (21). Medication use for depression and somatic comorbidities may compromise medication safety and increase the risk of adverse drug reactions (e.g., due to drug-drug, drug-disease and drug-age interactions), especially in patients with polypharmacy (which is most commonly defined as the use of five or more drugs simultaneously) (22).

Although depression is already one of the leading causes of disability worldwide and therefore represents an important public health issue, the prevalence and complexity of mental illnesses is in fact increasing as the population ages (23, 24). Therefore, the interdisciplinary research training group POKAL was created with the aim of improving the diagnosis and treatment of depression in patients with multimorbidity in primary care. This thesis is a subproject therein (24).

1.2 Polypharmacy

In view of persistent reports of preventable drug related harm, such as drug related hospital admissions (25), the World health Organization (WHO) has declared polypharmacy and medication safety a health care priority (26).

Prevalence and epidemiology

Studies suggest that polypharmacy is highly prevalent among older adults, with comparable rates observed in the United States (U.S.), Europe and Australia, where prevalence spans from approximately 23 to 45% (27-31). However, according to a recent systematic review, prevalence of polypharmacy can range wide from 2.6% to 86.6%, depending on the setting and study population (32). A multinational retrospective cohort study found that, in 2018, 58.3% of older adults aged 65 and older in Germany were prescribed 5 to 9 medications, while 28.5% were prescribed 10 or more drugs (33). Among older people, polypharmacy is therefore the rule rather than an exception.

Implications of polypharmacy

While the use of multiple medications is often appropriate and for certain indications clinically undisputable, polypharmacy significantly increases the risk of potentially inappropriate medication (including drug-drug interactions, drug-disease interactions, and drug-age interactions), and adverse drug reactions (ADRs). Such ADRs may have serious implications for individuals (including hospital admission or death) and society (increasing healthcare costs) (34-40). According to a recent meta-analysis, 8.3% of emergency hospital admissions are due to adverse drug reactions, with almost half deemed at least possibly preventable (25). The regular use of multiple medications has also independently been linked to increased risks of mortality, falls, fractures, as well as functional and cognitive decline (37, 38, 41).

In order to mitigate the risks associated with polypharmacy, guidelines recommend comprehensive medication reviews at least annually, which aim to assess and optimize the effectiveness and safety of medication regimens (42). Such reviews can sometimes lead to deprescribing, which is one way to reduce inappropriate polypharmacy. Deprescribing is characterized as a systematic approach of reducing, discontinuing or switching medication that is no longer needed, shows no or limited benefit or increases the risk of adverse effects (43-46), with the aim of reducing unnecessary healthcare utilization.

Polypharmacy medication regimens, mostly among older adults, are largely monitored in primary care. Such reviews often require difficult conversations with patients about benefits, risks and preferences and are therefore often clinically complex and time consuming. The need for regular critical assessments of continued use might particularly apply to antidepressants, due to the natural course of disease remission, sometimes more effective non-pharmacological alternatives such as psychotherapy and significant risks in the presence of risk factors such as polypharmacy and multimorbidity. In addition, one study even suggests, that the observed rise in polypharmacy in the U.S. between 1988 and 2010 among older adults was partly attributed to the increased use of cardioprotective and antidepressant therapies (47).

1.3 Antidepressant use

Antidepressants have an important role in treating people with depression and clinical guidelines recommend them complementary to psychotherapy for moderate and severe depressive episodes (2). Antidepressants can be best divided into the following groups based on their mechanism of action (Table 1).

Table 1 Main antidepressant groups and their mechanisms of action (2)

Antidepressant group/antidepressant drug	Mechanism of action	Drugs included in the antidepressant groups
Selective serotonin reuptake inhibitors (**SSRIs**)	Selective inhibition of serotonin reuptake from the synaptic cleft	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin and norepinephrine reuptake inhibitors (**SNRIs**)	Selective inhibition of serotonin and norepinephrine reuptake from the synaptic cleft	Duloxetine, venlafaxine, milnacipran
Tri- and tetracyclic antidepressants (**TCAs**)	Inhibition of serotonin and norepinephrine reuptake from the synaptic cleft; additional blockade of central and peripheral cholinergic, histaminergic or α1-adrenergic receptors	Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine
Monoamine oxidase inhibitors (**MAOIs**)	Inhibit the action of monoamine oxidase enzyme, that is responsible for catabolizing serotonin, norepinephrine and dopamine (increase in concentration)	Moclobemide → reversible selective MAO-A inhibitor Tranylcypromine → irreversible non- selective MAO-inhibitor
α_2-receptor antagonists/ Noradrenergic and specific serotonergic antidepressant (**NaSSA**)	By blocking the receptors → increased release of serotonin and norepinephrine into the synaptic cleft; additional antihistaminergic effect (i.e., sedative and weight increasing)	Mirtazapine, mianserin
Other antidepressants		
Norepinephrine-Dopamine Reuptake inhibitors (**NDRIs**)	Increases dopamine and norepinephrine levels in the synaptic cleft by selective reuptake inhibition	Bupropion
Trazodone	Antagonist of serotonin 2 receptors (5HT2 receptors) and, at higher doses, also a serotonin reuptake inhibitor; α2 receptor and histamine 1 receptor antagonist	-
Agomelatine	Serotonin 5-HT2C receptor antagonist, additional agonistic effects on melatonin receptors (MT1/MT2)	-

Prevalence

In recent years, treating depression has seen significant advances with measures to decrease stigma associated with mental diseases (48). In parallel, the use of antidepressants has been consistently increasing in the last two decades (49-55), with numerous studies indicating a doubling of antidepressant prescribing during this period (56), which cannot easily be explained by the increasing depression rates (11). Antidepressants are now among the most

commonly prescribed medications worldwide and western countries report that between 9-20% of adults take antidepressants annually (57-60). However, the reported prevalence rates vary by the particular population examined as well as study designs. For example, data from the National Health and Nutrition Examination Survey show that between 2015 and 2018, 13.2% of adults in the United States used antidepressant medications in the last month (58), while in England, nearly 20% of adults (8.6 million) were prescribed antidepressants in 2022/23 (60, 61). In addition, antidepressant use is also increasing with age, and studies report consistently higher rates among women than men (55, 57, 58, 62). Although increased diagnosis and reduced stigma may partially explain the surge in antidepressant use, there is also a growing concern regarding potential overuse of antidepressants and its adverse consequences, as described below.

1.3.1 Drivers of increasing antidepressant use

Several factors have been identified as contributing to the rise in antidepressant use (e.g., increased SSRI prescriptions) (63); however, the most consistently reported drivers are the growing proportion of individuals receiving long-term treatment and the use of antidepressants for a broader range of indications, as outlined below.

1.3.1.1 Long-term antidepressant use

In order to prevent relapse, clinical guidelines recommend treatment for 6 to 12 months after remission of a depressive episode, while longer use for up to two years is recommended in cases of multiple recurrent episodes (2). However, there is ample evidence supporting that one of the main reasons antidepressant prescriptions have increased in the last few decades has been an increase in the proportion of people with long-term use (56, 64), observing an approximate doubling every decade (49, 63). The vast majority of studies uses >2 years to define the exposure to long-term use, exceeding the evidence-based clinical recommendations, and those studies report that at least 40% (ranging from 47.1% in England to 57.4% in Switzerland) are long-term users (59, 65). Duration of antidepressant use is moving into years in western countries, with median durations of more than 2 years reported in the UK (65), 5 years in the U.S. (52) and mean duration of 4 years in Australia (17). Nevertheless, reliable evidence to support pharmacological treatment beyond clinical recommendations is missing, which is mostly explained by the short durations of clinical trials (66).

1.3.1.2 Missing clinical benefit, non-psychiatric or off-label indications

Clinical guidelines advise against prescribing antidepressants as initial treatment for mild depressive episodes (2). However, studies highlight a growing trend toward prescribing antidepressants in situations where guidelines criteria are not met, for instance for mild

depressive episodes, in situations without a known clinical benefit or without a formal psychiatric diagnosis (67-70).

Numerous studies also collectively suggest a significant trend of off-label antidepressant use in primary care settings across different populations, including older adults (71). Off-label indications most commonly include insomnia and various pain conditions. For example, two studies in primary care in Quebec, Canada report, that in one study, 29% of antidepressant prescriptions was for off-label indications (e.g., pain, insomnia or migraine) and in the second study, 45% of all antidepressant prescriptions were prescribed for non-depressive indications, such as anxiety disorders, insomnia, pain and panic disorders (72, 73). Similarly, in Germany, almost 44% of antidepressant prescriptions among older adults were off-label (74). These studies underscore the need for further research to better understand the implications of these prescribing practices, such as potential risks associated with using antidepressant for conditions that lack robust supporting evidence, particularly in vulnerable populations like the elderly (75).

1.3.2 Risks associated with antidepressant use

Older generation of antidepressants

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are typically not considered the first-line treatment for depression because of their well-documented side effects, potential for drug interactions, and the latter having dietary restrictions (76). Anticholinergic antidepressants contribute significantly to anticholinergic burden, which is associated with negative brain effects, poorer cognitive and functional outcomes (77). TCAs also pose substantial cardiovascular risks among older adults and their use is therefore generally discouraged (78-80).

New generation of antidepressants

Considering the risks of adverse drug reactions, newer generation antidepressants such as selective serotonin-reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs)) are generally safer and more tolerable (81). However, due to widespread and rising use of SSRIs and SNRIs, a number of studies have investigated potential risks associated with their long-term use (82). Several risks have been highlighted and might differentiate between those altering patients' quality of life, such as sexual dysfunction, weight gain, sleep disturbances or gastrointestinal symptoms (e.g., nausea or diarrhea) (83), and those associated with serious risks, such as increased risk of cerebrovascular disease, CVD (cardiovascular disease) mortality and all-cause mortality (82). One observational study including more than 60,000 older patients with depression found that use of SSRIs is also associated with a heightened risk of adverse outcomes including falls and

hyponatremia (84). The strong association of antidepressant use with falls was also demonstrated in a systematic review and meta-analysis (odds ratio 1.57 [95% confidence interval (CI) 1.43-1.74]) (85). SSRIs and SNRIs also inhibit the uptake of serotonin into platelets and if combined with antiplatelets, anticoagulants or nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit an increased risk of gastrointestinal bleeding (86, 87). However, studies also report the risk of intracranial bleeding associated with SSRIs (88). An overview of adverse events commonly associated with antidepressants and considered in this thesis is shown in Table 2.

Table 2 Adverse drug reactions associated with antidepressants

Adverse events	Antidepressant drugs	References
Cardiovascular adverse effects	SNRI, TCA, tranylcypromine, citalopram, escitalopram, fluoxetine, paroxetine, bupropion	(89-95)
Orthostatic hypotension/dizziness	TCA, trazodone, tranylcypromine, SSRI, SNRI, mirtazapine	(83, 91, 92, 96, 97)
Falls and fall-related injuries	Any antidepressant	(85, 98, 99)
Cognitive decline	TCA, opipramol, paroxetine	(100, 101)
Delirium	TCA, opipramol, paroxetine	(101, 102)
Serotonin syndrome	Tranylcypromine, SSRI, SNRI, TCA	(103-105)
Gastrointestinal bleeding	SSRI, SNRI	(86, 87, 106-109)
Non-gastrointestinal bleeding	SSRI	(88, 110-113)
Constipation	TCA, opipramol, paroxetine	(101, 114)
Hyponatremia	Any antidepressant	(115, 116)
Hepatic injury	Agomelatine	(117)
Voiding disorders	TCA, opipramol, paroxetine	(100, 101)
Glaucoma	TCA, opipramol, paroxetine	(100, 101)
Sleep disturbances/agitation	SSRI, SNRI, MAOI, bupropion	(118, 119)
Sexual dysfunction	SSRI, SNRI	(120, 121)

It becomes clear, that not only long-term use lacks sufficient evidence, but in patients with polypharmacy and multimorbidity, antidepressant use seriously increases the risk of clinically relevant drug-drug and drug-disease interactions, providing a strong rationale for deprescribing attempts (122).

1.4 Deprescribing

Deprescribing is a planned supervised process of tapering, discontinuing or switching medications in cases where the potential or actual harms outweigh the potential or actual benefits (123). Deprescribing is now recognized to be a key component of good prescribing practice (124). Individualizing the deprescribing process for each patient includes a series of steps, from initiating a thorough medication review, identifying potentially inappropriate medications (focusing on high-risk medications and medications without an evidence based indication or an expired indication), planning the potential discontinuation regimen (e.g., tapering if necessary) to ongoing monitoring (occurrence of potential discontinuation

symptoms or the need to restart treatment), and ensuring the sustainable discontinuation of medication (123, 125).

1.4.1 Barriers and facilitators to deprescribing

Each one of the above listed steps has its own specific barriers. However, in general, deprescribing is often viewed unfavourably by healthcare professionals for a number of reasons, including uncertainty regarding the benefits and risks of deprescribing specific medications (particularly when they are recommended by clinical guidelines targeting single conditions), organizational barriers (fragmented care and lack of resources in healthcare setting), and professional etiquette (healthcare providers may be reluctant to deprescribe medications prescribed by other clinicians) (126-129), to name a few. In addition, numerous patient-related barriers to deprescribing antidepressant have been identified, including previously failed discontinuation attempts, fears of relapse and withdrawal symptoms, perceived cause of depression (e.g., biochemical aetiology) and positive attitude toward psychiatric medications such as antidepressants (130). A significant concern shared by both healthcare professionals and patients during a deprescribing attempt is the risk of disease recurrence alongside the uncertainty surrounding discontinuation symptoms (131).

Due to competing priorities in primary care (e.g., acute symptoms, new prescriptions, new diagnostics), reviewing the continuous necessity and safety of antidepressants might often get overlooked. While in recent years, deprescribing initiatives (implementation strategies) are gaining traction (132, 133), specific guidelines on when this should be initiated, apart from general long-term use, are missing. Prior work is limited to a subset of more generic lists of potentially inappropriate medication that generally advise caution in the use of antidepressants among older adults (79). However, more specific advice as to when deprescribing of antidepressants should be considered (especial in the context of polypharmacy and multimorbidity) is desirable to guide the identification of deprescribing opportunities. A set of indicators with explicit criteria that should lead to a review is therefore a plausible strategy to support general practitioners in initiating the deprescribing process. This is a research question which is currently unanswered, and hence explored here.

2. Objectives

In light of the evidence highlighting not only the substantial increase in antidepressant use but also in its potentially inappropriate use and the complexities of deprescribing, it is imperative to support primary care clinicians in identifying patients, who might benefit most from a critical review of antidepressant continuation. Despite how commonly antidepressants are used and although a substantial number of observational studies highlighting the risks exist, little work has been done to identify specific settings in which they may have an unfavourable risk/benefit balance.

As an aid to encourage and guide primary care clinicians in antidepressant deprescribing where indicated, the specific objectives of this thesis are:

1) To develop explicit criteria for identifying inappropriate antidepressant use considering
   a) potential overprescribing and
   b) potential high-risk prescribing in primary care setting

2) To use this indicator-set to measure the potentially inappropriate antidepressant use by implementing the indicators as part of a population-based observational study using administrative claims data sources:
   a) To examine prevalence and time trends in antidepressant use
   b) To estimate the prevalence of long-term, potential high-risk antidepressant use as well as simultaneous long-term and potential high-risk use among antidepressant users identified under objective 2a using the consensus criteria-set
   c) To examine patient characteristics associated with simultaneous long-term and potential high-risk antidepressant use

3. Methods

3.1 RAND/UCLA Appropriateness method (Publication I)

For objective 1 of this cumulative thesis, a consensus approach following the RAND/UCLA (University of California) Appropriateness method (RAM) (134) was employed to derive a set of explicit indicators of potential high-risk and overprescribing of antidepressants that may suggest an unfavourable risk/benefit balance. First, a list of candidate indicators based on a structured literature review drawing from primary and secondary literature sources was compiled. Then the candidate indicators were evaluated through a three-round expert panel rating process accompanied with feedback and discussion of first and second round ratings prior to second and third round ratings (122). The steps of the RAM Process are outlined in Figure 1 according to publication I.

