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Development of an Intervention for Antidepressant Deprescribing in Primary Care: Qualitative Assessment of Implementation Factors and Systematic Guideline Review

Dissertation

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Zusammenfassung (Deutsch):

Einführung

Der Einsatz von Antidepressiva hat in den letzten Jahrzehnten weltweit zugenommen. Dieser Anstieg deutet auf eine wachsende Erkennung und Akzeptanz der zugrunde liegenden Indikationen (v.a. Depressionen) hin, wirft jedoch auch Bedenken hinsichtlich einer möglichen Überverschreibung auf.

Die Akutbehandlung einer depressiven Episode mit Antidepressiva stellt bei mittelschwerer und insbesondere schwerer Symptomatik eine klar empfohlene Therapieoption dar. Der Anstieg in der Verordnung von Antidepressiva wird jedoch auch auf eine zu schnelle und zu leichtfertige Verschreibung von Antidepressiva bei leichterer Symptomatik ohne Einbindung in ein Therapiekonzept zurückgeführt, auf eine zunehmende Verordnung außerhalb klar definierter depressiver Syndrome (wie etwa zur Dauertherapie von Schlafstörungen) und auf Daueranwendung (> 2 Jahre nach Remission) ohne Re-evaluation. In diesen Fällen ist der klinische Nutzen teils umstritten, während Risiken wie z.B. sexuelle Funktionsstörungen bei Jüngeren und Sturzrisiken bei Älteren zu berücksichtigen sind. Zudem beklagen einige Patienten unter Therapie mit Antidepressiva eine emotionale Abstumpfung („emotional blunting“), wobei u.a. kontrovers diskutiert wird, ob es sich hierbei tatsächlich um einen Effekt von Antidepressiva handelt oder um (Rest-) Symptome einer Depression.

Ziele

Unter Berücksichtigung der Richtlinien des UK Medical Research Council (MRC) zur Entwicklung und Bewertung komplexer Interventionen war es das Ziel dieser Doktorarbeit, einen strukturierten Interventionsansatz zu entwickeln, der dazu beiträgt, jene klinischen Situationen systematisch zu erkennen, in denen im Rahmen der hausärztlichen Langzeitbetreuung eine erneute Überprüfung der fortgeführten antidepressiven Medikation angezeigt sein könnte. Die Intervention soll hierbei gezielt einem zu leichtfertigen Einsatz ohne regelmäßige Überprüfung von Nutzen und Risiken entgegenwirken. . Die spezifischen Ziele der vorliegenden Arbeit bestanden in:

[1] der Erhebung versorgungsnaher Implementierungsdeterminanten (potenzielle Barrieren und Förderfaktoren) für die klinische Identifikation von Situationen, in denen eine Reevaluation einer laufenden antidepressiven Pharmakotherapie angezeigt sein könnte, sowie in der Prüfung eines möglichen Deprescribings im Rahmen ärztlich-patientenzentrierter Entscheidungsprozesse;

[2] der leitlinien- und evidenzorientierten Analyse nationaler und internationaler Empfehlungen mit dem Ziel, die konsensbasierte Entwicklung eines praxisrelevanten Indikatorensets zu unterstützen. Dieses Set soll eine strukturierte Überprüfung bestehender antidepressiver Medikation ermöglichen;

[3] der Konzeption einer hausärztlich einsetzbaren Intervention (basierend auf dem Indikatorenset) zur Überprüfung der Therapie mit Antidepressiva in der deutschen Primärversorgung, insbesondere durch die Erstellung eines Studienprotokolls zur Pilotierung der Intervention als Vorbereitung auf eine mögliche randomisierte kontrollierte Studie.