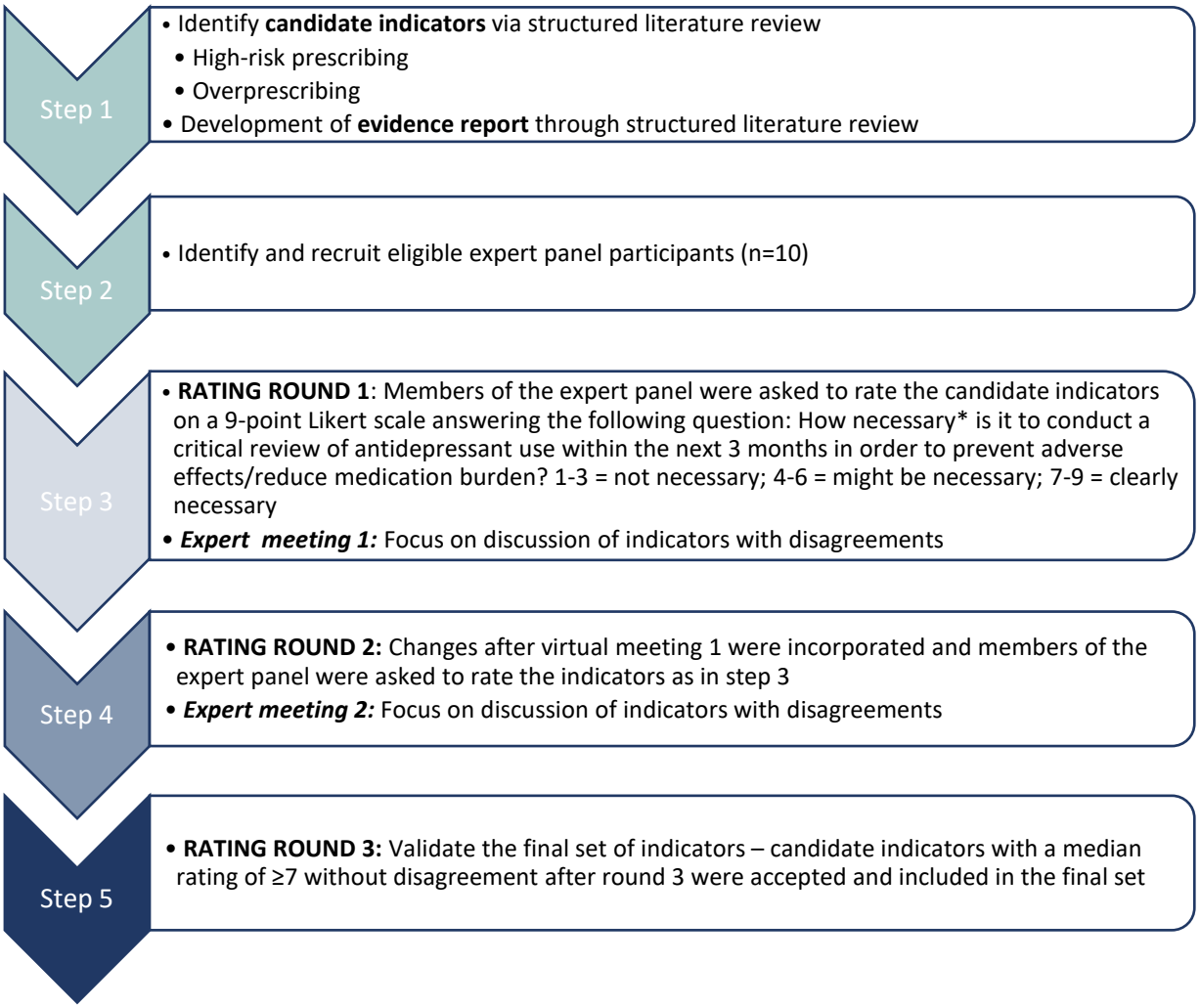

Figure 1 RAND/UCLA Appropriateness method (122)

3.1.1 Definition of high-risk prescribing

High-risk prescribing was one type of setting considered relevant for deprescribing of antidepressants, which was labelled as the use of antidepressants in the presence of risk factors that increase the likelihood of an ADR, whether:

- comedication (drug-drug interactions)
- comorbidities (drug-disease interactions) or
- advanced age (drug-age interactions) (Figure 2).

On the one hand, serious ADRs (i.e., can lead to hospital admission, such as falls or gastrointestinal bleeding) were prioritized, and on the other hand, less serious ADRs, that have the potential to significantly affect patient's quality of life (e.g., insomnia or sexual dysfunction), if antidepressant use would be continued, were also considered. Details about the identification of the indicators (structured literature review) can be found in publication I (122). The indicators were created as variations on the same topic, so that the thresholds beyond which a critical review would be considered necessary could be established.

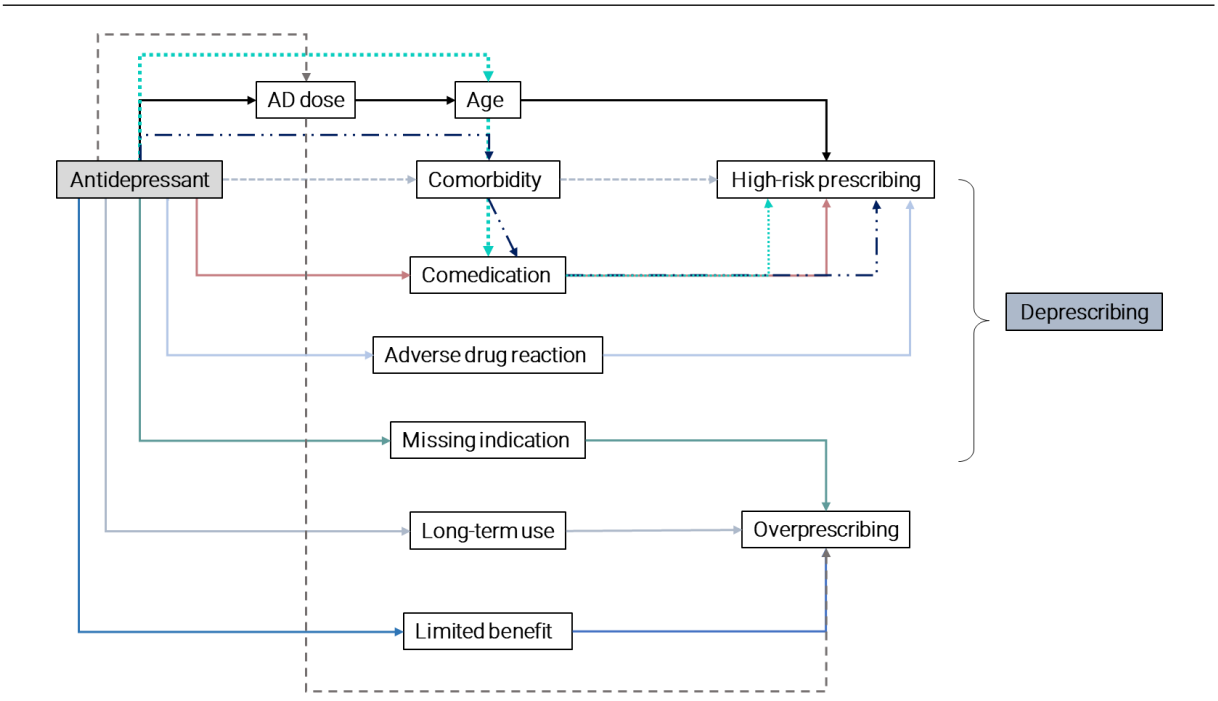

Figure 2 Various definitions of high-risk and overprescribing

3.1.2 Definition of overprescribing

Overprescribing was the second type of setting considered relevant for deprescribing of antidepressants, which was labelled as the prolonged use of antidepressants beyond recommended duration in clinical guidelines for depression, anxiety and insomnia. In addition, use of antidepressants for conditions lacking evidence of significant benefit (e.g., mild

depression) or at doses exceeding the recommendations in cases of pain and insomnia were also considered (Figure 2). Details about the identification of the indicators can be found in publication I (122). Same as for high-risk use, the indicators were created as variations on the same topic, so that the thresholds beyond which a critical review would be considered necessary could be established (122).

3.1.3 Rating construct and scale

Experts were asked to rate the indicators based on an average patient receiving antidepressant treatment in primary care (as illustrated in step 3 in Figure 1). Ordinal scales of 1 to 9 were used for all ratings (1-3=not necessary, 4-6=might be necessary, 7-9=clearly necessary). An indicator was deemed necessary if the median expert rating was ≥ 7 and no disagreement occurred. Disagreement was defined as at least 30% of experts scoring the item between 1-3 and another 30% scoring it between 7-9. Indicators with a median score below 7 or showing disagreement were excluded (122).

3.1.4 Selection of the expert panel

A diverse expert group with clinical and scientific experience in antidepressant use was assembled, drawing from various fields of professional practice to ensure a wide range of perspectives and expertise, which included general practitioners, psychiatrists, geriatricians, a gerontopsychiatrist, and clinical pharmacologists from Germany. The aim was to include around 12 participants, as recommended by the RAM (134), since this size ensured a balance of diverse expertise while maintaining efficient discussions (122).

3.2 A repeated cross-sectional study (Publication II)

3.2.1 Study design and data source

For objective 2 of this cumulative thesis, a repeated population-based cross-sectional study was conducted based on data provided by the University of Dundee/National Health Service (NHS) Tayside Health Informatics Centre (135).

3.2.2 Study population

Publication II of this thesis was based on 609,299 people aged ≥18 years resident in two regions of Scotland (Tayside and Fife) between 2012 and 2019.

3.2.3 Outcome definition/exposure assessment of the operationalized indicators

Antidepressant use

The prevalence of antidepressant use was estimated as exposure on a given index date of each year from 2012 to 2019, and June 30th was chosen as the mid-year time point.

Long-term use

Due to the unavailability of outpatient diagnoses and clinical patient information in the data source, such as remission status, only long-term use was appropriate for operationalization in this dataset. Long-term use was defined as the continuous use of the antidepressant for >2 years, i.e., for 8 quarters or more prior to index dates in 2012 and 2019, while a grace period of up to one quarter was allowed.

Potential high-risk use

Due to unavailability of outpatient diagnoses and clinical patient information, such as symptoms, 28 indicators from 37 originally consented in the indicator set were possible to be operationalized in this data set. All the definitions of ICD-10 codes (for hospital diagnoses) and British National Formulary (BNF) codes (recorded for each drug with its respective indication in the UK) used can be found in the appendix of publication II. For high-risk to be present, risk factors, such as age, comedication or previous hospital diagnosis, had to coexist in the three months prior to index dates in 2012 and 2019.

Potential deprescribing indications (PDIs)

Potential deprescribing indications (PDIs) were labelled as simultaneous exposure to both long-term and potential high-risk use on defined index dates (135).

3.2.4 Statistical methods

The prevalences of antidepressant use were calculated per 100 people for each antidepressant group for each year from 2012 to 2019, while the prevalences of long-term and high-risk use (separate) as well as PDIs (simultaneous long-term and high-risk use) were calculated on each index dates in 2012 and 2019 only. For high-risk use, the proportion of people triggering at least one of the 28 operationalized indicators of potential high-risk prescribing was estimated. Absolute numbers and rates of patients for all 4 situations were stratified by gender, age group, type of antidepressant drug class, socioeconomic status as well as residence. Those rates were compared between 2012 and 2019 for all 4 situations (135).

The relative risks between 2019 vs 2012 (and 95% confidence intervals (CI)) were calculated as non-standardised (crude) and age-sex standardized percentage rates to take into consideration the changes in population demographics between 2012 and 2019 (2019 data directly age-sex standardised to 2012 population structure). For the sensitivity analyses, the proportion of long-term users was considered by constricting the definition of long-term use to >2 years without a grace period, while for high-risk, the definition was restricted to triggering at least one high-risk use indicator, considering only those with a median of 8 or 9 on a 9-point Likert scale as rated in the consensus criteria-set (135).

To determine associations between patient characteristics and having PDIs, a binary logistic regression was performed. Initially, unadjusted odds ratios (ORs) with 95% CIs were calculated with subsequent multivariate analysis. Patient variables considered were age group, gender, total number of medication groups dispensed in the index quarter, type of antidepressant regimen as defined by the indicators, socioeconomic status and residence (135). Data management and statistical analyses were performed using SPSS (version 25, IMB Corporation 2018). A p-value < 0.05 was considered statistically significant.

4. Key findings

4.1 Findings of the RAM consensus process (Publication I)

The first publication addresses the first objective outlined in this thesis: development of explicit criteria for identifying inappropriate antidepressant use considering potential high-risk and overprescribing of antidepressants.

Ten clinically trained physicians with research and patient care experience participated in the three-round expert panel. The panel consisted of various specialists, including two general practitioners, two clinical pharmacologists, two psychiatrists, three geriatricians and 1 gerontopsychiatrist. Of the 212 candidate indicators of potential high-risk prescribing included in the first-round survey, 37 reached a consensus (median score of 7 or higher without significant disagreement) after the final round and of the 70 candidate indicators of potential overprescribing included in the first-round survey, 25 indicators reached a consensus on the necessity of a review (122).

Prioritized high-risk prescribing indicators included constellations of known anticholinergic (e.g., cognitive decline, delirium, constipation, voiding disorders, and glaucoma) and cardiovascular risks (e.g., QTc prolongation) but also falls, orthostatic hypotension/dizziness, bleeding, serotonin syndrome, hyponatremia, hepatic injury, sleep disturbances and sexual dysfunction. Among the indicators with the highest ratings (median = 9) were those that indicated the possibility of cardiovascular risks such as QTc prolongation associated with citalopram and escitalopram, delirium associated with anticholinergic antidepressants, gastrointestinal bleeding associated with SSRIs and SNRIs, and liver injury associated with agomelatine. Overprescribing indicators target patients with long treatment durations for depression, anxiety, and insomnia as well as high doses for pain and insomnia (122).

4.2 Findings of the repeated population-based analysis (Publication II)

The second publication addresses the key objective 2 outlined in this thesis: to measure the potentially inappropriate antidepressant use (estimation of antidepressant use, long-term and high-risk antidepressant use, and investigation of patient characteristics associated with PDIs).

Antidepressant use

The findings demonstrate that between 2012 and 2019, antidepressant use in adult residents of two Scottish regions increased by more than a quarter (sRR 1.27) from 12.0% to 15.3%. Antidepressant use grew specifically for SSRI, SNRI and NASSA (sRR 1.32, 1.89 and 1.95, respectively). When we stratified by patient characteristics, we see that people aged ≥40 years exhibited a higher prevalence in antidepressant use compared to younger individuals (77.5%

were ≥40 years in 2019), however, the largest relative increase (sRR of 1.49) was seen in younger adults aged 18 - 39 years. Antidepressant use was much more common among women (20.2%) compared to men (10.1%), however rose for both sexes between 2012 and 2019 (sRR 1.34 for men vs sRR 1.24 for women). Antidepressant use was also nearly twice as high among residents in the most socially deprived (21.0%) compared to least deprived (11.3%) areas in 2019 (135).

Long-term use

In the course of this work, it was shown that the proportion of antidepressant users with long term use (> 2 years) increased from 54.3% in 2012 to 61.9% in 2019 (sRR 1.16). When we considered stricter definitions of long-term use in sensitivity analyses, the prevalence of long-term antidepressant use in 2019 was rather lower compared to primary analyses (48.8% vs 61.9%). Similar to general antidepressant use, long-term use was more common among women (64.2%) than among men (57.3%), but consistently rose for both sexes (sRR 1.17 for women vs sRR 1.15 for men). In terms of age distribution, we observed a similar trend to that of antidepressant use; while the proportion of antidepressant long-term users was higher among older adults, it increased more significantly among younger adults (sRR 1.24).

Potential high-risk use

Results also show that the proportion of antidepressant users triggering at least one high-risk use indicator decreased from 37.9% in 2012 to 34.7% in 2019 (sRR 0.93), however, the total number of patients with any high-risk use of antidepressants increased between 2012 and 2019 from 27,861 to 32,131. High-risk use most commonly related to indicators targeting fall risk (16.0% of all antidepressant users), cardiovascular risks (14.1%), insomnia (10.6%) and risk of orthostatic hypotension (8.6%).

Potential deprescribing indications (PDIs)

Proportion of antidepressant users with PDIs (defined in this study as simultaneous long term and potential high-risk use) increased from 23.7% to 25.8% (sRR 1.11). When we considered both stringent definitions for long-term and high-risk use in sensitivity analyses, the prevalence of PDIs was considerably lower compared to primary analyses (6.5% vs 25.8%). The results of multivariate logistic regression show that the presence of PDI was most strongly associated with increasing age and with more drugs taken concomitantly, but also with the use of TCAs (at doses ≥50mg) and concomitant use of 2 or more antidepressants compared to the use of SSRIs only. More details about the results can be found in publication II.

5. Discussion

5.1 Summary of findings

In the first part of this thesis, a panel of 10 experts, including general practitioners, clinical pharmacologists, psychiatrists, and geriatricians, reached a consensus on 37 high-risk and 25 overprescribing indicators of potentially inappropriate antidepressant use. By applying these indicators in a population-based observational study using administrative claims data from two Scottish regions between 2012 and 2019, we observed that antidepressant use among adults increased approximately by a third (from 12.0 to 15.3%). Additionally, the proportion of patients on long-term antidepressant treatment increased from 54.3 to 61.9%. Although the proportion of antidepressant users triggering at least one high-risk indicator decreased from 37.9% to 34.7%, the absolute number of people affected by high-risk prescribing increased. Furthermore, when examining simultaneous long-term and high-risk use, the proportion of patients with potential deprescribing indications (PDIs) also rose to more than 1 in 4 antidepressant users impacted in 2019.

5.2 Comparison to literature

While largely consistent with previously published tools listing PIMs, our targeted approach - focusing on a single medication group - enabled us to identify a more nuanced and comprehensive set of indicators. For example, compared to the widely used STOPP (Screening Tool of Older Person's Prescriptions)/START (Screening Tool to Alert doctors to Right Treatment) PIM tool (79), the number of indicators relating to high-risk use of antidepressants in our tool is much higher (37 vs 10) and we target a much broader spectrum of adverse outcomes (including fall risk, bleeding, sexual dysfunction, and insomnia), which are often overlooked in other PIM lists or clinical guidelines, despite robust supporting evidence (85, 106). While not directly comparable, other studies have examined the prevalence of general high-risk prescribing in primary care (136). However, we are unaware of any studies that specifically quantify high-risk antidepressant use and deprescribing potential. Our findings indicate a comparable (if slightly higher) proportion of individuals prescribed antidepressant treatment long-term (61.9%), compared to 57.4% in a similar study in a Swiss population (59). However, our findings are consistent with the broader trend of rising long-term antidepressant use, as well as the overall increase in antidepressant prescriptions (52). Furthermore, the use of SSRIs, SNRIs, and mirtazapine continues to rise, reflecting trends reported in other observational studies (137).

5.3 Methodological considerations

5.3.1 Strengths

Within the scope of the first publication, an indicator-set was developed using the RAND/UCLA Appropriateness Method as opposed to the otherwise commonly used Delphi process (138). The RAM process affords the experts many opportunities to exchange their arguments in between rating rounds, which is where the strength of this method lies. In addition, the multidisciplinary expert panel allowed for a consideration of diverse clinical perspectives, considering primary care settings, as well as geriatric and psychiatric distinctive factors, among others. Another strength is the comprehensive approach in developing these indicators, which addresses both high-risk and overprescribing of antidepressants. Compared to other generic lists of potentially inappropriate medications (78, 80), which also include antidepressants, this study focused on one medication group only. Thereby allowing for greater granularity, which has previously been missing in other PIM lists. At the same time, our approach has identified clinical situations of high clinical relevance (i.e., those, for which there was expert consensus that they should trigger pro-active review of deprescribing indications). Thereby minimizing the risk of over-alerting clinicians.