Methoden

Für die Entwicklung der Intervention folgten wir der aktualisierten Version des Medical Research Council Frameworks zur Entwicklung und Bewertung komplexer Interventionen aus dem Jahr 2021. Wir konzentrierten uns auf die Entwicklungsphase des Frameworks. Für Ziel [1] führten wir zunächst qualitative semistrukturierte Interviews mit HausärztInnen durch, um o.g. Implementierungsfaktoren zu untersuchen. Die Entwicklung des Interviewleitfadens wurde auf Basis des Capability-Opportunity-Motivation-Behaviour (COM-B) Frameworks von Michie et al. (2014) durchgeführt. Bei dem Zielverhalten („Behaviour“) handelte es sich hierbei um eine kritische Überprüfung einer antidepressiven Medikation, ggf. mit anschließender partizipativen Entscheidungsfindung. Anschließend arbeiteten wir Interventionskomponenten aus, um Barrieren, die dem Zielverhalten entgegenstehen, zu überwinden. Hierzu wurden die TDF Domänen (Theoretical Domains Framework) den passenden Interventionsfunktionen (IF-Intervention functions) zugeordnet. Danach wurden die IFs möglichen Verhaltenstechniken (BCT-Behaviour-Change-Techniques) zugeordnet. Für Ziel [2] führten wir eine systematische Überprüfung der klinischen Praxisleitlinien durch und extrahierten alle Empfehlungen zur Vermeidung von UAW durch Antidepressiva. Ergebnisse des systematischen Reviews flossen in die konsensbasierte Entwicklung eines Indikatorensets ein, das potenzielle Absetzindikationen für Antidepressiva spezifiziert (1). Auf dieser Basis wurde eine Checkliste erstellt, die Hausärzte u. Hausärztinnen bei der Erkennung von Situationen unterstützen soll, in denen eine kritische Überprüfung der Medikation mit Antidepressiva angezeigt ist. Für Ziel [3] wurden die unter [1] und [2] generierten Ergebnisse verwendet und gemäß des CONSORT Statements sowie der CRISP-Checkliste ein Studienprotokoll entwickelt.

Ergebnisse

Faktoren, die das Verhalten zugunsten oder gegen eine kritische Überprüfung der antidepressiven Medikation und das Absetzen von Antidepressiva beeinflussen, wurden in der qualitativen, semi-strukturierten Interviewstudie identifiziert. An der Studie nahmen 20 HausärztInnen aus dem Raum Südostbayern, einschließlich der Stadt München, teil. Gemessen an den Nennungen wurden mehr Aussagen zu Barrieren als zu Förderfaktoren genannt. In der Praxis vorhandene Förderfaktoren für das Absetzen von Antidepressiva waren Selbstvertrauen und berufliche Erfahrung. Die meist genannten Barrieren waren der Mangel an interdisziplinärer Zusammenarbeit, Unsicherheiten bei der Entscheidung für oder gegen ein Absetzen sowie unzureichende oder fehlende digitale Tools zur Unterstützung einer Entscheidungsfindung. Darüber hinaus wurden durch die Interviews Frustration und Enttäuschung über die Zusammenarbeit mit anderen Berufsgruppen und über politische Regelungen deutlich.. Des Weiteren wurden die HausärztInnen dazu befragt, was aus ihrer Sicht geeignet wäre, die Arzneimitteltherapiesicherheit im Hinblick auf die Identifikation von Situationen zu verbessern, in denen eine Reevaluation einer laufenden antidepressiven Pharmakotherapie - einschließlich der Option eines Absetzens - angezeigt sein könnte. Dies waren: gemeinsame Entscheidungsfindung (shared-decision-making), gute Beziehungen zu den PatientInnen, Online-Tools als Entscheidungshilfen und eine umfassendere Praxisverwaltungssoftware, die auf ein potenziell ungünstiges Verhältnis von Nutzen und Risiken einer antidepressiven Therapie hinweist.

Durch einen Priorisierungsprozess, der auf den zwei Frameworks BCW (Behaviour Change Wheel) und TDF (Theoretical Domains Framework) basiert, wählten wir eine Checkliste als geeignete Interventionskomponente aus, um AllgemeinmedizinerInnen eine effiziente Identifizierung von PatientInnen zu ermöglichen, die potenziell von einer Otimierung der antidepressiven Medikation (z.B. Austausch, Dosisreduktion oder Absetzen) profitieren könnten. Die Checkliste wurde durch eine Empowerment-Broschüre für PatientInnen ergänzt, um sie aktiv in den Entscheidungsprozess einzubinden.