The second publication draws on a large, representative population-based sample from the Scottish population with its longitudinal scope. By analysing trends over eight years (2012–2019), the study provides a comprehensive view of changes in antidepressant use as well as long-term and high-risk use over time. A very granular analysis by age, gender, type of antidepressant, and socioeconomic status make the findings more nuanced and clinically relevant. The study demonstrates that the indicator set can yield a meaningful assessment of the status quo of potentially inappropriate use of antidepressants at population level as well as time trends, thereby enabling identification of patient safety priorities for intervention and international comparisons.

5.3.2 Limitations

Our indicator set addresses a wide range of adverse effects and common indications for antidepressant use in primary care setting, however, it does not capture all instances of overprescribing or sources of antidepressant related risks, as our focus was specifically on adverse drug reactions in the context of polypharmacy and multimorbidity. While the panel was multidisciplinary, it was confined to experts from Germany. Although the supporting evidence is internationally valid, some adaptations to local context of the indicators or their operationalization may be necessary.

Some of the indicators could not be implemented in the routine data set, as we lacked information on outpatient diagnoses and patient-reported outcomes. Using reliable proxies to

determine the prevalence rates, which were limited, may have introduced some uncertainty into the results (potential under- or overestimation of the prevalence). However, the repeated cross-sectional nature of the study meant we investigated the prevalence for two different years, therefore comparisons between the years 2012 and 2019 remain robust results as any measurement errors affected both years equally. In addition, due to the nature of cross-sectional studies, chronic use of medication could also not be ascertained for aspects of high-risk prescribing (e.g., timely occurrence of drug-drug interaction). Moreover, our analysis could not account for the indication of antidepressant use, which could have added valuable insights to our analysis (e.g., limiting ability to assess whether long-term use was clinically justified). The study is also restricted to two Scottish health boards, which may limit its applicability to regions with different health systems or patient demographics.

Although strong evidence links antidepressants to identified adverse events, individual risk factors may play an even more significant role in their development. Randomized controlled trials typically establish the benefits and risks of medications in younger patients with a single condition, making their results less applicable to older individuals with multimorbidity. In older adults, medication appropriateness goes beyond pharmacological effects, encompassing patient-specific factors such as necessity, potential for adverse reactions, drug-drug/drug-disease interactions, adherence, and personal preferences (125). Our indicators do not account for patient preferences or individualized risk-benefit assessments, which are crucial for deprescribing decisions.

Although the indicator set developed here is evidence based, it is clear that pre-specified criteria can only identify medication use that is *potentially* inappropriate, rather than identifying *actual* need for medication changes, which depends on balancing risk and benefit. While the indicator set developed here identifies high-risk and potentially longer than evidence-based treatment with antidepressants, it does not assess individual treatment benefit (which in the case of antidepressants is inherently difficult to assess objectively at individual patient level and currently impossible to assess at population level using administrative claims data).

5.4 Implications for practice and research

Implications for practice

Antidepressants are commonly prescribed in the primary care context and require a stringent consideration of their continuous use particularly in the context of multimorbidity and polypharmacy (139). The findings of this thesis show, that approximately 1 in 4 antidepressant users have been prescribed this medication group >2 years and simultaneously trigger at least one high-risk use indicator due to presence of risk factors. However, manual application of the indicator set by general practitioners as part of routine practice is not a realistic prospect. However, automating the assessment to identify patients for a more detailed review (case

finding) is a promising implementation strategy. Studies have shown that electronic health-record based risk identification using safety indicators can effectively reduce high-risk prescribing in primary care (140). In addition, the indicator set can be used in clinical surveillance (audit and feedback) at the population level to drive and monitor quality improvement initiatives at regional, national or international levels.

In Germany, strict data protection regulations have historically limited the use of routine health care and insurance claims data for quality improvement and research purposes. However, in 2023, the German Federal Government has passed The Health Data Utilization Act (GDNG), which provides new opportunities for both population and individual level assessment of medication use. For population level analyses, the Forschungsdatenzentrum (FDZ) will provide access to statutory health insurance claims data (including dispensed prescribing, diagnoses and hospital admissions) for all people with statutory health insurance in Germany; and at individual patient level, health insurance companies will be allowed to directly contact individual members for medication safety concerns (141).

The latter approach, may be a particularly promising strategy to support the implementation of deprescribing of antidepressants and other psychotropic drugs, as demonstrated by the EMPOWER intervention and trial (142). In this intervention, older patients with long term use of benzodiazepines were identified based on pharmacy dispensing records. Identified individuals were then provided with “empowerment brochures”, informing them of the limited benefits and significant risks of long-term use and encouraging them to discuss deprescribing with their physician. The intervention led to a significant reduction in long term use of benzodiazepines at 6 months (27% in the intervention and 5% in the control group). Implemented in insurance claims data, the indicator set developed here may therefore be used in a similar way to identify patients with potential deprescribing indications for antidepressants.

Implications for research

The indicator set developed in this thesis is designed to address one important component of deprescribing, i.e., identification of patients who may benefit from deprescribing interventions. However, as highlighted above, it is currently not known, to which extent the indicator set identifies actual deprescribing opportunities.

One approach to further explore to which extent there is actual opportunity for improving antidepressant use is by studying variation in the prevalence of deprescribing indicators across different primary care practices, as outlined in a related study on mental health safety indicators (143). This has several important applications, including identifying practices with higher rates of potential high-risk prescribing or overprescribing (136). By focusing on these practices for targeted interventions, resources could be allocated more effectively, ultimately promoting more equitable care.

A further approach is to actually test the indicator set in clinical practice. In order to examine, which proportion of potential deprescribing indications identified by the indicator set represent actual deprescribing opportunities, we are currently conducting a pilot study in 8 general practices, in which general practitioners examine patients with potential deprescribing indications identified by the indicators.

Assuming a favourable outcome of this pilot study, further intervention components are likely to be necessary to increase more widespread implementation of antidepressant deprescribing. As highlighted above, key additional implementation barriers are patients' misconceptions about the benefits and risks of antidepressant use, anxieties about adverse withdrawal effects as well as prescriber uncertainties around how to design tapering schedules and practically implement them (127, 128). These barriers are exacerbated by time pressures and competing priorities of health care professionals (127). Complementary intervention components could therefore be educational material (e.g., guidelines) or practical tools to impart knowledge, correct misconceptions and provide practical advice. In addition, increasing motivation (e.g., incentives) and resources to implement the prescribing process are likely to be important (127, 128).

In order to increase the resources available in primary care to support deprescribing by general practitioners, the PARTNER trial is currently evaluating an interdisciplinary approach to deprescribing psychotropic, sedating and anticholinergic medications (144). In this model, pharmacists play a key role by conducting medication reviews and educating patients about the risks associated with potentially inappropriate medications.

6. Conclusion

This thesis has identified a comprehensive set of clinical situations that are intended to trigger a timely critical review of the continuation of antidepressants, which is a critical first step in initiating and implementing the deprescribing process. Given the ubiquity of antidepressant prescribing in primary and secondary care settings, it will have the potential to counterbalance the prevalent use of this medication group in situations where they have no measurable benefit, or no longer have relevant benefits, or are associated with high risk of harm. Over time, changes in health, the addition of medications, or new conditions can shift the balance of risks and benefits, making previously appropriate medications potentially inappropriate. This is particularly relevant among older adults, which is the age group that will be most affected by demographic shifts and population aging. Therefore, there is an urgent need for general practitioners to be equipped with clear, evidence-based guidelines for safe deprescribing.

Our findings also shed light on the widespread and increasing prevalence of potential deprescribing indications using the validated indicator set developed in this study and heighten the overall concern about the increasing use of antidepressants. The results provide a basis for further comparative analyses of the appropriateness of antidepressant use internationally as well as highlighting the need for and informing interventional studies to improve it.

The indicator set developed and applied in this thesis therefore addresses an important barrier to the broader implementation of antidepressant deprescribing, namely the identification of potential deprescribing indications at patient and population levels. The increasing accessibility and use of routinely collected health care and claims data in Germany and internationally, provide new opportunities for timely implementation of the indicator set into routine clinical practice, quality improvement and research.

7. Publications

7.1 Publication I

Title: Deprescribing of antidepressants: development of indicators of high-risk and overprescribing using the RAND/UCLA Appropriateness Method

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Deprescribing of antidepressants: development of indicators of high-risk and overprescribing using the RAND/UCLA Appropriateness Method

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Abstract

Background Antidepressants are first-line medications for many psychiatric disorders. However, their widespread long-term use in some indications (e.g., mild depression and insomnia) is concerning. Particularly in older adults with comorbidities and polypharmacy, who are more susceptible to adverse drug reactions, the risks and benefits of treatment should be regularly reviewed. The aim of this consensus process was to identify explicit criteria of potentially inappropriate antidepressant use (indicators) in order to support primary care clinicians in identifying situations, where deprescribing of antidepressants should be considered.

Methods We used the RAND/UCLA Appropriateness Method to identify the indicators of high-risk and overprescribing of antidepressants. We combined a structured literature review with a 3-round expert panel, with results discussed in moderated meetings in between rounds. Each of the 282 candidate indicators was scored on a 9-point Likert scale representing the necessity of a critical review of antidepressant continuation (1–3 = not necessary; 4–6 = uncertain; 7–9 = clearly necessary). Experts rated the indicators for the necessity of review, since decisions to deprescribe require considerations of patient risk/benefit balance and preferences. Indicators with a median necessity rating of ≥ 7 without disagreement after 3 rating rounds were accepted.

Results The expert panel comprised 2 general practitioners, 2 clinical pharmacologists, 1 gerontopsychiatrist, 2 psychiatrists, and 3 internists/geriatricians (total $N = 10$). After 3 assessment rounds, there was consensus for 37 indicators of high-risk and 25 indicators of overprescribing, where critical reviews were felt to be necessary. High-risk prescribing indicators included settings posing risks of drug-drug, drug-disease, and drug-age interactions or the occurrence of adverse drug reactions. Indicators with the highest ratings included those suggesting the possibility of cardiovascular risks (QTc prolongation), delirium, gastrointestinal bleeding, and liver injury in specific patient subgroups with additional risk factors. Overprescribing indicators target patients with long treatment durations for depression, anxiety, and insomnia as well as high doses for pain and insomnia.

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Conclusions Explicit indicators of antidepressant high-risk and overprescribing may be used directly by patients and health care providers, and integrated within clinical decision support tools, in order to improve the overall risk/benefit balance of this commonly prescribed class of prescription drugs.

Keywords Antidepressants, Deprescribing, High-risk prescribing, Overprescribing, Adverse drug events

Background

Antidepressants are first-line medications for many psychiatric disorders (including depression, anxiety disorders, and obsessive–compulsive disorder) and have proven to have substantial benefits particularly in patients with moderate to severe symptoms of depression or anxiety disorders [1]. Antidepressants are also some of the most commonly prescribed prescription drugs globally, and their use has increased over time. For example, according to one cross-sectional study in the USA, the proportion of persons aged ≥ 18 years using antidepressants increased by 60% from 6.5 to 10.4% between 1999 and 2010 [2]. More recently, the volume of antidepressant prescribing increased by 97% in England between 2008 and 2018 [3] and by 30% in Germany between 2012 and 2021 [4]. Increased use is desirable if this reflects increased awareness and diagnoses of mental health conditions and reduced stigma associated with affective disorders. However, the increasing use of antidepressants for longer durations than recommended by the guidelines has also been identified as a key driver [5]. General practitioners typically manage maintenance treatment with antidepressants and are therefore often faced with decisions around continuing or deprescribing antidepressants.

While antidepressants play an important role in the pharmacologic management of common and debilitating psychiatric illnesses as well as neuropathic pain and migraine, medication review interventions show they are also used in situations where they may have an unfavorable risk/benefit balance. For example, in one prospective cohort study, antidepressant use could be stopped, reduced, or switched (deprescribed) in almost one-quarter (23.2%) of antidepressant users [6]. Potential indications for stopping antidepressants in primary care include their use in mild forms of depression (where benefits are limited [1, 7, 8]), their long-term use for non-psychiatric illnesses such as primary sleep disorders [9, 10], and excessive treatment durations [5, 11–13]. Newer generation antidepressants (e.g., selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs)) are generally considered safer than traditional ones (e.g., tricyclic antidepressants (TCAs)) [14]. However, even SSRIs and SNRIs are not risk-free, especially among vulnerable older people, where long treatment durations are particularly common [15–17] and where comorbidity and comedication may increase the risk of adverse effects, such as falls and fractures, gastrointestinal bleeding, electrolyte imbalances, and cardiovascular events [18–21]. For example, a recent systematic review shows that antidepressants as a group are associated with a significantly increased risk of falls (odds ratio 1.57 [95% confidence interval (CI) 1.43–1.74]) [20], and in one observational study, the 1-year numbers needed to harm for fractures were 247 (for SSRIs) and 308 (for TCAs) among 65 to 74-year-olds, and 53 and 81 for people 75 years or older, respectively, while mirtazapine only significantly increased fracture risk among the older age group [22].

Despite the opportunities to improve the overall risk/benefit balance of antidepressant use in clinical practice, such opportunities may easily be overlooked by primary care clinicians due to competing priorities. The explicit criteria could help alert prescribers to *consider* deprescribing where indicated, even when *decisions* to deprescribe require considerations of patient-specific balance of benefits and risks as well as patient preferences. In addition to discontinuing antidepressants, deprescribing may also encompass dose reduction or switching to a safer agent, which may be the preferred option if antidepressant therapy continues to be necessary to control symptoms. Although existing generic lists of potentially inappropriate medication (PIM) generally advise caution in the use of antidepressants in the elderly [23], more specific advice as to when deprescribing of antidepressants should be considered is desirable to guide the identification of deprescribing opportunities. As an aid to encourage antidepressant deprescribing where indicated, the aim of this study was to establish evidence-based expert consensus on situations, where a critical review of antidepressant continuation would be warranted in primary care. We envisioned that by prompting earlier and proactive reviews of antidepressant use, the resulting set of explicit criteria could help prevent antidepressant-related harm, especially in vulnerable older people.

Methods

Study design

We used a consensus process based on the RAND/UCLA (University of California) Appropriateness Method (RAM) [24] to develop our indicators. First, we assembled a list

of candidate indicators based on a structured literature review including primary and secondary English and German literature sources. The candidate indicators were subjected to a three-round expert consensus process, with feedback and synchronous discussion of first and second round ratings before second and third round ratings were placed, respectively.

Selection of the expert panel

We recruited a diverse set of experts with clinical or scientific experience in the use of antidepressants from different fields of professional practice in order to achieve a broad range of perspectives and expertise. We therefore recruited general practitioners, psychiatrists, geriatricians, a gerontopsychiatrist, and clinical pharmacologists from Germany. We identified an initial set of 20 potential experts using our professional networks, planning for the ultimate inclusion of approximately 12 participants. Experts participating in the consensus process did not receive any compensation for their participation.

Identification of candidate indicators

Definitions

For the purposes of this study, we distinguished between two types of settings, where antidepressant deprescribing should be considered. We defined high-risk prescribing as the use of antidepressants in the presence of risk factors increasing the likelihood of an adverse drug reaction (ADR), whether comedication (drug-drug interactions), comorbidities (drug-disease interactions), or advanced age (drug-age interactions). We defined overprescribing as the use of antidepressants for longer periods than indicated or for indications without evidence of relevant benefit or at higher doses than indicated. We included SSRIs, SNRIs, TCAs, monoamine oxidase inhibitors (MAOIs), and atypical antidepressants such as mirtazapine, trazodone, bupropion, agomelatine, and opipramol in this study. Structurally, opipramol belongs to the class of TCAs and is widely prescribed in Germany for insomnia.

High-risk prescribing

In order to identify candidate indicators of high-risk prescribing of antidepressants, we initially searched for previously developed indicators targeting potentially inappropriate antidepressant prescribing [25–29]. We also considered systematic and clinical reviews of adverse antidepressant effects as well as clinical practice guidelines in English and German language. Based on consensus among a subset of co-authors (T.D. and V.B.), we prioritized ADRs for which a continuation of antidepressant use could either lead to serious harm, such as hospital admission, or severely affect patients' quality of life. We conducted further searches in PubMed/MEDLINE and EMBASE to identify candidate indicators linked to each ADR of interest. To this end, we conducted searches including carefully selected (MeSH and non-Mesh) terms for each specific adverse drug reaction of interest and combined these with terms for each group of antidepressants (e.g., SSRIs). We initially searched for recent systematic reviews and meta-analyses but also considered primary literature where reviews were not available or required updating. If applicable, we also examined the reference lists of important reviews for additional studies. We provide more details of the literature search and the search terms used in Additional file 1.

Overprescribing

In order to identify candidate indicators of overprescribing of antidepressants, we considered clinical practice guidelines in English and German languages for depression, anxiety and panic disorders, insomnia, and pain [30–33]. We searched for recommendations concerning treatment duration and the recommended doses when prescribed for insomnia and pain. In addition, we also searched for clinical guideline recommendations (e.g., for dementia) specifically not recommending antidepressants for a first depressive episode.

Design of the rating form and supporting materials

Members of the expert panel were sent the following materials: the rating form, a summary of clinical evidence summary, and rating instructions. The rating form included the candidate indicators, which were organized into 2 sections (high-risk and overprescribing), and each section was divided into chapters. In the high-risk prescribing section, there were 23 chapters for candidate indicators relating to each ADR (e.g., fall, GI bleeding), while in the overprescribing section, there was 1 chapter for candidate indicators relating to each indication (depression, anxiety, insomnia, pain). The indicators followed a standardized format and were designed as variations around the same topic in order to determine thresholds beyond which a critical review would be considered necessary (1 example is provided in Table 1). For each chapter, we developed a summary of clinical evidence supporting the candidate indicators to be considered by the expert panel as part of the rating process. The rating instructions defined rating constructs and assumptions and provided guidance on how the rating form was to be completed and returned.

We piloted the rating form, the summary of clinical evidence, and the supporting instructional materials with one psychiatrist, one clinical pharmacologist, and one general practitioner, using their feedback to optimize the final version of the first round survey. All materials are available from the authors upon request.