Die Literaturrecherche schloss 14 Leitlinien aus Australien, Kanada, Deutschland, Neuseeland, dem Vereinigten Königreich und den USA ein. Die Qualität der Leitlinien wurde mit gut-sehr gut bewertet. Wir extrahierten 173 Aussagen mit Empfehlungen beziehungsweise Warnungen zur Vermeidung oder Überwachung einer Therapie mit Antidepressiva oder mit allgemeinen Informationen zu Interaktionen ohne konkrete Handlungsempfehlung. In drei der 14 untersuchten Leitlinien fanden wir 11 spezifische Aussagen darüber, wann die Therapie mit Antidepressiva beendet werden sollte. Die meisten Aussagen bezogenen sich auf die Therapie mit Selektiven Serotonin Wiederaufnahmehemmern (SSRIs). Die stärksten Warnungen fanden wir für Monoamine Oxidase Inhibitoren (MAOIs). Insgesamt stellten wir Inkonsistenzen in den Aussagen zu Nebenwirkungen, Hochrisiko- und Überverordnungen fest. In dem Review extrahierten wir Ansatzpunkte für das Absetzen von Antidepressiva basierend auf den Warnhinweisen und Empfehlungen der Leitlinien. Die Ergebnisse flossen in die Entwicklung eines Indikatoren-Sets im Rahmen einer anderen Dissertation ein. Dieses Set enthielt Kriterien zur Detektion von Situationen, in denen eine kritische Reevaluation der antidepressiven Medikation angezeigt ist. Das Indikatoren-Set wurde zur Erstellung einer Checkliste für Allgemeinmediziner verwendet.

Ein Protokoll für eine Pilotstudie zur Bewertung der Durchführbarkeit, Akzeptanz und Nützlichkeit der Intervention wurde basierend auf dem CONSORT-Statement und der CRISP-Checkliste erstellt.

Schlussfolgerung

Im Rahmen dieser Dissertation wurde auf Basis einer qualitativen Interviewstudie, eines systematischen Reviews und strukturierter Frameworks eine Intervention entwickelt, die deutschen HausärztInnen helfen soll, effektiv PatientInnen zu identifizieren, die von einer Reevaluation (Bewertung Nutzen-Risiko-Verhältnis, Fortführen oder Absetzen eines Antidepressivums) profitieren könnten. Um die Durchführbarkeit, Akzeptanz und Nützlichkeitder Intervention zu testen, wurde ein Studienprotokoll für eine Pilotstudie entwickelt, das inzwischen von der Ethikkommission der medizinischen Fakultät der LMU genehmigt wurde.

Schlüsselwörter

Absetzen von Medikamenten, unerwünschte Arzneimittelwirkungen, Hochrisikoverschreibung, Langzeitverschreibung, Intervention

Abstract (English):

Introduction

Antidepressant use has increased globally in recent decades. This rise suggests growing detection and acceptance of underlying indications (especially depression) but also raises concerns about potential overprescribing.

The acute treatment of a depressive episode with antidepressants is a clearly recommended therapeutic option in cases of moderate, and particularly severe, symptomatology. However, the increase in antidepressant prescriptions has also been attributed to overly rapid and uncritical prescribing without integration into a comprehensive treatment plan, to a growing use beyond clearly defined depressive syndromes (e.g., for the long-term treatment of sleep disorders), and to prolonged use (> 2 years after remission) without regular re-evaluation. In such cases, the clinical benefit is partly disputed, whereas potential risks - such as sexual dysfunction in younger individuals and an increased risk of falls in older adults - must be taken into account. Moreover, some patients report emotional numbing (“emotional blunting”) during antidepressant treatment. It remains a matter of debate whether this phenomenon represents a pharmacological side effect or residual (or ongoing) symptoms of depression.

Aim and components of this work:

Consistent with the UK’s Medical Research Council’s (MRC) Framework on the development and evaluation of complex interventions, the aim of this doctoral thesis was to develop a structured intervention approach to systematically identify clinical situations in which a re-evaluation of continued antidepressant medication may be warranted in the context of long-term care in general practice. The intervention is specifically intended to counteract the overly casual use of antidepressants without regular evaluation of their benefits and risks.The specific objectives of this project were :

[1] to investigate implementation determinants relevant to routine care (i.e., potential barriers and facilitators) for the clinical identification of situations in which re-evaluation of ongoing antidepressant pharmacotherapy may be appropriate, as well as to explore the potential for deprescribing within physician–patient-centred decision-making processes;

[2] to conduct a guideline- and evidence-based analysis of national and international recommendations with the aim of supporting the consensus-based development of a practice-oriented set of indicators intended to facilitate the structured review of existing antidepressant medication;

[3] to design a general practice–applicable intervention (based on the indicator-set) for reviewing antidepressant treatment in the German primary care context, in particular through the development of a study protocol to pilot the intervention in preparation for a future randomized controlled trial.

Methods

For the development of the intervention, we followed the updated 2021 version of the MRC Framework for the development and evaluation of complex interventions. Our focus was on the development phase of the framework.

For objective [1], we initially conducted qualitative semi-structured interviews with general practitioners to explore above mentioned implementation factors. The development of the interview guide was based on the Capability-Opportunity-Motivation-Behaviour (COM-B) framework by Michie et al. (2014). The target behaviour in this context was the critical review of an antidepressant prescription, potentially followed by a shared decision-making process regarding continuation or discontinuation.Subsequently, we developed intervention components to overcome barriers that hinder the target behaviour. The domains of the Theoretical Domains Framework (TDF) were matched to the appropriate intervention functions (IFs), which were then linked to possible behaviour change techniques (BCTs). For objective [2], we conducted a systematic review of clinical practice guidelines, extracting all recommendations regarding appropriate treatment durations and strategies to avoid adverse drug reactions (ADRs) from antidepressants. The results of the systematic review contributed to the consensus-based development of an indicator set specifying potential deprescribing indications for antidepressants (1). Based on the indicator-set, a checklist was created to assist general practitioners in in identifying situations in which a critical re-evaluation of antidepressant medication is indicated.

For objective [3], the results generated from objectives [1] and [2] were used to develop a study protocol in accordance with the CONSORT guidelines and The CRISP checklist.

Results

Factors influencing behaviour either in favour of or against a critical review and the discontinuation of antidepressants were identified in a qualitative, semi-structured interview study involving 20 general practitioners from the Southeast Bavaria region, including the city of Munich. The findings revealed that more statements were made regarding barriers than facilitators. In practice, identified facilitators for critical re-evaluation and potential discontinuation of antidepressants included self-confidence and professional experience. The most frequently cited barriers were a lack of interdisciplinary collaboration, uncertainties in making decisions about discontinuation, and insufficient or absent digital tools to support decision-making. Furthermore, interviews revealed frustration and disappointment regarding collaboration with other professional groups and political regulations.

General practitioners were also asked to share their views on what measures might improve medication safety with regard to identifying situations in which a re-evaluation of ongoing antidepressant pharmacotherapy - including the option of discontinuation - may be warranted.. Suggested strategies included shared decision-making, fostering good relationships with patients, utilizing online tools as decision aids, and implementing more comprehensive practice management software, capable of indicating a potentially unfavourable benefit–risk ratio of ongoing antidepressant treatment..

Through a prioritization process based on the two frameworks, the Behaviour Change Wheel (BCW) and the Theoretical Domains Framework (TDF), we selected a checklist as an appropriate intervention component to enable general practitioners to efficiently identify patients who may potentially benefit from optimising their antidepressant medication - such as through switching, dose reduction, or discontinuation. This checklist was complemented by an empowerment brochure for patients, aimed at actively involving them in the decision-making process.

The literature review included 14 eligible guidelines from Australia, Canada, Germany, New Zealand, the United Kingdom, and the United States, with the quality of the guidelines rated as good to very good. We extracted 173 statements with recommendations or warnings regarding the avoidance or cautiousness of antidepressant therapy, as well as general information on interactions without specific action recommendations. Among the 14 included guidelines, we found 11 specific statements regarding when antidepressant therapy should be discontinued, The majority of recommendations related to the use of selective serotonin reuptake inhibitors (SSRIs). The strongest warnings were associated with monoamine oxidase inhibitors (MAOIs). Overall, we noted inconsistencies in the statements concerning adverse effects and high-risk scenarios.