Table 1 Examples of candidate indicators[a] linked to falls/fall injuries

Candidate indicators	Median "necessity" rating after rating round 2	Accepted for the 3rd round
ADR: falls and fall-related injuries		
A. History of fall and prescribed one single antidepressant with sedating, anticholinergic, or orthostatic properties (TCA, mirtazapine, or trazodone)	7	Accepted
B. History of fall and prescribed one single antidepressant with sedating, anticholinergic, or orthostatic properties (TCA, mirtazapine, or trazodone) with one further fall risk-increasing drug	8	Redundant
C. History of fall and prescribed one single antidepressant with sedating, anticholinergic, or orthostatic properties (TCA, mirtazapine, or trazodone) with two or more further fall risk-increasing drugs	9	Redundant

[a] Multiple variations of candidate indicators were rated in order to identify thresholds beyond which a critical review of antidepressant use was considered necessary. Candidate indicators B and C were found to be redundant after candidate indicator A was accepted (necessity rating of ≥ 7)

Rating constructs and scales

Each expert rated each candidate indicator based on a 9-point Likert scale representing the necessity of a critical review of that particular clinical instance (1 to 3 = not necessary; 4 to 6 = might be necessary; 7 to 9 = clearly necessary). We also asked experts to rate the subset of indicators reflecting high-risk prescribing for "likelihood of harm," and each linked ADR was additionally rated for "severity of harm." For all candidate indicators, the necessity to review was the decisive criterion for the acceptance of indicators, and we used these latter ratings to inform discussion in case of disagreements.

Necessity of review

We asked for the necessity of review rather than the necessity of deprescribing since deprescribing decisions may depend on a patient-specific balance of benefits and risks as well as patient preferences, which are unfeasible to pre-specify. We defined "critical review" as a critical assessment of the balance of benefits and risks of antidepressant use to be conducted within 3 months, which would involve patient empowerment and shared decision-making and take at least 30 min to conduct. A critical review may result in dose reduction, switching, or discontinuation of an antidepressant (deprescribing). Consistent with RAM, we defined "necessary" to mean that omitting the review would be considered improper care, that conducting the review would have a reasonable chance of benefitting the patient and that the benefit is not small (Table 2).

Likelihood and severity of harm

We defined *likelihood of harm* as the likelihood of the adverse drug reaction happening if the clinical situation was to be continued for another year and *severity of harm* as the severity of the harm if the adverse drug events happened as a result of antidepressant use.

Rating scales

We used ordinal scales of 1 to 9 for all ratings. We prespecified that an indicator would be accepted as *necessary*, when the median across all expert assessments was ≥ 7, and there was no disagreement. Disagreement was pre-specified to mean that at least 30% of the experts rated items 1–3, and at least 30% rated items 7–9. Candidate indicators with a median of < 7 or disagreement were rejected.

Table 2 Rating constructs, definitions, and rating scales used in all three rounds of expert panel ratings

Rating construct	Definition and rating scales
Necessity of review	For an average patient treated with antidepressants in primary care: Assuming no overprescribing/high-risk prescribing, how necessary[a] is it to conduct a critical review* of antidepressant use within the next 3 months in order to prevent adverse effects/reduce medication burden? 1–3 = not necessary; 4–6 = might be necessary; 7–9 = clearly necessary
Likelihood of harm	How likely is it that the patient will experience an adverse drug reaction if the clinical situation was to be continued for another year? 1–3 = unlikely; 4–6 = possible; 7–9 = probable
Severity of harm	If the patient experienced an adverse drug event as a result of antidepressant use, how severe would it be? 1–3 = minor; 4–6 = moderate; 7–9 = major

[a] See the "Methods" section for further detail regarding the definitions of a critical review and the rating construct of necessary

RAM process

The RAM process comprised two virtual discussions and three rating rounds. All expert panel members were sent the first RAM survey by e-mail (on 01/08/2022), together with a one-page overview of the project, rating instructions, and the summarized clinical evidence for each overarching topic. Experts were instructed to place their ratings based on both the evidence report and clinical judgment. The experts were instructed to place their ratings in relation to an average patient on antidepressants treated in primary care. The panel members were given 4 weeks to complete the first round of the RAM survey.

The experts met in a moderated videoconference (moderated by TD) on 01/09/2022. The first round assessments were summarized and presented to the experts, highlighting the median and distribution of ratings as well as the presence of disagreement. The focus of the videoconference was the discussion of indicators with disagreement for the necessity ratings after the first round assessment. After discussing the candidate indicators relating to each ADR (in case of high-risk prescribing indicators) or each indication (in case of overprescribing indicators), the panel members had time to complete the second round assessment.

Indicators reaching a median of ≥ 7 after the second round of assessment were summarized, and the redundant indicators were removed (see Table 1 for an example). The pre-final list of indicators was sent to expert panel members on 24/02/2023. The experts met on 16/03/2023 for a second virtual discussion. The summarized list of indicators allowed the experts to discuss the remaining indicators in more detail and if necessary optimize them for implementation in primary care. Requests for changes in the indicators were implemented and put to a final vote in a third rating round using the same rating constructs and scales as before.

Results

Expert panel composition

The first round RAM survey was sent to 11 expert panel members. All 11 experts participated in the moderated videoconference, and 10 (90.9%) members successfully completed the second and third round survey (general practitioners ($n=2$), clinical pharmacologists ($n=2$), psychiatrists ($n=2$), geriatricians ($n=3$), and a gerontopsychiatrist ($n=1$)). All 10 experts were clinically trained physicians (with an average [range] of 30 [13 to 46] years since training) with regular patient care experience, and 9 (90.0%) also had current research experience.

Candidate indicators

High-risk prescribing

The literature search identifying potential candidate indicators yielded a recent systematic review that contained an extensive list of potential prescribing safety indicators related to mental health [34]. Antidepressant-associated indicators from this review were combined with those included in commonly used PIM lists [25–29]. Further high-risk prescribing candidate indicators were identified from clinical practice guidelines, such as those for depression or chronic heart failure [30, 35], literature reviews of adverse events associated with antidepressant drugs [14, 36–38], and further reviews from searches for selected ADRs (detailed in Additional file 1). The first round of the survey included 212 variations of potential candidate indicators for high-risk prescribing. It should be noted that many indicators were highly dose-specific, e.g., experts were asked to differentiate between the risk of different dose levels of TCAs per day and also between the risk of synergistic pharmacological effects combining 2 or more drugs (e.g., with anticholinergic properties). This allowed for a very fine differentiation between potentially high-risk constellations.

Overprescribing

For depression and anxiety, the indicators of overprescribing focused mainly on the duration of treatment without symptom improvement or on the total duration of treatment. With the exception of doxepin, antidepressants are not officially approved for insomnia, and guidelines are not clear on dose recommendations or duration of treatment for antidepressants as a sedative [32]. Dose recommendations were also considered for pain [33]. The first round of the survey included 70 variations of potential candidate indicators for overprescribing.

RAM process

High-risk prescribing

Figure 1 shows that after round 1, 121 (57.1%) of 212 candidate indicators were accepted as "clearly necessary to review." Six indicators (2.8%) were consented as "not necessary" and 81 indicators (38.2%) as "might be necessary to review." There was disagreement for 4 indicators (1.9%). Changes after the first round assessment and during the moderated videoconference resulted in 222 potential high-risk prescribing indicators being rated in the second round, of which 129 candidate indicators (58.1%) were accepted as "clearly necessary," 6 indicators (2.7%) as "not necessary," and 86 indicators (38.7%) as "might be necessary to review." There was disagreement for 1 indicator (0.5%). We provide the expert ratings of round 2 in Additional file 2. Removing redundant candidate criteria yielded 50 indicators

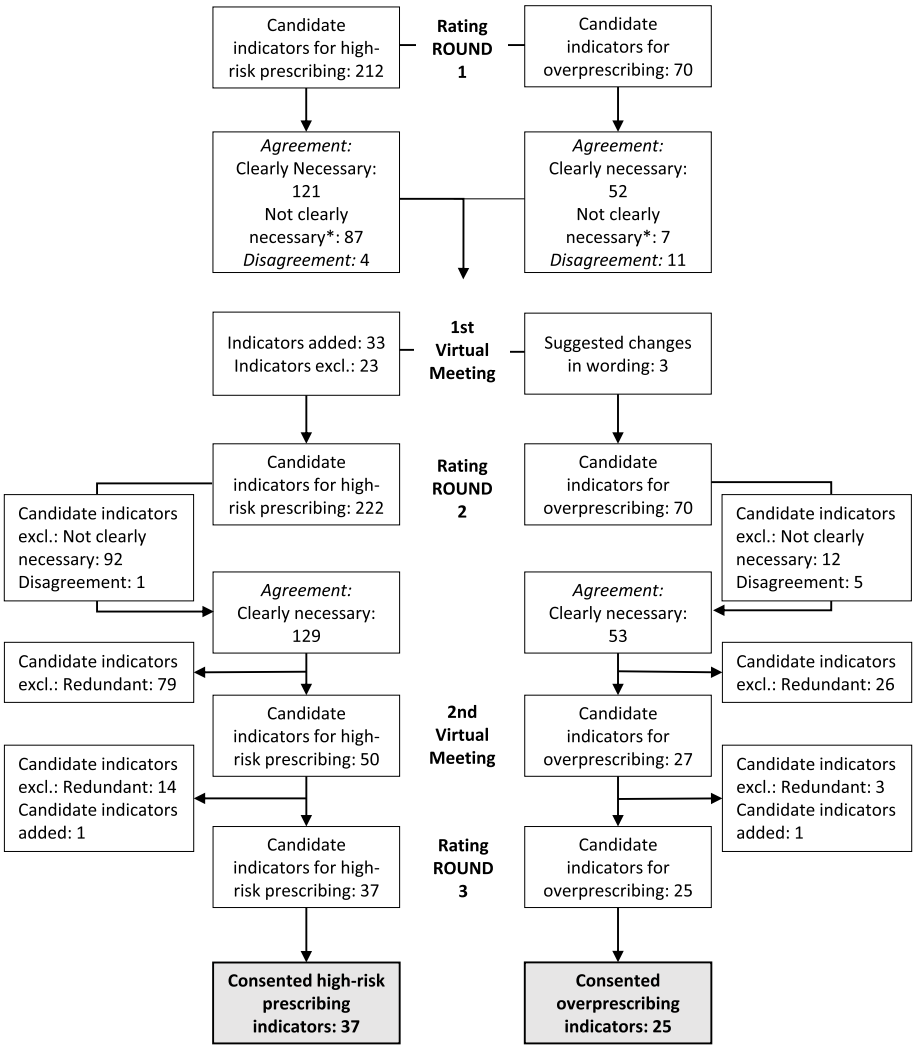

Fig. 1 Flow chart showing the RAM process. *Not clearly necessary: might be necessary 4 to 6 or not necessary 1 to 3

for high-risk prescribing. After the second moderated videoconference, 37 remaining indicators were validated in the third round of assessment, and all were agreed to be "clearly necessary to review." Changes to the indicators after the second round of assessment and the rationale for the changes are detailed in Additional file 3. Table 3 reports the consented indicators after the third round of assessment. Prioritized indicators target patients who are particularly vulnerable to (risk factors: drug-drug, drug-disease, or drug-age interactions) or who have developed adverse drug reactions. High-risk prescribing indicators included constellations of known anticholinergic (e.g., cognitive decline, delirium, constipation, voiding disorders, and glaucoma) and cardiovascular (e.g., QTc prolongation) risks but also falls, orthostatic hypotension/dizziness, bleeding, serotonin syndrome, hyponatremia, hepatic injury, sleep disturbances, and sexual dysfunction. Some of these constellations could lead to serious harm, if antidepressants are continued, particularly in older adults with comedication and comorbidities (e.g., cardiovascular adverse effects, fall-related injuries, delirium, gastrointestinal and intracranial bleeding, hyponatremia). The remaining constellations with the corresponding adverse drug reactions can severely affect patients' quality of life (constipation, sleep disturbances, and sexual dysfunction). Indicators with the highest ratings (median = 9) included those suggesting the possibility of cardiovascular risks such as QTc prolongation associated with citalopram and escitalopram, delirium associated with anticholinergic antidepressants, gastrointestinal bleeding associated with SSRIs and SNRIs, and liver injury associated with agomelatine.

Table 3 Summary of the final indicators of high-risk prescribing with median ratings of 7 to 9 on the necessity to review without disagreement

High-risk prescribing indicators	Median	Agreement	Range
A. Cardiovascular adverse effects			
1. Prescribed SNRI, TCA (in doses ≥ 50 mg/day)[A], or tranylcypromine[B] - and the patient has a history of chronic heart failure	8	90%	6–9
2. Prescribed TCA (in doses ≥ 50 mg/day) - and the patient has a history of ischemic heart disease	8	100%	7–9
3. Prescribed > 20 mg citalopram or > 10 mg escitalopram daily - and the patient is aged ≥ 65 years (risk of QTc prolongation)	7	70%	2–9
4. Prescribed citalopram and escitalopram - and the patient has long QT syndrome or is at risk of long QT syndrome (e.g., (advanced) chronic heart failure, ischemic heart disease, myocardial hypertrophy, bradyarrhythmias, or an ongoing risk of hypokalaemia[C])	9	100%	7–9
5. Prescribed citalopram, escitalopram, or TCA (in doses ≥ 50 mg/day) - and the patient is co-prescribed ≥ 1 further drug with any risk of TdP[C]	7	78%	6–9
6. Prescribed TCA (in doses ≥ 50 mg/day), SNRI, bupropion, or tranylcypromine[B] - and the patient has developed tachycardia	8	90%	6–9
7. Prescribed fluoxetine, paroxetine, or bupropion - and the patient is co-prescribed metoprolol or propranolol (risk of bradycardia)	7	60%	2–9
8. Prescribed SNRI, TCA (in doses ≥ 50 mg/day), bupropion, or tranylcypromine - and the patient has uncontrolled hypertension[C]	8	100%	7–9
9. Prescribed SNRI, TCA (in doses ≥ 50 mg/day), bupropion, or tranylcypromine - and achieving hypertension control requires ≥ 3 antihypertensive drugs	8	80%	4–9
B. Orthostatic hypotension (OH)/dizziness			
1. Prescribed TCA (in doses ≥ 50 mg/day), trazodone, or tranylcypromine - and the patient has developed persistent OH/dizziness under treatment	8	100%	7–9
2. Prescribed SSRI, SNRI, or mirtazapine - and the patient is aged ≥ 65 years and has developed persistent OH/dizziness under treatment	8	100%	7–9
3. Prescribed TCA (in doses ≥ 50 mg/day), trazodone, or tranylcypromine - and the patient is aged ≥ 65 years and co-prescribed ≥ 1 further drug with known blood pressure lowering effect (e.g., α-blockers, β-blockers, nitrates, SGLT inhibitors, levodopa, antipsychotics)[C]	7	60%	5–9
4. Prescribed SSRI, SNRI, or mirtazapine - and the patient is aged ≥ 65 years and co-prescribed ≥ 2 further drugs with blood pressure lowering effect (e.g., α-blockers, β-blockers, nitrates, SGLT inhibitors, levodopa, antipsychotics)	7	67%	5–9
C. Falls and fall-related injuries			
1. Prescribed any antidepressant - and the patient is aged ≥ 65 years and co-prescribed ≥ 1 further fall risk-increasing drug[C]	7	60%	2–9
2. Prescribed any antidepressant - and the patient has a history of falls	8	60%	2–9
3. Prescribed any antidepressant - and the patient has cognitive impairment or dementia	7	60%	2–9
4. Prescribed any antidepressant - and the patient has a history of stroke and co-prescribed ≥ 1 further fall-risk-increasing drug	8	70%	2–9
D. Cognitive decline and delirium			
1. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient has cognitive impairment or dementia	8	90%	6–9
2. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient has a history of delirium and co-prescribed ≥ 1 further drug known to induce delirium (e.g., benzodiazepines, opioids, antihistamines, diuretics)[C]	8	100%	7–9
3. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient is aged ≥ 65 years and co-prescribed ≥ 2 further drugs known to induce delirium (e.g., benzodiazepines, opioids, antihistamines, diuretics)	9	100%	7–9
E. Serotonin syndrome			
1. Prescribed tranylcypromine - and the patient is co-prescribed ≥ 1 further serotonergic drug (e.g., tramadol, fentanyl, triptans, metoclopramide, SSRI, SNRI, TCA)[C]	7	70%	5–9
2. Prescribed SSRI, SNRI, or TCA (in doses ≥ 50 mg/day) - and the patient is co-prescribed ≥ 2 further serotonergic drugs other than tranylcypromine (e.g., tramadol, fentanyl, triptans, metoclopramide, another serotonergic antidepressant)	8	80%	5–9

Table 3 (continued)

High-risk prescribing indicators	Median	Agreement	Range
F. Gastrointestinal bleeding			
1. Prescribed SSRI or SNRI - and the patient is aged ≥ 65 years and co-prescribed a single of the following without GI protection: antiplatelet, anticoagulant, and NSAID	7	60%	6–9
2. Prescribed SSRI or SNRI - and the patient is aged ≥ 65 years and co-prescribed ≥ 2 of the following: antiplatelet, anticoagulant, and NSAID (regardless of GI protection)	8	100%	7–9
3. Prescribed SSRI or SNRI - and the patient has at least one risk factor for GI bleeding (history of peptic ulcer disease, GI bleeding, or hemophilia) and co-prescribed ≥ 1 of the following: antiplatelet, anticoagulant, and NSAID (regardless of GI protection)	9	70%	2–9
G. Bleeding			
1. Prescribed SSRI - and the patient has a history of a bleeding event and co-prescribed ≥ 1 of the following: anticoagulant or antiplatelet	8	70%	6–9
2. Prescribed SSRI - and the patient has at least one risk factor for intracranial bleeding (aged ≥ 65 years, history of stroke, history of dementia) and co-prescribed ≥ 1 of the following: anticoagulant or antiplatelet	7	90%	5–9
H. Constipation			
1. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient has persistent constipation	7	70%	5–9
2. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient is aged ≥ 65 years and co-prescribed ≥ 2 further drugs known to have constipating effects (e.g., calcium antagonists, opioid, antihistamines, antipsychotics)	8	90%	5–9
I. Hyponatremia			
1. Prescribed any antidepressant - and the patient has developed hyponatremia (< 130 mmol/l) under treatment without being treated with a diuretic	7	90%	6–9
2. Prescribed SSRI or SNRI - and the patient is aged ≥ 65 years and co-prescribed ≥ 2 further drugs known to cause hyponatremia (e.g., (thiazide) diuretics, antipsychotics, anticonvulsants, proton pump inhibitors)[c]	8	80%	2–9
J. Hepatic injury			
1. Prescribed agomelatine - and the patient has developed elevated serum transaminase levels (> 3 times the upper normal range) under treatment	9	90%	6–9
2. Prescribed agomelatine - and the patient has a hepatic impairment (i.e., cirrhosis or active liver disease)	8	80%	
K. Voiding disorders			
1. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient has a history of voiding disorders (e.g., urinary retention or benign prostatic hyperplasia) or has developed urinary retention under treatment	7	60%	3–9
L. Glaucoma			
1. Prescribed anticholinergic antidepressant opipramol, other TCAs (in doses ≥ 50 mg/day), or paroxetine - and the patient has a history of angle closure glaucoma or has developed angle closure glaucoma under treatment	8	60%	6–9
M. Sleep disturbances/agitation			
1. Prescribed SSRI, SNRI, MAOI, or bupropion - and the patient has persistent sleeping disturbances (e.g., insomnia, restless leg syndrome) or is experiencing agitation	7	90%	6–9
N. Sexual dysfunction			
1. Prescribed SSRI or SNRI - and the patient has developed sexual dysfunction	8	90%	6–9

SSRI selective serotonin reuptake inhibitors, *SNRI* selective serotonin-norepinephrine reuptake inhibitors, *TCA* tricyclic antidepressant, *TdP* torsades de pointes, *NSAID* nonsteroidal anti-inflammatory drugs, *GI* gastrointestinal, *MAOI* monoamine oxidase inhibitors

[a] It cannot be excluded that low-dose TCAs also have significant adverse effects, as evidence of the safety of low-dose TCAs is sparse

[b] Especially when co-administered with tyramine-containing food

[c] See Additional file 3 for further details regarding the definitions and further examples of comedication

Overprescribing

Fig. 1 shows that after round 1, 52 (74.3%) of 70 candidate indicators were accepted as "clearly necessary to review." One indicator (1.4%) was consented as "not necessary" and 6 indicators (8.6%) as "might be necessary to review." There was disagreement for eleven indicators (15.7%). A total of 53 candidate indicators (75.7%) were accepted as "clearly necessary," 0 indicators (0%) as "not necessary," and 12 indicators (17.1%) as "might be necessary to review" in the second round of assessment. There was disagreement for 5 indicators (7.1%). We provide the expert ratings of round 2 in Additional file 4. Removing redundant candidate criteria yielded 27 indicators for overprescribing. After the second moderated videoconference, 25 remaining indicators were validated in the third round of assessment, and all were agreed to be "clearly necessary to review." Table 4 reports the consented indicators after the third round of assessment. Prioritized indicators target patients who have a high medication burden potentially associated with antidepressants due to long treatment durations, inappropriate indications, or high doses.

Discussion

Summary of findings

Antidepressants are some of the most commonly prescribed drugs in the world. Despite their value, there are instances where they may have an unfavorable risk/benefit balance. We performed a structured literature review and expert consensus process (RAM) in order to synthesize and reach consensus on a set of 62 explicit indicators (37 indicators of high-risk prescribing and 25 indicators of overprescribing of antidepressants) that should prompt a critical review of antidepressant continuation. Indicators with the highest ratings included those suggesting the possibility of cardiovascular risks such as QTc prolongation, delirium, gastrointestinal bleeding, and liver injury associated with certain antidepressants in specific patient subgroups with additional risk factors.

Comparison to literature

To the best of our knowledge, this is the first consensus study focused on identifying indicators for high-risk and overprescribing of antidepressants. Compared to more generic lists of potentially inappropriate medications [23, 39], our focus on a specific class of drugs allowed for the development of a comprehensive set of indicators specifically related to antidepressants. For example, STOPP (Screening Tool of Older Person's Prescriptions/START (Screening Tool to Alert doctors to Right Treatment) version 3 includes 10 indicators related to antidepressants (7.5%) [23], while FORTA (Fit fOR The Aged) identifies individual antidepressants for 6 indications [39]. In comparison, this study identified 37 high-risk prescribing indicators related to a broad spectrum of adverse outcomes. Our findings also include certain risks that are inconsistently listed in clinical guidelines, such as bleeding and fall risks associated with SSRIs, despite systematic reviews supporting these risks [18, 20].

Although broadly consistent with previously published tools for identifying PIMs [23], some differences are worth highlighting. First, the indicator set developed here is likely to identify more patients at risk of bleeding. For example, in contrast to the STOPP criteria, our set also considers the bleeding risk associated with SNRIs [40, 41] as well as co-prescription with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or antiplatelets [40, 42]. Second, in contrast to STOPP Fall, our expert panel did not confirm a higher fall risk for tricyclic antidepressants than other antidepressants [43], and our set identifies additional patients at risk for falls, such as those with cognitive impairment or dementia. Third, our set identifies a particular need to review antidepressants in patients with hyponatremia who are not co-prescribed diuretics (which would then primarily require review) and also accounts for the co-prescription of antidepressants with other hyponatremia-inducing drugs. Fourth, unlike previously published lists [23], our indicator set considers the risk of insomnia with activating antidepressants (such as SSRIs, SNRIs, MAOIs, or bupropion). Fifth, our indicators also identify antidepressant risks related to serotonin syndrome, hepatic injury, and sexual dysfunction, which are usually not included in PIM lists as they are not unique to older adults. Several factors may contribute to these differences, including our focus on identifying patients in need of a review specifically targeting antidepressants, the composition of our expert panel, and the evolution of clinical evidence.

Strengths and limitations

Our study has several strengths. First, an important advantage of the RAM compared to the commonly used Delphi process is that panelists have the opportunity to exchange perspectives in between rounds and for moderators to ensure that rating constructs are understood correctly and applied consistently. Second, our expert panel included generalists and specialists that promoted informed discussions regarding how to optimally balance comprehensiveness, relevance, and feasibility of implementation in primary care. Third, our indicators present a more holistic view of the patient and his or her individual situation combining patient-specific risk factors (e.g., certain comorbidities, co-prescribed medications). Moreover, pharmacological features such as dose-related and synergistic effects were taken into account. While the experts practiced in Germany, our literature review and supporting evidence base were comprehensive and

Table 4 Summary of final indicators of overprescribing with median ratings of 7 to 9 on the necessity to review without disagreement

Overprescribing indicators	Median	Agreement	Range
Depression			
1. Prescribed an antidepressant - and the patient has a first episode of mild depression	8	70%	3–9
2. Co-prescribed two antidepressants - and the patient has a first episode of moderate depression	8	67%	3–9
3. Prescribed an antidepressant in monotherapy for ≥ 4 weeks - and the patient is aged < 65 years with no signs of clinically relevant symptom improvement[1]	7	80%	4–9
4. Prescribed an antidepressant in monotherapy for ≥ 6 weeks - and the patient is aged ≥ 65 years with no signs of clinically relevant symptom improvement[1]	9	90%	6–9
5. Prescribed an antidepressant in monotherapy - and the patient has previously used two or more different antidepressants (inadequate response)	7	70%	3–9
6. Prescribed an antidepressant in monotherapy, combination, or augmentation > 12 months for a first episode of moderate or severe depression - and the patient has achieved full remission	7	80%	3–9
7. Prescribed an antidepressant in monotherapy, combination, or augmentation > 2 years with a history of 2 or more depressive episodes with functional impairment in the last 5 years - and the patient has achieved full remission	7	70%	4–9
8. Prescribed SSRI at a dose of > 1 DDD - and the patient has no clinically relevant symptom improvement under an SSRI dose ≤ 1 DDD (no further dose increase if symptoms remain/worsen)	8	70%	3–9
9. Prescribed two antidepressants **-** and none of those is mirtazapine, mianserin, or trazodone	8	90%	6–9
Anxiety			
1. Prescribed an antidepressant for ≥ 8 weeks - and the patient is aged < 65 years with no signs of clinically relevant symptom improvement[1]	8	90%	6–9
2. Prescribed an antidepressant for ≥ 12 weeks - and the patient is aged ≥ 65 years with no signs of clinically relevant symptom improvement	8	100%	7–9
3. Prescribed an antidepressant > 12 months for anxiety - and the patient has achieved full remission	7	70%	2–9
4. Prescribed an antidepressant for anxiety - and the patient is co-prescribed benzodiazepine > 4 weeks	9	100%	7–9
Insomnia			
1. Prescribed TCA ≥ 50 mg/day for insomnia[2] - and the patient has no other indications for an antidepressant	7	70%	5–9
2. Prescribed trazodone ≥ 50 mg/day for insomnia - and the patient has no other indications for an antidepressant	8	80%	5–9
3. Prescribed mirtazapine ≥ 30 mg/day for insomnia - and the patient has no other indications for an antidepressant	7	80%	3–9
4. Prescribed a sedating antidepressant > 8 weeks for insomnia - and the patient has no other indications for an antidepressant	8	80%	5–9
Pain			
1. Prescribed a TCA ≥ 75 mg/day for neuropathic pain - and the patient has no other indications for an antidepressant	7	60%	3–9
2. Prescribed venlafaxine ≥ 150 mg/day for neuropathic pain - and the patient has no other indications for an antidepressant	8	80%	6–9
3. Prescribed SSRI or mirtazapine for neuropathic pain - and the patient has no other indications for an antidepressant	8	90%	6–9
4. Prescribed any antidepressant for non-specific low back pain - and the patient has no other indications for an antidepressant	8	90%	6–9
5. Prescribed TCA or SNRI as analgesic for pain (e.g., pain other than neuropathic pain, tension headache, migraine, or fibromyalgia syndrome) - and the patient has no other indications for an antidepressant	8	70%	5–9
Miscellaneous			
1. Prescribed any antidepressant - and the patient has chronic heart failure and a first episode of mild or moderate depression	7	70%	2–9
2. Prescribed any antidepressant - and the patient has dementia and a first episode of mild or moderate depression	7	70%	2–9
3. Prescribed agomelatine - and the patient is aged ≥ 75 years	7	70%	5–9

DDD defined daily dose, *SSRI* selective serotonin reuptake inhibitors, *SNRI* selective serotonin-norepinephrine reuptake inhibitors, *TCA* tricyclic antidepressant

[1] At the maximum tolerated or recommended dose

[2] Irrespective of the length of the treatment

international in scope. Although we cannot exclude that the selection and wording of candidate indicators may have influenced our findings, all experts were given an opportunity to suggest additional indicators and clarify ambiguous wording during panel meetings. Our indicator set focuses on a broad set of adverse effects and common indications for antidepressant use, but it is important to note that it cannot cover all instances of overprescribing or sources of antidepressant-related adverse events.

Implications for clinical practice and research

The indicators consented in this study may be used to inform clinical practice as well as clinical surveillance and

research. Clinical practice guidelines typically focus on the appropriate use of antidepressants but do not explicitly state when their use may require caution or review with a view to deprescribing. This set of indicators may therefore complement such guidelines and could be used in conjunction with other established PIM lists [23, 39, 44]. Decision aids, ideally implemented in practice management systems, can trigger a process of shared decision-making, thereby strengthening the physician–patient interaction, ensuring desired effects, and preventing adverse effects of antidepressants before they occur. Indicators could also be used as a decision aid prior to starting antidepressants, but this may not be sufficient given that patients' clinical circumstances may change during treatment. The indicators could also be used to monitor antidepressant use at the population level and as endpoints to evaluate the impact of interventions to enhance the appropriate use of antidepressants in primary care. The indicators may also be useful in informing and empowering patients, which may be particularly relevant in disjointed health care systems, where changes in comorbidity and comedication that could unfavorably affect the benefit/risk ratio of antidepressant use may remain unnoticed by the antidepressant prescriber. However, providing detailed information about potential risks must be balanced against the risk of adversely affecting patient adherence.

In addition, it is important to note that despite its potential benefits, deprescribing antidepressants implies a risk of disease recurrence and withdrawal symptoms. The risk of the latter can be reduced by close monitoring and timely adaptation of tapering schemes, but their implementation may be time-consuming to clinicians and patients alike. The indicators developed here may therefore only serve as a prompt to consider deprescribing, but whether deprescribing should be attempted (or whether alternative measures to reduce the risk of adverse effects are preferable or suffice) requires clinicians to consider individual patient circumstances and also patient preferences. In cases where an adverse drug reaction from antidepressants is suspected (e.g., sexual dysfunction or insomnia), it is also important to carefully consider whether there may be alternative causes prior to changing treatment. In addition, whether and to which extent the implementation of the indicators developed here produces a net benefit to patients and/or health care systems requires evaluation in prospective studies.

Conclusions

This study has identified a comprehensive set of clinical situations that require a timely critical review of the continuation or deprescribing of antidepressants. It thereby closes an important gap in the current clinical guidelines, which has the potential to counterbalance the use of antidepressants in situations, where they have no relevant benefit, no longer have relevant benefit, or are associated with a high risk of harm. While antidepressants have an irreplaceable role in the treatment of moderate to severe forms of depression and anxiety disorders, in some cases (e.g., in combination with comedication, comorbidity, or age), the risks may outweigh the benefits of therapy, particularly in cases involving milder symptoms as frequently observed in primary care. If the use of the indicators developed here leads to a negative benefit-risk assessment, decisions to deprescribe antidepressant treatment should also take into account the potential harms of deprescribing, including withdrawal symptoms and a potential relapse of symptoms (which may occur with some latency), particularly in those with a history of severe psychiatric disorders. It is also important to note that in some cases, dose reduction or switching to a safer antidepressant may be a better alternative than discontinuation. The explicit indicators of high-risk and overprescribing of antidepressants developed here may be used directly by patients and health care providers in primary care, as well as integrated within clinical decision support tools, in order to improve the overall risk/benefit balance of this commonly prescribed class of prescription drugs. Further research is underway (as part of the POKAL project [45]) to examine the prevalence and longitudinal time trends of the developed indicators using claims data, to examine their acceptability among primary care clinicians, and to evaluate the performance (sensitivity and specificity) of the indicator set in identifying actual opportunities for antidepressant deprescribing.

Abbreviations

ADR	Adverse drug reaction
FORTA	Fit fOR The Aged
MAOI	Monoamine oxidase inhibitors
NSAID	Nonsteroidal anti-inflammatory drugs
PIM	Potentially inappropriate medication
RAM	RAND/UCLA Appropriateness Method
SNRI	Selective serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
STOPP/START	Screening Tool of Older Person's Prescriptions/Screening Tool to Alert doctors to Right Treatment
TCA	Tricyclic antidepressant

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03397-w.

Additional file 1. Search strategy examples.

Additional file 2. Expert ratings of round two of the RAM-Survey for high-risk prescribing.

Additional file 3. Table with corresponding references and comments in the event of changes between round 2 and round 3 of the RAM-assessment.

Additional file 4. Expert ratings of round two of the RAM-Survey for overprescribing.

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Authors' contributions
Conceptualization: T.D. and V.B. Methodology: T.D. and V.B. Formal analysis: V.B. Investigation: V.B. Data curation: V.B. Writing—original draft: V.B. Writing—review and editing: V.B., T.D., J.V., C.J.-S., K.L., G.C.A., U.T., P.T., C.S., S.F., E.B., M.D., S.H., W.N., U.J., O.K., and J.G. All authors read and approved the final manuscript.

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Availability of data and materials
The data generated during this study are included in this published article in Tables 3 and 4 [and in Additional files 2 and 4]. Further supporting materials relating to the RAM process described in this article are available upon request.

Declarations

Ethics approval and consent to participate
This study did not require ethical approval.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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7.2 Publication II

Title: Potential deprescribing indications for antidepressants between 2012 and 2019: repeated cross-sectional analysis in two Scottish health boards

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Potential deprescribing indications for antidepressants between 2012 and 2019: repeated cross-sectional analysis in two Scottish health boards

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Abstract

Background Antidepressants have a pivotal role in the treatment of many psychiatric disorders, but there are concerns about long-term use and adverse effects. The objectives of this study were (1) to examine time trends in antidepressant use, (2) to estimate the prevalence of long-term and potential high-risk antidepressant use, and (3) to examine patient characteristics associated with potential deprescribing indications (PDIs) (i.e., simultaneous long-term and potential high-risk antidepressant use).

Methods Repeated population-based cross-sectional study for all 609,299 people aged ≥ 18 years resident in the Tayside or Fife regions of Scotland. The prevalence of antidepressant use was examined on June 30th (index date) of each year from 2012 to 2019, while the prevalence of long-term and potential high-risk use as well as PDIs was assessed and compared on the same dates in 2012 and 2019. Binary logistic regression modeling was used to examine patient characteristics associated with PDIs.

Results Antidepressant use increased by 27% from 12.0 to 15.3% among adult residents between 2012 and 2019. While the proportion of antidepressants users dispensed ≥ 1 antidepressant for > 2 years increased from 54.3 to 61.9% between 2012 and 2019, the proportion of antidepressant users triggering ≥ 1 indicator of potential high-risk use decreased slightly from 37.9 to 34.7%. In 2019, potential high-risk use most commonly related to indicators targeting fall risk (16.0%), cardiovascular risks (14.1%), insomnia (10.6%), and risk of orthostatic hypotension (8.6%). More than 1 in 4 (25.8%) antidepressant users had PDIs. The main risk factors associated with PDIs included increasing age (65–79, adjusted OR 14.12; 95% CI, 13.15–15.17), increasing number of drugs taken concomitantly (≥ 15 drugs, adjusted OR 7.37; 95% CI, 6.71–8.10), use of tricyclic antidepressants (≥ 50 mg) (adjusted OR 5.49; 95% CI, 5.02–6.01), and concomitant use of ≥ 2 antidepressants (adjusted OR 5.52; 95% CI, 5.20–5.85).

Conclusions Long-term and potential high-risk use of antidepressants is widespread, and potential deprescribing indications (PDIs) are increasing, suggesting the need for a critical review of their ongoing use by clinicians. If deemed

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necessary, future deprescribing interventions may use the criteria applied here for identification of patients with PDIs and for evaluating intervention effectiveness.