In the review, we extracted points of departure for the discontinuation of antidepressants based on the warnings and recommendations from the guidelines. The results contributed to the development of an indicator set as part of a separate doctoral thesis. This set included criteria for the detection of situations in wich a critical re-evaluation of antidepressant therapy is indicated.This indicator set was utilized in the creation of a checklist intended for use by general practitioners.

A protocol for a pilot study to assess the feasibility, acceptance, and utility of the intervention was developed based on the CONSORT statement and the CRISP checklist.

Conclusion

Within the scope of this dissertation, we developed an intervention based on a qualitative interview study, a systematic review, and structured frameworks, aimed at assisting German general practitioners in effectively identifying patients who could benefit from re-evaluation (assessment of the benefit-risk ratio, continuation or discontinuation of antidepressant medication). To assess the feasibility, acceptability, and usefulness of the intervention, we proposed a pilot study protocol, which has since been approved by the ethics committee of the medical faculty at LMU Munich.

Keywords

Deprescribing, medication review, adverse drug reactions, high risk prescribing, long-term prescribing, intervention

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List of Abbreviations

AAGP	American Association for Geriatric Psychiatry
ACP	American College of General Practitioners
AD	Antidepressant
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ARS	Anticholinergic Risk Scale
AHRQ	Agency for Healthcare Research and Quality
AMTS	Arzneimitteltherapiesicherheit
APA	American Psychological Association
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BAP	British Association for Psychopharmacology
CANMAT	Canadian Network for Mood and Anxiety Treatments
CPG Infobase	Clinical Practice Guidelines Infobase
CCSMH	Canadian Coalition for Seniors' Mental Health
CI	Contraindications
CMAI	Canadian Medical Association Infobase
CPA	Canadian Psychiatric Association
CPG	Clinical Practice Guideline
CRISP	Consensus Reporting Items for Studies in Primary Care
DEXIMED	Deutsches Experten-Informationssystem für medizinische Entscheidungen
DDD	Defined Daily Dose
DFG	Deutsche Forschungsgemeinschaft
EHR	Electronic Health Records
GAD-7	Generalized Anxiety Disorder-7 Questionnaire
GI	Gastrointestinal
GoR	Grade of Recommendations
GP	General Practitioner
GrK	Graduiertenkolleg
HSE	Health Service Executive

ICGP	Irish College of General Practitioners
ICSI	Institute for Clinical Systems Improvement
LoE	Level of Evidence
MAOI	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
MiChe	Mini Checklist
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NGC	National Guideline Clearinghouse
NHMRC	National Health and Medical Research Council
NICE	National Institue for Health and Care Excellence
NVL	Nationale Versorgungsleitlinie
NZGG	New Zealand Guidelines Group
OAE	Overall Assessment Evaluation
PACIC	Patient Assessment of Chronic Illness Care
PHQ-9	Patient Health Questionnaire-9
PHQ-15	Patient Health Questionnaire-15
PICAR	Population-Interventions-Comparators-Attributes-Recommendation-Characteristics
PIM	Potentially Inadequate Medication
POKAL	PrädiktOren und Klinische Ergebnisse bei depressiven ErkrAnkungen in der hausärztLichen Versorgung
PTSD5	Post-Traumatic Stress Disorder-5 Questionnaire
PRISMA	Prefered Reporting Items for Systematic Reviews and Meta-Analyses
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCPSYCH	Royal College of Psychiatrists
SIGN	Scottish Intercollegiate Guidelines Network
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TDF	Theoretical Domains Framework
VA/DoD	Department of Veterans Affairs Department of Defense

Chapter 1: Introduction

Background

Antidepressants are the mainstay for the treatment of psychiatric disorders, such as moderate to severe depression and anxiety- and panic disorder (2). Their usage has markedly increased over recent decades, making them one of the most commonly prescribed medications worldwide (3). While the rise in use may partially reflect improved diagnosis and reduced stigma around mental illness, concerns persist regarding their efficacy and potential risks (4). For individuals with milder symptoms, especially older people who are at increased risk of adverse drug reactions (ADRs), the risks of antidepressants may often outweigh their benefits (5, 6).

Most patients with mild to moderate mental health issues are managed by general practitioners (GPs), who may feel that pharmacotherapy is the only viable option for addressing symptoms of depression and related conditions, such as insomnia and pain (7). Antidepressants have an established role in the treatment of depression and they may also be beneficial in the treatment of certain pain syndromes and in the short-term treatment of insomnia. However, their long term use without regular review of benefits and risks is problematic given their potential undesired effects. (8). Additionally, uncertainty regarding when and how to deprescribe antidepressants is growing, given that both the prevalence and duration of antidepressant continue to increase (9, 10).

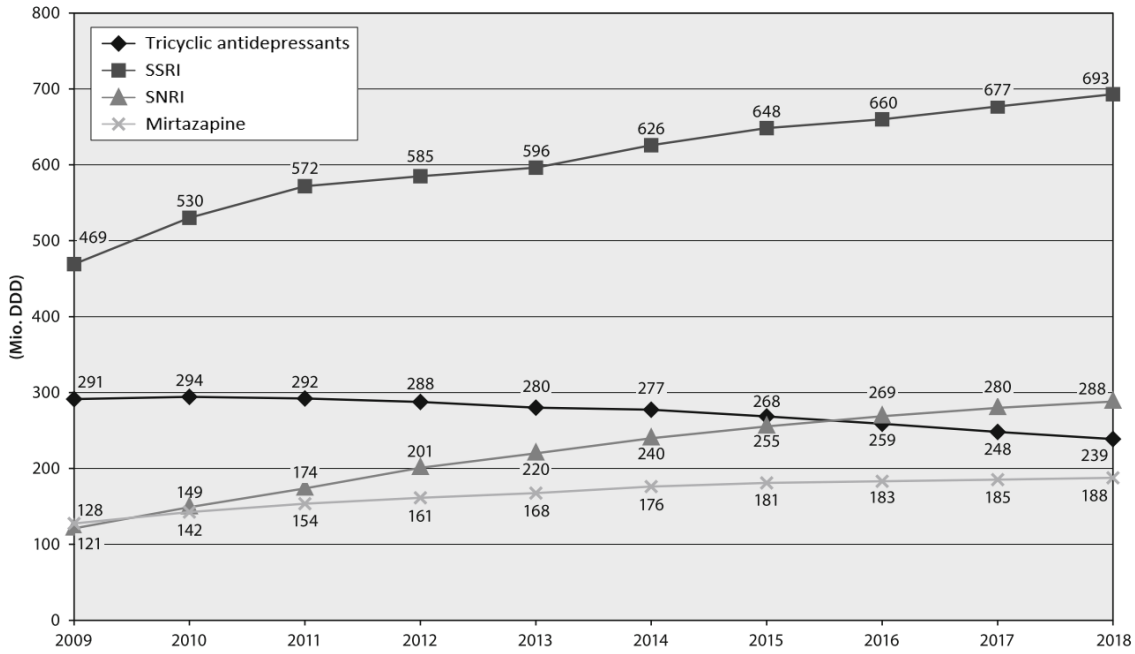
In order to support general practitioners, effective interventions are needed to maximise the benefits while minimising harms from antidepressant use.

Epidemiology of antidepressant use and adverse drug reactions

Volume of antidepressant use

Especially in Western countries, prescribing rates of antidepressants have increased tremendously over recent decades. For example in England, their use increased by 96% between 2008 and 2018 (11). In the USA, the prevalence among people aged 18 and older rose from 6.5% to 10.4% between 1999/2000 and 2009/2010 (12). In Germany, the prescription volume (Defined Daily Doses, DDD) of antidepressants rose ninefold between 1995 until 2019 (13) and by more than 40% between 2009 and 2018 (14). In Germany, the rise is predominantly driven by selective serotonin-reuptake-inhibitors (SSRI, e.g. sertraline, citalopram, escitalopram), serotonin-noradrenaline-reuptake-inhibitors (SNRI, e.g. duloxetine, venlafaxine), and mirtazapine, while the prescription volume of tricyclic antidepressants (TCAs) has been slowly decreasing since 2010 (see Figure 1) (13, 15).