Keywords Antidepressants, Deprescribing, Long-term use, Adverse drug events

Background

Antidepressants are among the most commonly prescribed prescription drugs globally and have a pivotal role in the treatment of many psychiatric disorders, particularly in moderate to severe symptoms of depression and anxiety disorders [1–4]. For relapse prevention, clinical guidelines recommend treatment up to two years (or more depending on the number of recurrent episodes) [3]. However, longer than recommended use of antidepressants is prevalent [5–9] and has been identified as a key driver for the global increase in antidepressant use [10, 11]. For example, studies in Switzerland, the Netherlands, and UK have found rates of long-term use of more than 40% [6, 7, 9], while the median duration has been reported to exceed 2 years in the UK [9] and 5 years in the USA [12]. This raises safety concerns, particularly in patients at increased risk of adverse drug reactions, such as older people with polypharmacy [13–15]. Several studies also suggest that a substantial proportion of antidepressant users in primary care may be using these drugs without a significant benefit, including those with mild depression [16–19], where antidepressant use is discouraged by guidelines [1].

The concept of deprescribing denotes a systematic approach to reducing, discontinuing, or switching medication [20] for those who no longer need a medicine, do not benefit from it, or may be at increased risk of adverse effects. The process of deprescribing antidepressants can be complex and time consuming, as it may require a nuanced balancing of benefits and risks of continued antidepressant use versus cessation, with the latter including consideration of potential risk of disease recurrence and withdrawal symptoms [21]. In addition, a barrier to prescribers implementing deprescribing is lack of guidance on when it is appropriate to consider it, especially when patients are at increased risk of serious adverse effects, e.g., acute bleeding or fall injuries, but have not experienced them [22, 23].

To support prescribers in reviewing the use of antidepressants, a set of explicit criteria of potentially inappropriate antidepressant use (indicators) was recently developed in an expert consensus process [24], covering clinical situations of potential high-risk and overprescribing. Overprescribing criteria identify patients who use antidepressants for indications where they have little benefit [18] or for longer durations than recommended [3], while potential high-risk prescribing criteria identify patients at increased risk of adverse drug reactions, such as falls, gastrointestinal bleeding, cardiovascular adverse effects, and hyponatremia [25–29].

The objectives of this study were (1) to examine time trends in antidepressant use and to use a recently developed consensus criteria-set, (2) to estimate the prevalence of long-term and potential high-risk antidepressant use, and (3) to examine patient characteristics associated with potential deprescribing indications (PDIs) (i.e., simultaneous long-term and potential high-risk antidepressant use).

Methods

Study design

We conducted a repeated population-based cross-sectional study of community-dispensed antidepressant prescribing for all 609,299 people aged 18 years or older resident in the Tayside and Fife regions of Scotland. In order to examine time trends in antidepressant use, we estimated exposure on a given index date of each year from 2012 to 2019, and chose June 30th as the mid-year time point. In order to estimate the prevalences of long-term and potential high-risk use (separate and simultaneous) on the same dates in 2012 and 2019, we used indicators previously developed in an expert consensus process [24] and compared these rates in 2012 and 2019. We used a binary logistic regression modeling to examine patient characteristics associated with simultaneous long-term and potential high-risk use among antidepressant users in 2019.

Data source

Data were obtained from a large, population-based data set from Scotland provided by the University of Dundee/National Health Service (NHS) Tayside Health Informatics Centre. The data set included prescriptions by general practitioners (GPs) dispensed by community pharmacies (drug names and British National Formulary (BNF) codes [30]) and demographic data (date of birth, gender, registration and de-registration date with NHS Tayside or NHS Fife, date of death, socioeconomic status (according to the Scottish Index of Multiple Deprivation) [31], area of patient's residence (classified by the Scottish Executive Urban–rural Classification) [32]), as well as hospital admissions (including ICD-10 coded diagnoses) for all people aged ≥ 18 years residing in the Tayside and Fife regions of Scotland. Tayside and Fife have

a total population of approximately 900,000 people and are broadly representative of Scotland in terms of age and socioeconomic status. In order to receive public health care, each resident is registered with a single NHS general practice, who is responsible for all community prescribing to patients. Individual study ethical review was not required as all analyses were conducted using non-identifiable data and were carried out in the ISO27001 and Scottish Government approved Health Informatics Centre (HIC) Safe Haven (www.hic.dundee.ac.uk) whose standard operating procedures have been approved by the Caldicott Guardian on behalf of the NHS data controllers.

Definitions

Antidepressant use

We classified antidepressants as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), selective serotonin-norepinephrine reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressants (NASSA), monoamine oxidase inhibitors (MAOIs), and other ADs (trazodone, agomelatine, nefazodone, reboxetine, vortioxetine, bupropion). In order to determine exposure on the index date, we considered any dispensations of antidepressants in the 2nd quarter (i.e., three months from April 1st to June 30th) on the basis that usual dispensing intervals in the UK are 8 weeks and there may be irregularities, e.g., due to holidays.

Long-term use

The indicator set developed by a previous expert-based consensus process [24] originally included 25 indicators of long-term use for indications of depression, anxiety, and insomnia as well as otherwise potentially unnecessary use of antidepressants, such as for indications without evidence of relevant benefit (e.g., mild depression) or at higher doses than indicated (e.g., $\geq$ 50 mg TCA for insomnia). The definitions of antidepressant long-term use vary depending on indication (i.e., from > 8 weeks for treatment of insomnia to > 2 years for treatment of recurrent depression). However, the data source used did not contain information on indications for treatment. Long-term use was therefore conservatively defined as a single measure of continuous prescription for > 2 years, i.e., for 8 quarters or more prior to index dates in 2012 and 2019 (while allowing for a grace period of up to one quarter). Details are provided in the Additional file 1: Fig. S1.

Potential high-risk use

The indicator set originally included 37 indicators of potential high-risk antidepressant use [24], with each indicator identifying patient risk factors (i.e., advanced age, comedication, daily dose [in case of tricyclic antidepressants only], and/or comorbidity) that may increase the risk of antidepressant adverse drug reactions. To identify relevant comorbidities in the absence of ambulatory care diagnoses in the data source, we either used hospital diagnoses (e.g., hospital admission with gastrointestinal ulcer or bleeding, falls or fall injuries) or drug proxies (e.g., previous use of antidementia drugs as a proxy for dementia). However, there were no reliable drug proxies for 9 indicators (e.g., tachycardia, dizziness, hepatic impairment, or angle closure glaucoma), which were therefore omitted from this analysis. The complete list of the 28 operationalized indicator definitions (including ICD-10 codes for hospital diagnoses and BNF Codes for medication) is provided in the Additional file 2: Table S1, S2, and S3.

Potential deprescribing indications (PDIs)

Although any long-term use or potential high-risk prescribing of antidepressants may justify a critical review of antidepressant use, we opted to define PDIs more conservatively as instances where patients were identified to be simultaneously exposed to both long-term and potential high-risk use.

Statistical methods

To determine time trends in antidepressant use, we included individuals who were aged 18 years or older and registered with a GP in the Tayside or Fife regions at any point during the three months prior to index dates (i.e., April 1st to June 30th) of each year from 2012 through 2019 (denominator). We calculated the proportion of all adults who had been exposed to antidepressants on June 30th in each year. The prevalence was calculated per 100 people and for each antidepressant group separately. The prevalence of antidepressant users was stratified by gender, age group (18–39, 40–64, 65–79, 80–100), type of antidepressant drug class (SSRI, TCA, SNRI, NASSA, MAOI, other ADs), and socioeconomic status (1 = most deprived, 5 = least deprived, according to the Scottish Index of Multiple Deprivation) as well as residence (large urban area, urban area, accessible rural area, and remote rural area) according to the Scottish Executive Urban–rural Classification. The relative risks between 2019 vs 2012 (and 95% confidence intervals (CI)) were calculated as non-standardized (crude) and age-sex standardized percentage rates to account for changes in population demographics between 2012 and 2019 (2019 data directly age-sex standardized to 2012 population structure).

To determine the prevalence of long-term and potential high-risk use, separately and simultaneous (PDIs), we considered the proportion of all antidepressant users on each index dates in 2012 and 2019, who triggered one

or more of the above. Among prevalent antidepressant users, the absolute numbers and rates of patients triggering long-term use, potential high-risk use or PDIs were stratified by gender, age group, type of antidepressant drug class, and socioeconomic status as well as residence and rates compared between 2012 and 2019. The relative risk between 2019 vs 2012 (and 95% confidence intervals (CI)) were calculated as non-standardized (crude) and age-sex standardized percentage rates.

For 2019, the associations between patient characteristics and having PDIs were examined using binary logistic regression models. Initially, unadjusted odds ratios (ORs) with 95% CIs were calculated with subsequent multivariate analysis. Patient variables considered were age group, gender, total number of medication groups dispensed in the index quarter of 2019 (1–4, 5–9, 10–14, 15+; defined as subsections of the BNF, typically containing a single class of agent with similar mechanism of action as described by reference [33]), type of antidepressant regimen as defined by the indicators (SSRI, SNRI, TCA (prescribed ≥ 50 mg), mirtazapine (prescribed ≤ 15 mg—low dose), NASSA (mirtazapine > 15 mg, mianserin, maprotiline), or other antidepressants in monotherapy or a combined use of ≥ 2 antidepressants)), socioeconomic status, and residence. Data management and statistical analyses were performed using SPSS (version 25, IMB Corporation 2018). A p-value < 0.05 was considered statistically significant.

Sensitivity analysis

We conducted four sensitivity analyses (SAs) to test the robustness of our findings. In SA1, we restricted the definition of long-term use to the use of antidepressants in each of 8 consecutive quarters (i.e., without grace periods) to examine potential overestimation of long-term use (by allowing grace periods of one quarter). We also explored the impact of more conservative definitions of high-risk use co-prescriptions with high prevalence (i.e., co-prescription of antidepressants with two or more rather than one or more fall risk increasing drug in SA2 and co-prescription of certain antidepressants with two or more rather than one or more drug known to increase the risk of torsades des pointes in SA3). For SA4, we restricted the definition of high-risk use to indicators which had achieved the highest consensus ratings (median of 8 or 9 on a 9-point Likert scale) within the expert panel [24], in order to examine potential overestimation of high-risk use.

Results

Study population

There were 614,421 individuals aged ≥ 18 years resident and registered in the Tayside and Fife regions in the 2nd quarter of 2012, with a mean (standard deviation (SD)) age of 50.3 (18.7) years, decreasing to 607,215 in 2nd quarter of 2019, with a mean (SD) age of 51.5 (19.0) years (Table 1). The proportion of residents aged ≥ 65 years rose from 25.0% in 2012 to 27.6% in 2019.

Changes in the prevalence of antidepressant use between 2012 and 2019

Between 2012 and 2019, the crude proportion of adults dispensed one or more antidepressants increased from 12.0 to 15.3% with an age-sex standardized relative risk (sRR) of 1.27 [95% CI, 1.26–1.28]. Figure 1 shows the proportion of adults, who were dispensed one or more antidepressant drug class from 2012 to 2019. There were marked increases in SSRI, SNRI, NASSA users over the 8 years (sRR 1.32 [95% CI, 1.30–1.34], 1.89 [95% CI, 1.83–1.96], and 1.95 [95% CI, 1.89–2.00], respectively). While TCA users (sRR 1.02 [95% CI, 1.00–1.03]) and users of other antidepressants (e.g., trazodone, sRR 1.04 [95% CI, 0.99–1.10]) remained stable, MAOI use decreased (sRR 0.81 [95% CI, 0.64–1.02], although declining from a very low base prevalence) between 2012 and 2019.

Table 1 Characteristics of the study population

	Second quarter 2012	Second quarter 2019
	No. of patients (crude %)	
Total	614,421	607,215
Sex		
Women	315,046 (51.3)	310,363 (51.1)
Men	299,375 (48.7)	296,852 (48.9)
Mean age (SD)	50.3 (18.7)	51.5 (19.0)
Age groups (years)		
18–39	191,155 (31.1)	186,719 (30.8)
40–64	269,912 (43.9)	252,871 (41.6)
65–79	111,195 (18.1)	121,229 (20.0)
80–100	42,159 (6.9)	46,396 (7.6)
Deprivation quintile[a]		
1 (most deprived)	95,057 (15.5)	95,467 (15.7)
2	106,030 (17.3)	104,903 (17.3)
3	114,450 (18.6)	112,059 (18.5)
4	154,800 (25.2)	150,633 (24.8)
5 (least deprived)	110,532 (18.0)	107,279 (17.7)
Residence[a,b]		
Large urban area	118,366 (19.3)	115,689 (19.1)
Urban area	258,032 (42.0)	253,421 (41.7)
Accessible rural area	179,545 (29.2)	177,669 (29.3)
Remote rural area	24,926 (4.1)	23,562 (3.9)

[a] Deprivation and residence missing for 33,552 (5.5%) people registered in the index quarter of 2012 and 36,874 (6.1%) in 2019

[b] Scottish Executive Urban–Rural Classification

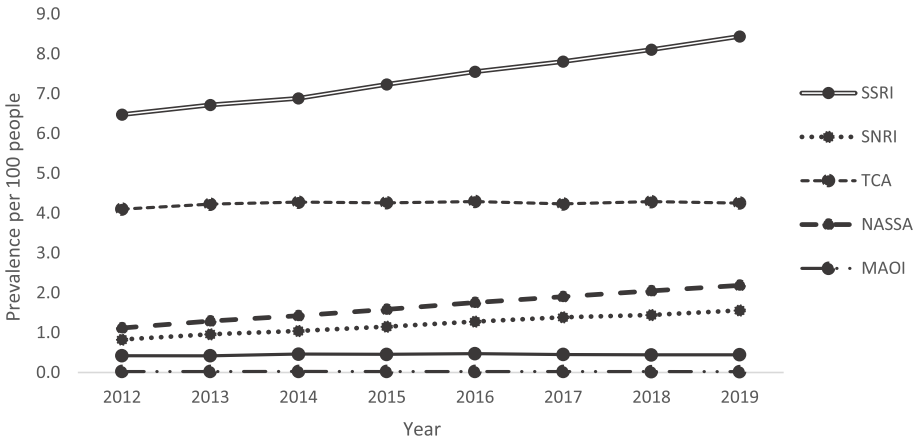

Fig. 1 Proportion of residents aged ≥ 18 years dispensed ≥ 1 antidepressant between 2012 and 2019

Distribution of antidepressant groups among all antidepressant users is provided in the Additional file 3: Table S4.

Table 2 shows that in both years, the proportions of women prescribed at least 1 antidepressant were much higher than for men, but rose for both sexes between 2012 and 2019, especially in men (sRR 1.34 [95% CI, 1.32–1.36] for men vs sRR 1.24 [95% CI, 1.23–1.26] for women). In both years, the prevalence of antidepressant users was higher among people aged 40 years and older (highest prevalence among people aged 40 to 64 in 2019 and highest among people aged 80 or older in 2012) than in the younger age group, but the highest increase in antidepressant use was seen for people aged 18 to 39 years (from 7.4% in 2012 to 11.2% in 2019; sRR of 1.49 [95% CI, 1.46–1.52]). In both years, the vast majority of antidepressant users were dispensed a single agent but the prevalence of people who were dispensed two or more antidepressants in a quarter increased markedly between 2012 and 2019 (from 1.0 to 1.6%; sRR 1.67 [95% CI, 1.62–1.72]).

Consistent with the overall trend, antidepressant use increased between 2012 and 2019 in all 5 deprivation groups and all groups of urban vs rural residence. However, in both years, the prevalence of antidepressant use was markedly higher among those living in the most versus least socio-economically deprived areas (16.4% vs 8.9% in 2012 and 21.1% vs 11.3% in 2019), and it was higher among residents of urban vs rural areas (13.9% vs 10.1% in 2012 and 17.5% vs 12.3% in 2019).

Changes in long-term use of antidepressants between 2012 and 2019

Table 3 shows that among antidepressant users, the crude proportion of long-term users increased from 54.3 to 61.9% between 2012 and 2019 (sRR of 1.16 [95% CI, 1.15–1.17]). Twice as many antidepressant users were dispensed two or more antidepressants long term in 2019 compared to 2012 (2.0% in 2012 vs. 4.0% in 2019). The proportions of women prescribed antidepressants long term were higher than for men in both years, but rose for both sexes between 2012 and 2019 (sRR 1.17 [95% CI, 1.16–1.18] for women vs sRR 1.15 [95% CI, 1.13–1.17] for men).

In both years, long-term use was common among users of all antidepressant classes (ranging from 37.3 to 69.4% in 2012 and from 45.8 to 74.2% in 2019) and increased in all classes, most markedly among users of SSRIs (sRR 1.29 [95% CI, 1.27–1.31]), NASSAs (sRR 1.22 [95% CI, 1.17–1.27]), and other antidepressants (sRR 1.28 [95% CI, 1.21–1.35]). As for antidepressant use overall, the prevalence of long-term antidepressant use was higher among antidepressant users aged 40 years or older than among younger people, but it increased more among younger people (sRR 1.24 [95% CI, 1.20–1.28]) than for people aged 40 years or older (sRRs ranging from 1.12 [95% CI, 1.09–1.15] for people aged 80 or older to 1.17 [95% CI, 1.16–1.18] for people aged between 40 and 64).

The trend of long-term antidepressant use was generally similar across socioeconomic deprivation quintiles and across urban vs rural residence quartiles with the exception of a larger increase in long-term antidepressant users among residents in remote rural vs more accessible rural and urban areas (sRR 1.29 vs 1.17 to 1.14).