Figure 1: DDD of antidepressants in Germany, 2009-2018



Source: Lohse MJ, Müller-Oerlinghausen B. Psychopharmaka. In: Schwabe U, Paffrath D, Ludwig W-D, Klauber J, editors. Arzneiverordnungs Report 2019. Berlin, Heidelberg: Springer Berlin Heidelberg; 2019. p. 927-59.

Patient characteristics associated with antidepressant use

Indications for antidepressants, including depression, anxiety- and panic disorders, are more common in women than in men, which explains a higher prevalence of antidepressant use among women (16). For example, in Switzerland the prevalence of prescribed antidepressants in 2021 was almost double in women compared to men (11.6% vs 6.3%), with similar findings in the US in 2018 (17).

Mental health problems particularly affect older patients, with depression being the most common disorder. In a cohort study in Switzerland from 2023, nearly half of all antidepressant prescriptions (49.6%) were issued to patients aged over 60 years. Most prescriptions were long-term (i.e. more than two years) and the majority of long term users (56.1%) were older adults (> 60 years of age) (15). Similarly, an Italian cohort study from 2020 showed that 48.1% of all antidepressant users were 60 years or older and 54% of “chronic users” (defined as 180 defined daily doses) of anti-depressant medications per year for three years) (18). A study from the UK found that 14% vs 6% of individuals aged 75 years or older vs younger people were prescribed an antidepressant, and nearly half of the older group were using them for more than two years (19).

Adverse drug reactions

As outlined in guidelines such as the NVL Unipolare Depression(2), antidepressant treatment - while considered effective and appropriate in many clinical contexts - may, in some instances, be associated with adverse drug reactions (ADR). These can include weight gain, sexual dysfunction, cardiovascular changes, and an increased risk of bleeding, particularly when administered alongside medications such as NSAIDs or aspirin.

For example, older adults with multimorbidity and polypharmacy may be especially vulnerable to ADR, which can arise from pharmacodynamic interactions or age-related physiological changes (20). In this population, events such as falls, fractures, bleeding complications, or cognitive disturbances including delirium have been reported with greater frequency. Given that falls are a leading cause of injury and mortality among older individuals worldwide, these risks may warrant proactive preventive strategies and tailored clinical management (21, 22).

In younger patients, some of the aforementioned effects may be perceived as distressing and could impact quality of life (23). A retrospective cohort study published in 2023 suggested that SSRI-associated sexual dysfunction might, in a subset of cases, persist beyond the active treatment phase (24).

However, despite clear evidence for existing adverse effects, these findings should be interpreted with appropriate caution, considering methodological limitations and the complexity of differentiating between treatment-related effects and outcomes related to underlying conditions or other confounding factors. **Table 1** summarises common and long-term ADRs of antidepressants.

Table 1: Possible ADRs and long-term effects of selected antidepressants

Antidepressant	Possible ADR	Long-term Effects
Amitriptyline (TCA)	Drowsiness, dry mouth, blurred vision, constipation, weight gain	Cardiovascular risks, liver damage, increased risk of falls, cognitive impairment
Bupropion (NDRI)	Dry mouth, insomnia, headache, weight loss, increased sweating	Seizures, high blood pressure, liver damage, manic episodes
Citalopram (SSRI)	Nausea, dry mouth, drowsiness, increased sweating, tremor	Sexual dysfunction, weight gain, heart rhythm problems
Duloxetine (SNRI)	Nausea, dry mouth, fatigue, constipation, sweating	Liver damage, withdrawal symptoms, increased risk of bleeding, sexual dysfunction
Escitalopram (SSRI)	Nausea, insomnia, fatigue, dry mouth, increased sweating	Sexual dysfunction, weight gain, sleep disturbances
Fluoxetine (SSRI)	Nausea, dizziness, drowsiness, dry mouth, loss of appetite	Sexual dysfunction, weight gain, sleep disturbances
Mirtazapine (NaSSA)	Sedation/drowsiness, dry mouth, fatigue, increased appetite, constipation	Significant weight gain, increased risk of diabetes, sedation/fatigue, cardiovascular risks, sexual dysfunction