Changes in potential high-risk use of antidepressants between 2012 and 2019

Table 4 shows that between 2012 and 2019, the prevalence of any high-risk use among antidepressant users decreased slightly (from a crude rate of 37.9 to 34.7%; sRR 0.93 [95% CI, 0.92–0.95]). Nevertheless, the total number of patients with any high-risk use of antidepressants

Table 2 Antidepressants dispensed to residents aged ≥ 18 years in 2012 and 2019

	Second quarter 2012	Second quarter 2019	Relative risk 2019 vs 2012 (95% CI)	
	No. of patients (crude %)	No. of patients (crude %, age-sex standardised[a] %)	Crude	Age-sex stand
Use of any antidepressant in population				
Total	73,600/614,421 (12.0)	92,601/607,215 (15.3; **15.2)**	1.27 (1.26–1.28)	1.27 (1.26–1.28)
Single AD	67,688/614,421 (11.0)	82,900/607,215 (13.7; **13.6**)	1.24 (1.23–1.25)	1.24 (1.23–1.25)
≥ 2 ADs	5912/614,421 (1.0)	9701/607,215 (1.6; **1.6**)	1.66 (1.61–1.71)	1.67 (1.62–1.72)
Sex				
Women	51,083/315,046 (16.2)	62,556/310,363 (20.2; **20.1**)	1.24 (1.23–1.26)	1.24 (1.23–1.26)
Men	22,517/299,375 (7.5)	30,045/296,852 (10.1; **10.1**)	1.35 (1.32–1.37)	1.34 (1.32–1.36)
Age groups (years)				
18–39	14,179/191,155 (7.4)	20,831/186,719 (11.2; **11.1**)	1.50 (1.47–1.53)	1.49 (1.46–1.52)
40–64	36,965/269,912 (13.7)	44,493/252,871 (17.6; **17.5**)	1.28 (1.27–1.30)	1.28 (1.27–1.30)
65–79	15,710/111,195 (14.1)	19,310/121,229 (16.0; **16.0**)	1.13 (1.11–1.15)	1.13 (1.11–1.16)
≥ 80	6746/42,159 (16.0)	7967/46,396 (17.2; **17.4**)	1.07 (1.04–1.11)	1.09 (1.05–1.12)
Type of antidepressant drug class				
SSRI	39,791/614,421 (6.5)	51,244/607,215 (8.4; **8.5**)	1.30 (1.29–1.32)	1.32 (1.30–1.34)
TCA	25,198/614,421 (4.1)	25,833/607,215 (4.3; **4.2**)	1.04 (1.02–1.06)	1.02 (1.00–1.03)
SNRI	5092/614,421 (0.8)	9470/607,215 (1.6; **1.6**)	1.88 (1.82–1.95)	1.89 (1.83–1.96)
NASSA	6865/614,421 (1.1)	13,279/607,215 (2.2; **2.2**)	1.96 (1.90–2.01)	1.95 (1.89–2.00)
MAOI	160/614,421 (0.0)	128/607,215 (0.0; **0.0**)	0.81 (0.64–1.02)	0.81 (0.64–1.02)
Others	2586/614,421 (0.4)	2700/607,215 (0.4; **0.4**)	1.06 (1.00–1.11)	1.04 (0.99–1.10)
Deprivation quintile[b]				
1 (most deprived)	15,599/95,057 (16.4)	20,109/95,467 (21.1; **21.0**)	1.28 (1.26–1.31)	1.28 (1.25–1.30)
2	15,120/106,030 (14.3)	19,099/104,903 (18.2; **18.2**)	1.28 (1.25–1.30)	1.27 (1.25–1.30)
3	13,594/114,450 (11.9)	16,890/112,059 (15.1; **15.1**)	1.27 (1.24–1.30)	1.27 (1.24–1.30)
4	16,065/154,800 (10.4)	19,081/150,633 (12.7; **12.7**)	1.22 (1.20–1.24)	1.22 (1.20–1.25)
5 (least deprived)	9856/110,532 (8.9)	12,122/107,279 (11.3; **11.2**)	1.27 (1.24–1.30)	1.26 (1.22–1.29)
Residence[b,c]				
Large urban area	16,470/118,366 (13.9)	20,278/115,689 (17.5; **17.5**)	1.26 (1.24–1.28)	1.26 (1.23–1.28)
Urban area	32,305/258,032 (12.5)	40,939/253,421 (16.2; **16.1**)	1.29 (1.27–1.31)	1.29 (1.27–1.31)
Accessible rural area	18,953/179,545 (10.6)	23,187/177,669 (13.1; **13.1**)	1.24 (1.21–1.26)	1.24 (1.22–1.27)
Remote rural area	2506/24,926 (10.1)	2897/23,562 (12.3; **12.4**)	1.22 (1.16–1.29)	1.24 (1.18–1.30)

[a] Direct age-sex standardization to the 2012 population

[b] Deprivation and residence missing for 33,552 (5.5%) people registered in the index quarter of 2012 and 36,874 (6.1%) in 2019

[c] Scottish Executive Urban–Rural Classification

increased between 2012 and 2019 from 27,861 to 32,131. In both years, approximately half of patients with any high-risk use triggered only one indicator (50.1% in 2012 and 54.2% in 2019), while the remainder triggered two or more.

Stratification by age showed that high risk use decreased mainly among people aged < 65 years (sRR 0.80 for people aged 18 to 39 years [95% CI, 0.76–0.84] and sRR 0.86 [95% CI, 0.84–0.88] for people aged 40 to 64 years), while it remained stable among people aged 65 years or older (sRR 1.03 [95% CI, 1.01–1.04] for people aged 65 to 79 years and sRR 1.02 [95% CI, 0.99–1.04] for people aged 80 years or older). Among users of each antidepressant class, the proportion of people triggering any high-risk indicator increased markedly for MAOI users (sRR 1.32 [95% CI, 0.92–1.91]) during the observed period, decreased for SSRI users (sRR 0.87 [95% CI, 0.85–0.88]), and remained stable for TCAs, SNRIs, NASSAs, and other antidepressants (sRR 1.09 [95% CI, 1.06–1.11], sRR 0.96 [95% CI, 0.92–1.00], sRR 1.00 [95% CI, 0.96–1.04], and sRR 0.99 [95% CI, 0.93–1.06], respectively). However, the total number of patients triggering any indicator of potential high-risk use of antidepressant increased among all antidepressant user groups.

High-risk use most commonly related to indicators targeting fall risk (16.0% of all antidepressant users),

Table 3 Long-term (> 2 years) use among antidepressant users in 2012 and 2019

	Second quarter 2012	Second quarter 2019	Relative risk 2019 vs 2012 (95% CI)	
	No. of patients (crude %)	No. of patients (crude %, age-sex standardised[a] %)	Crude	Age-sex stand
≥ 1 AD	39,984/73,600 (54.3)	57,361/92,601 (61.9; **63.1**)	1.14 (1.13–1.15)	1.16 (1.15–1.17)
≥ 2 AD	1480/73,600 (2.0)	3632/92,601 (4.0; **4.0**)	1.95 (1.84–2.07)	2.00 (1.88–2.13)
Sex				
Women	28,450/51,083 (55.7)	40,161/62,556 (64.2; **65.0**)	1.15 (1.14–1.16)	1.17 (1.16–1.18)
Men	11,534/22,517 (51.2)	17,200/30,045 (57.3, **58.7**)	1.12 (1.10–1.14)	1.15 (1.13–1.17)
Age groups (years)				
18–39	4632/14,179 (32.7)	8061/20,831 (38.7, **40.5**)	1.18 (1.15–1.22)	1.24 (1.20–1.28)
40–64	21,143/36,965 (57.2)	29,928/44,493 (67.3, **66.9**)	1.18 (1.16–1.19)	1.17 (1.16–1.18)
65–79	10,186/15,710 (64.8)	14,063/19,310 (72.8, **72.9**)	1.12 (1.11–1.14)	1.13 (1.11–1.14)
≥ 80	4023/6746 (59.6)	5309/7967 (66.6, **66.9**)	1.12 (1.09–1.15)	1.12 (1.09–1.15)
Long–term use among each antidepressant drug class				
SSRI	17,428/39,791 (43.8)	28,231/51,244 (55.1, **56.5**)	1.26 (1.24–1.28)	1.29 (1.27–1.31)
TCA	13,764/25,198 (54.6)	14,906/25,833 (57.7, **57.9**)	1.06 (1.04–1.07)	1.06 (1.04–1.08)
SNRI	2744/5092 (53.9)	5482/9470 (57.9, **58.0**)	1.07 (1.04–1.11)	1.08 (1.04–1.11)
NASSA	2560/6865 (37.3)	6082/13,279 (45.8, **45.5**)	1.23 (1.19–1.27)	1.22 (1.17–1.27)
MAOI	111/160 (69.4)	95/128 (74.2, **75.6**)	1.07 (0.93–1.24)	1.09 (0.95–1.25)
Others	1161/2586 (44.9)	1550/2700 (57.4, **57.3**)	1.28 (1.21–1.35)	1.28 (1.21–1.35)
Deprivation quintile[b]				
1 (most deprived)	8775/15,599 (56.3)	12,659/20,109 (63.0; **64.2**)	1.12 (1.10–1.14)	1.14 (1.12–1.16)
2	8478/15,120 (56.1)	11,970/19,099 (62.7; **63.9**)	1.12 (1.10–1.14)	1.14 (1.12–1.16)
3	7403/13,594 (54.5)	10,502/16,890 (62.2; **63.3**)	1.14 (1.12–1.16)	1.16 (1.14–1.19)
4	8599/16,065 (53.5)	11,864/19,081 (62.2; **63.3**)	1.16 (1.14–1.18)	1.18 (1.16–1.20)
5 (least deprived)	5133/9856 (52.1)	7375/12,122 (60.8; **61.8**)	1.17 (1.14–1.20)	1.19 (1.16–1.22)
Residence[b,c]				
Large urban area	9450/16,470 (57.4)	13,109/20,278 (64.6; **65.7**)	1.13 (1.11–1.15)	1.14 (1.13–1.16)
Urban area	17,533/32,305 (54.3)	25,170/40,939 (61.5; **62.9**)	1.13 (1.12–1.15)	1.16 (1.14–1.17)
Accessible rural area	10,158/18,953 (53.6)	14,279/23,187 (61.6; **62.5**)	1.15 (1.13–1.17)	1.17 (1.15–1.19)
Remote rural area	1247/2506 (49.8)	1812/2897 (62.5; **64.0**)	1.26 (1.20–1.32)	1.29 (1.22–1.35)

[a] Direct age-sex standardization to the 2012 population

[b] Deprivation and residence missing for 3366 (4.6%) antidepressant users in 2012 and 5300 (5.7%) in 2019

[c] Scottish Executive Urban–Rural Classification

cardiovascular risks (14.1%), insomnia (10.6%), and risk of orthostatic hypotension (8.6%). Figure 2 shows that older and younger people differed substantially in terms of types of indicators triggered. For example, indicators targeting risk of fractures, orthostatic hypotension, hyponatremia, bleeding, and delirium were mostly relevant to people aged 65 years or older, whereas indicators targeting risk of cardiovascular events, insomnia, and serotonin syndrome were also relevant to younger people. Details on the prevalence of each individual potential high-risk use indicator in 2012 and 2019 are provided in the Additional file 3: Table S5, S6, and S7.

Changes in the prevalence of potential deprescribing indications (PDIs) between 2012 and 2019

Among all 92,601 antidepressant users in 2019, only 29.1% had no long-term or potential high-risk prescription, 36.2% had long-term but no potential high-risk prescription, 8.9% had potential high-risk prescription but no antidepressant long-term use, and 25.8% had both long-term and potential high-risk prescription (defined in this study as PDI) (Fig. 3). Between 2012 and 2019, the total number of patients with PDIs increased from 17,465 (23.7%) to 23,885 (25.8%), with sRR of 1.11 [95% CI, 1.10–1.13]. Details on the prevalence of PDIs

Table 4 Potential high-risk use among antidepressant users in 2012 and 2019

	Second quarter 2012	Second quarter 2019	Relative risk 2019 vs 2012 (95% CI)	
	No. of patients (crude %)	No. of patients (crude %, age-sex standardised[a] %)	Crude	Age-sex stand
No. of potential high-risk use indicators triggered				
Any	27,861/73,600 (37.9)	32,131/92,601 (34.7, **35.3**)	0.92 (0.90–0.93)	0.93 (0.92–0.95)
1	13,957/73,600 (19.0)	17,395/92,601 (18.8; **18.9**)	0.99 (0.97–1.01)	1.00 (0.98–1.02)
2	6300/73,600 (8.6)	7617/92,601 (8.2; **8.4**)	0.96 (0.93–0.99)	0.99 (0.95–1.02)
3	3343/73,600 (4.5)	3664/92,601 (4.0; **4.1**)	0.87 (0.83–0.91)	0.90 (0.86–0.94)
≥ 4	4261/73,600 (5.8)	3455/92,601 (3.7; **3.9**)	0.64 (0.62–0.67)	0.67 (0.64–0.70)
Sex				
Women	19,327/51,083 (37.8)	21,911/62,556 (35.0; **35.5**)	0.93 (0.91–0.94)	0.94 (0.92–0.95)
Men	8534/22,517 (37.9)	10,220/30,045 (34.0; **34.8**)	0.90 (0.88–0.92)	0.92 (0.90–0.94)
Age groups (years)				
18–39	3165/14,179 (22.3)	3653/20,831 (17.5; **17.9**)	0.79 (0.75–0.82)	0.80 (0.76–0.84)
40–64	11,193/36,965 (30.3)	11,714/44,493 (26.3; **26.1**)	0.87 (0.85–0.89)	0.86 (0.84–0.88)
65–79	9180/15,710 (58.4)	11,578/19,310 (60.0; **59.9**)	1.03 (1.01–1.04)	1.03 (1.01–1.04)
≥ 80	4323/6746 (64.1)	5186/7967 (65.1; **65.0**)	1.02 (0.99–1.04)	1.02 (0.99–1.04)
High-risk use among each antidepressant drug class				
SSRI	19,376/39,791 (48.7)	21,013/51,244 (41.0; **42.2**)	0.84 (0.83–0.85)	0.87 (0.85–0.88)
TCA	7375/25,198 (29.3)	8197/25,833 (31.7; **31.8**)	1.08 (1.06–1.11)	1.09 (1.06–1.11)
SNRI	2514/5092 (49.4)	4532/9470 (47.9; **47.2**)	0.97 (0.94–1.00)	0.96 (0.92–1.00)
NASSA	2846/6865 (41.5)	5616/13,279 (42.3; **41.3**)	1.02 (0.99–1.06)	1.00 (0.96–1.04)
MAOI	37/160 (23.1)	39/128 (30.5; **30.6**)	1.32 (0.90–1.94)	1.32 (0.92–1.91)
Others	1014/2586 (39.2)	1146/2700 (42.4; **38.9**)	1.08 (1.01–1.16)	0.99 (0.93–1.06)
Deprivation quintile[b]				
1 (most deprived)	5952/15,599 (38.2)	7027/20,109 (34.9; **35.8**)	0.92 (0.89–0.94)	0.94 (0.91–0.97)
2	5755/15,120 (38.1)	6545/19,099 (34.3; **35.0**)	0.90 (0.88–0.93)	0.92 (0.89–0.95)
3	5167/13,594 (38.0)	5855/16,890 (34.7; **35.0**)	0.91 (0.89–0.94)	0.92 (0.89–0.95)
4	6247/16,065 (38.9)	6914/19,081 (36.2; **36.8**)	0.93 (0.91–0.96)	0.95 (0.92–0.97)
5 (least deprived)	3705/9856 (37.6)	4235/12,122 (34.9; **34.8**)	0.93 (0.90–0.96)	0.92 (0.89–0.96)
Residence[b,c]				
Large urban area	6445/16,470 (39.1)	7102/20,278 (35.0; **35.7**)	0.90 (0.87–0.92)	0.91 (0.89–0.94)
Urban area	12,170/32,305 (37.7)	14,251/40,939 (34.8; **35.6**)	0.92 (0.91–0.94)	0.95 (0.93–0.96)
Accessible rural area	7163/18,953 (37.8)	8125/23,187 (35.0; **35.2**)	0.93 (0.90–0.95)	0.93 (0.91–0.96)
Remote rural area	1048/2506 (41.8)	1098/2897 (37.9; **38.4**)	0.91 (0.85–0.97)	0.92 (0.86–0.98)

[a] Direct age-sex standardization to the 2012 population

[b] Deprivation and residence missing for 3366 (4.6%) antidepressant users in 2012 and 5300 (5.7%) in 2019

[c] Scottish Executive Urban–Rural Classification

stratified by patient variables are provided in the Additional file 3: Table S8.

Patient characteristics associated with potential deprescribing indications in 2019

In the multivariate logistic regression analysis (Table 5), having potential deprescribing indications (PDIs) for antidepressants was most strongly associated with older age (65–79 versus 18–39; adjusted OR 14.12; 95% CI, 13.15–15.17) and the number of drugs dispensed (≥ 15 drugs versus 1–4 drugs; adjusted OR 7.37; 95% CI, 6.71–8.10). Women were slightly more likely to have PDIs than men (adjusted OR 1.07; 95% CI, 1.02–1.11). Compared to SSRIs, TCA use (higher dose) (adjusted OR 5.49; 95% CI, 5.02 to 6.01) and taking two or more antidepressants (adjusted OR 5.52; 95% CI, 5.20 to 5.85) were more likely to trigger PDIs, while other antidepressant use (in monotherapy) (SNRI, mirtazapine, other antidepressants e.g., trazodone) were less likely to trigger deprescribing indications compared to SSRI users. People living in more remote rural areas were less likely to have PDIs (adjusted OR 0.85; 95% CI, 0.76–0.95). After

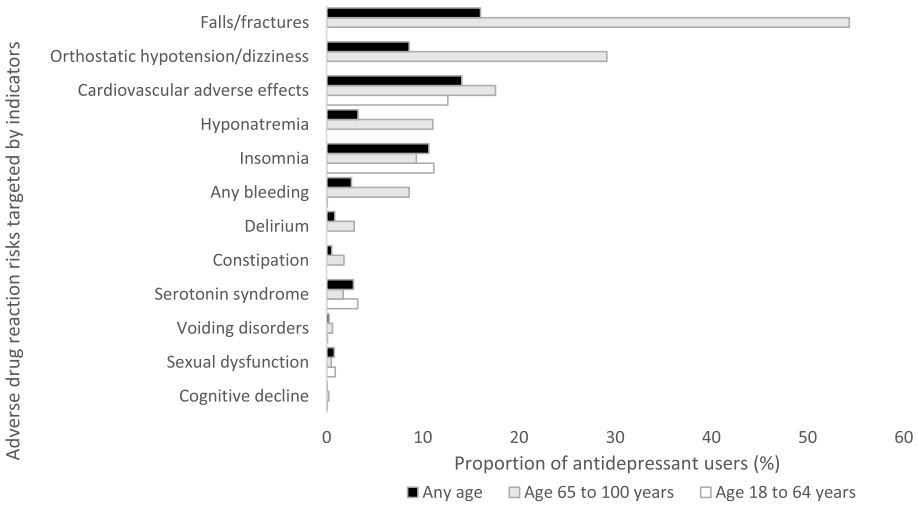

Fig. 2 Proportion of antidepressant users triggering indicators targeting specific adverse drug reaction risks

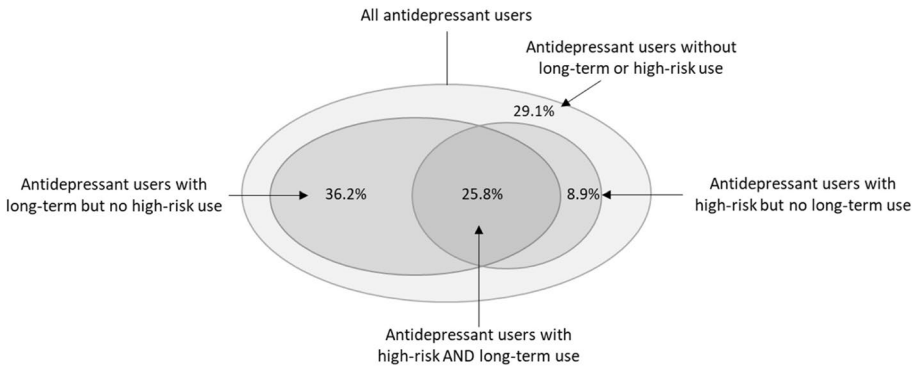

Fig. 3 Venn diagram showing overlaps between long-term and potential high-risk use for primary analysis in 2019

adjustment, socioeconomic status was not significantly associated with PDIs.

Sensitivity analyses

Restricting the definition of long-term use to continuous use without grace periods in SA1, the proportion of long-term use in 2019 decreased from 61.9 to 48.8% but the proportionate increase in long-term use between 2012 and 2019 was more pronounced (sRR 1.30 [95% CI, 1.29–1.32]).

When we restricted high-risk use to instances where antidepressants were co-prescribed with ≥ 2 fall-risk increasing drugs (FRIDs) in SA 2 (as opposed to ≥ 1 FRID in primary analysis), the prevalence of patients at risk from this specific indicator in 2019 reduced from 51.4 to 28.2%, although there was only minimal reduction in the proportion of people triggering ≥ 1 potential high-risk indicator in 2019 (from 34.7 to 32.6%). When we restricted high-risk use to instances where patients were co-prescribed ≥ 2 drugs increasing the risk of Torsades de Point in SA3 (as opposed to ≥ 1 drug in primary analysis), the prevalence of patients at risk from this specific indicator in 2019 reduced from 12.2 to 4.9%, but again with minimal reduction in the proportion of people triggering ≥ 1 potential high-risk indicator in 2019 (from 34.7 to 30.3%). When we restricted high risk use to indicators with median 8 and 9 in SA4 (which also excluded the falls risk and Torsade de Point indicators in SA2 and SA3), the prevalence of patients with antidepressant potential high-risk prescribing in 2019 decreased from 34.7 to 9.4%. Among all antidepressant users in 2019, 6.5% had both long-term use (without grace periods (SA1)) and potential high-risk prescription (taking in account only indicators with the highest ratings (8 and 9) (SA4)). The results of the sensitivity analysis for 2012 are provided in Additional file 3: Table S9.

Table 5 Patient characteristics associated with PDIs (simultaneous long-term and potential high-risk use) in Q2 2019

Variable (no. of patients)[d]	Odds ratio (95% CI) crude	Odds ratio (95% CI) adjusted[a]
Sex		
Men (*n* = 23,633)	Reference	Reference
Women (*n* = 48,428)	1.17 (1.14–1.21)	1.07 (1.02–1.11)
Age groups		
18–39 (*n* = 17,390)	Reference	Reference
40–64 (*n* = 35,587)	2.82 (2.67–2.97)	2.17 (2.03–2.31)
65–79 (*n* = 13,453)	9.51 (8.99–10.05)	14.12 (13.15–15.17)
80–100 (*n* = 5631)	8.42 (7.88–8.98)	12.26 (11.23–13.37)
Total no. of drugs dispensed Q2 2019		
1 to 4 drugs (*n* = 34,165)	Reference	Reference
5 to 9 drugs (*n* = 24,322)	4.53 (4.35–4.71)	3.43 (3.27–3.59)
10 to 14 drugs (*n* = 10,251)	8.17 (7.80–8.56)	5.24 (4.94–5.57)
≥ 15 drugs (*n* = 3323)	12.72 (11.87–13.63)	7.37 (6.71–8.10)
Antidepressant agent[b]		
SSRI (*n* = 42,057) only	Reference	Reference
SNRI (*n* = 6518) only	1.25 (1.18–1.32)	0.95 (0.89–1.02)
TCA (≥ 50 mg) (*n* = 3388) only	7.04 (6.53–7.58)	5.49 (5.02–6.01)
Mirtazapine (low dose) (*n* = 3289) only	0.66 (0.60–0.72)	0.23 (0.21–0.26)
NASSA (high dose) (*n* = 5849) only	0.78 (0.73–0.84)	0.40 (0.37–0.43)
Other AD (*n* = 1824) only	0.90 (0.81–1.01)	0.39 (0.34–0.44)
Combined use of ≥ 2 ADs (*n* = 9136)	6.29 (6.00–6.59)	5.52 (5.20–5.85)
Residence[c]		
Large urban area (*n* = 17,336)	Reference	Reference
Urban area (*n* = 33,674)	0.95 (0.91–0.98)	0.90 (0.86–0.95)
Accessible rural area (*n* = 18,718)	0.93 (0.89–0.97)	0.86 (0.81–0.90)
Remote rural area (*n* = 2333)	1.01 (0.93–1.10)	0.85 (0.76–0.95)

[a] Adjusted for all variables shown in the table

[b] The list includes all antidepressants with potential deprescribing indications identified by the indicators (TCA < 50 mg only does not trigger any indicator)

[c] Scottish Executive Urban–Rural Classification

[d] Number of patients included in the multivariate analysis

Discussion

Summary of findings

Between 2012 and 2019, antidepressant use in adult residents of two Scottish regions increased by more than a quarter (sRR 1.27) from 12.0 to 15.3%. While antidepressant users were mostly older (77.5% were ≥ 40 years in 2019), the largest relative increase (sRR of 1.49) was seen in younger adults aged 18–39 years. Antidepressant use was nearly twice as high among residents in the most socially deprived (21.0%) versus least deprived (11.3%) areas in 2019. Among antidepressant users, long-term use (> 2 years) increased from 54.3% in 2012 to 61.9% in 2019 (sRR 1.16), while potential high-risk use decreased from 37.9% in 2012 to 34.7% in 2019 (sRR 0.93). Nevertheless, the absolute number of people with potential high-risk use of antidepressants was higher in 2019 vs 2012 (32,131 vs 27,861). Potential deprescribing indications (PDIs) (defined in this study as simultaneous long-term and potential high-risk use) increased from 23.7 to 25.8% (sRR 1.11). When we applied stricter definitions of long-term and potential high-risk use in sensitivity analyses vs primary analyses, the prevalence of long-term antidepressant use in 2019 was somewhat lower (48.8% vs 61.9%), whereas the prevalence of PDIs (6.5% vs 25.8%) was substantially lower. The presence of PDI was most strongly associated with increasing age and with more drugs taken concomitantly, but also with the use of TCAs (at doses ≥ 50 mg) and concomitant use of 2 or more antidepressants compared to the use of SSRIs only.

Comparison to literature

To the best of our knowledge, there are no directly comparable investigations of potential high-risk use of antidepressants. However, our findings are consistent with previous studies demonstrating increased use

of antidepressants in general and of increasing long-term use in particular [5–7, 9, 12, 34, 35]. For example, in the Swiss population in 2019, 57.4% of antidepressant users were long-term users [6]. Similarly, in a prospective cohort study in UK general practice in 2012, the prevalence of long-term antidepressant use was 47.1% [9], while our findings show slightly higher prevalences of long-term use in both years (54.3% in 2012 and 61.9% in 2019). Twice as many women were prescribed at least one antidepressant in 2019, a pattern that has repeatedly been reported in other studies [5, 6, 36]. Socio-economic deprivation is a known risk factor for depression [37], which is consistent with our finding of a higher prevalence of antidepressant use in the socio-economically deprived population.

Current clinical guideline recommendations and general consensus is that SSRIs, SNRIs, and mirtazapine are first-line or preferred antidepressants, mainly due to their favorable safety profile in comparison to other antidepressants [29, 38, 39]. This may at least partially explain why the use of these antidepressants has particularly increased between 2012 and 2019. Increased use of mirtazapine has also been observed in a study conducted in Spain, Germany, Denmark, and Sweden [40] and may also be attributed to clinical guideline recommendations advocating combination therapy with mirtazapine for patients who do not respond to initial antidepressant treatments with SSRIs and SNRIs [1, 3]. In addition, an increasing use of SNRIs and mirtazapine for indications other than depression, such as chronic pain and insomnia, may also be a contributing factor [41–43]. For example, some resources consider off-label use of mirtazapine as a safer alternative to benzodiazepines in the treatment of insomnia [44, 45].

Our results show a high proportion of antidepressant and long-term use among older adults, similar to studies from other countries [6, 46, 47]. For example, in the Swiss population in 2019, 56.1% of long-term antidepressant users were older than 60 years compared to 33.8% of long-term users being 65 years or older in this study.

While there are no directly comparable investigations of potential deprescribing indications of antidepressants, our findings in this population-based database study are consistent with a prospective cohort study in UK general practice, where GP review of antidepressant use revealed that antidepressants could be stopped, reduced, or switched (deprescribed) in almost one-quarter (23.2%) of antidepressant users [9].

Strengths and limitations

To our knowledge, this is the first study to investigate potential deprescribing indications for antidepressants using validated explicit criteria [24]. Key methodological strengths include the large population-based sample, the measurement of antidepressant use based on pharmacy-dispensed prescriptions, enabling reliable comparisons over time across a number of measures, as well as stratified analysis by gender, age, socioeconomic deprivation, and residency in rural vs urban areas.

Our study has a few limitations, which may affect the levels of long-term and potential high-risk use measured. Unavailability of over the counter dispensed drugs that may interact with antidepressants (e.g., non-steroidal anti-inflammatory drugs and antihistamines), unavailability of ambulatory care diagnoses (and use of dispensed drugs or hospital diagnoses as proxies), and unavailability of dosing instructions (and use of drug strength as a proxy for daily dosing of TCAs) decrease the observed levels of potential high-risk use (as defined by this validated indicator set). In contrast, our definition of combined use of antidepressants with interacting drugs (dispensation in the same 3-month period) may overestimate the prevalence of potential high-risk drug-drug interactions. Although these factors may influence the precision of period-prevalence estimates, comparisons between the years 2012 and 2019 remain valid since any measurement errors affected both years equally.

While our analysis was based on data from two Scottish health boards, we cannot exclude that the prevalence in other regions may differ. Nonetheless, Tayside and Fife are representative of Scotland in terms of age and socioeconomic deprivation [48].

Although we assessed prevalences of antidepressant use and their long-term and/or high-risk use at a single point in time in 2012 and 2019, there is minimal seasonal variation in antidepressant dispensing [30], and for all comparisons between years, we used the same time points.

Implications for clinical practice and research

Our results confirm the global trend of increasing antidepressant use and their prevalent long-term prescriptions. Long-term use may be a consequence of few discontinuations attempts in primary care, which may be due to fear of relapse and withdrawal effects [22, 49]. Given that longer duration of use may be associated with increased severity and duration of withdrawal symptoms [21], timely identification of PDIs is clearly important. Lack of awareness of the potential risks associated with long-term antidepressant use could also be one of the reasons for few discontinuation attempts [23]. Our findings that potential high-risk use most commonly relates to increased risk of falls/fractures, orthostatic hypotension, cardiovascular adverse effects, insomnia, and bleeding emphasizes that increased risk awareness is particularly relevant

in frail, older people. Although the prevalence of any high-risk use among antidepressant users seemed to decrease, the higher absolute number of patients indicates a greater absolute burden on the healthcare system due to increased risks of adverse drug events.

The indicator set applied here has been developed to enable continuous monitoring of potentially inappropriate use of antidepressants at population level (e.g., for clinical surveillance or research purposes), as a basis for (computerized) decision support and for case finding (e.g., to identify patients in need of a medication review) [50, 51]. While most randomized trials on deprescribing antidepressants target patients with long-term use [52], our analysis highlights the potential importance of also considering high-risk use of antidepressants as a reason to critically review their continued use. This study has demonstrated that most (but not all) indicators in the set can be operationalized in administrative data sources and that implemented indicators can detect changes in long-term and potential high-risk antidepressant use and highlight priorities for improvement. Higher precision in the measurement of period prevalence of potential high-risk use will be achievable in data sources that additionally include ambulatory care diagnoses and dosing instructions.

When all indicators were implemented, we found that 1 in 4 antidepressant users have potential deprescribing indications and may require review, while restriction to indicators with the highest ratings in the preceding expert consensus study yielded substantially fewer antidepressant users with potential deprescribing indications (1 in 15). Although all indicators were validated as scenarios in which a review of antidepressant use was deemed "necessary" (see definition here [24]), focusing on indicators of particular importance may be a pragmatic implementation strategy in resource restricted settings.

Although all criteria used in this study were systematically developed using evidences synthesis and expert consensus [24], it is important to note that explicit criteria applied to routine data sources, as this study has done, can only highlight *potential* deprescribing indications. Decisions to stop or alter treatment in individual patients requires careful consideration of the benefits and risks of continuing vs altering antidepressant treatment (and/or co-medication increasing risk of adverse antidepressant effects) by clinicians and their patients. Empirical validation studies are required in order to examine the performance of the indicator set (sensitivity and specificity) in identifying *actual* deprescribing opportunities and to guide any indicator adaptation and optimization.

Conclusions

While antidepressants have an essential role in the treatment of severe forms of depression and anxiety, we found that long-term and potential high-risk use is widespread and potential deprescribing indications (PDIs) are increasing, suggesting a need for effective deprescribing interventions. This study demonstrates that the indicator set applied here may be used as an instrument to monitor potentially inappropriate use of antidepressants at population level and to identify patients with PDIs, who might benefit from a critical review of antidepressant continuation. As antidepressant use continues to increase internationally, these indicators may encourage comparative analyses of the prevalence of deprescribing indications in other settings.

Abbreviations

PDIs	Potential deprescribing indications
NHS	National Health Service
BNF	British National Formulary
HIC	Health Informatics Centre
TCA	Tricyclic antidepressants
SSRI	Selective serotonin-reuptake inhibitors
SNRI	Selective serotonin-norepinephrine reuptake inhibitors
NASSA	Noradrenergic and specific serotonergic antidepressants
MAOIs	Monoamine oxidase inhibitors
AD	Antidepressant
CI	Confidence interval
SA	Sensitivity analysis
SD	Standard deviation
sRR	Standardized relative risk
FRIDs	Fall-risk increasing drugs
TdP	Torsades de Point

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03584-9.

Additional file 1: Fig. S1. Operationalisation of long-term us.

Additional file 2: Tables S1-S3. Table S1. Original and operationalised indicators for high-risk prescribing. Table S2. Specification of exposure to comorbidity. Table S3. Specification of exposure to comedication.

Additional file 3: Tables S4-S9. Table S4. Distribution of antidepressant groups among all antidepressant users. Table S5. Prevalence of each potential high-risk use indicator in 2012 and 2019. Table S6. Proportion of antidepressant users triggering indicators targeting specific adverse drug reaction risks (2012). Table S7. Proportion of antidepressant users triggering indicators targeting specific adverse drug reaction risks (2019). Table S8. PDIs among antidepressant users in 2012 and 2019. Table S9. Sensitivity analysis.

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Conceptualization: T.D. and V.B.; Methodology: T.D., V.B., and M.R.; Formal analysis and Investigation: V.B.; Writing – original draft preparation: V.B.; Writing – review and editing: V.B., T.D., M.R., J.V., M.S., K.L, C.J.S., J.G., U.T., M.D., N.K., A.M., B.G. and S.F.; Supervision: TD. All authors read and approved the final manuscript.

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Availability of data and materials
The data underlying this article are available in the article and in its online supplementary material. Further supporting materials are available upon request.

Declarations

Ethics approval and consent to participate
All research procedures adhered to HIC Policies and Standard Operating Procedures (Data Access Approvals—HIC Policies and Standard Operating Procedures—Confluence (atlassian.net)). These are approved by the East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian with agreement that studies adhering to the standard operating procedures do not require individual ethical review. Data linkage and analysis used non-identifiable data and all data were analyzed in an ISO27001 and Scottish Government accredited data Safe Haven.

Consent for publication
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Competing interests
The authors declare no competing interests.

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Affidavit

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I hereby declare, that the submitted thesis entitled

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is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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München, 26.03.2025

Place, Date

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List of all publications

1. Gensichen J, Lukaschek K, Jung-Sievers C, Falkai P, Schmitt A, Henningsen P, Dreischulte T, Pitschel-Walz G, Krcmar H, Böhm M, Prommegger B, Linde K, Drescher A, Schönweger P, Haas C, Brand C, Younesi P, Vukas J, **Brisnik V**, Schillok H, Raub J, Kaupe L, Biersack K, Gökce F, Eder J, Hattenkofer L, Reindl-Spanner Ph, von Schrottenberg V, Teusen C, Sterner Ph, Bühner M, Schneider A. Predictors and outcomes in primary depression care (POKAL) - a research training group develops an innovative approach to collaborative care. BMC Prim Care. 2022;23(1):309.

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