Nortriptyline (TCA)	Drowsiness, dry mouth, constipation, weight gain, increased appetite	Cardiovascular risks, liver damage, increased risk of falls, cognitive impairment
Paroxetine (SSRI)	Nausea, drowsiness, dizziness, dry mouth, weight gain	Sexual dysfunction, weight gain, withdrawal symptoms
Sertraline (SSRI)	Nausea, insomnia, diarrhoea, dizziness, dry mouth	Sexual dysfunction, weight gain, increased risk of bleeding
Venlafaxine (SNRI)	Nausea, dizziness, dry mouth, insomnia, sweating	Increased blood pressure, cholesterol level changes, withdrawal symptoms

NaSSA-noradrenergic and specific serotonergic antidepressant; SNRI-serotonin norepinephrine reuptake inhibitor; SSRI-selective serotonin reuptake inhibitor; TCA-tricyclic antidepressants; NDRI-norepinephrine dopamine reuptake inhibitor

Based on sources: 1- https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/medicines-and-psychiatry/antidepressants; **2**- Carvalho et al., 2016 **(23). 3- NVL Unipolare Depression (2),** Own configuration.

Economic burden of adverse drug reactions

The societal costs due to adverse drug reactions (ADRs) from antidepressants affect both healthcare systems and individual patients. These costs can arise from increased hospital stays, additional medical treatments, and from the broader impact on patient health and productivity (25). Research indicates that ADRs from antidepressant therapy, particularly involving anticholinergic burden, significantly contribute to increased healthcare costs, especially due to complications such as falls and fractures. An American systematic review from 2020 found that higher anticholinergic burden among older adults elevated the risks of falls and fractures, with a corresponding rise in medical expenses, including more frequent hospital admissions and extended recovery periods (26). A Japanese meta-analysis from 2021 revealed that each additional point on the anticholinergic risk scale (ARS) was associated with a progressively higher risk of fractures, with risks increasing by 28% to 77% depending on the level of exposure to anticholinergic medications, including certain antidepressants like amitriptyline, nortriptyline, and paroxetine. The resulting fractures often lead to expensive hospital stays and long recovery times (27). A Korean systematic review and meta-analysis from 2012 discovered similar results with great clinical impact of fractures associated with SSRI use (28). Due to growing and aging population, the economic burden of mental health disorders in general will increase to an estimated $7.3 trillion (29).

These findings highlight the importance of enhancing medication safety and monitoring to reduce the incidence and impact of adverse drug reactions associated with antidepressants. Reducing ADRs can help improve patient outcomes and lessen the economic strain on healthcare systems, as well as on society and individuals. Older adults may particularly benefit from efforts to more carefully balance any benefits of antidepressant use with potential harms (30) because of their increased susceptibility to ADRs and because long term use is particularly common in this patient group.

Beyond Indication: Critical Reflections on Antidepressant Use in General Practice

Use of antidepressants in the management of depression

The acute treatment of a depressive episode with antidepressants is a clearly recommended therapeutic option in cases of moderate, and especially severe, symptomatology. In mild depression, guidelines emphasize that antidepressants may be considered in selected cases - e.g., if psychological interventions are not accessible or have been declined - but recommend caution in initiating medication without structured follow-up and patient-centred discussion (2, 31). Despite their clear role in the management of depression, the increase in the prescription of antidepressants is partly attributed to overly rapid and careless prescribing without integration into a therapeutic concept, to a growing use outside clearly defined depressive syndromes (such as for long-term treatment of sleep disturbances), and to long-term use (> 2 years after remission) without re-evaluation (2, 32-35). In such cases, the clinical benefit is partly disputed, while risks such as sexual dysfunction in younger individuals and fall risks in the elderly - must be taken into account (23, 24, 36-38).

Off-label use of antidepressants

Off-label use refers to the application of medications for indications that have not been explicitly approved by regulatory agencies (e.g., FDA, EMA or BfArM). From a clinical standpoint, off-label use of antidepressants is often driven by practical necessity and the lack of better therapeutic options for certain conditions. Examples include the use of antidepressants in the long-term treatment of insomnia, fibromyalgia, and chronic back pain. From a scientific standpoint, however, there is insufficient robust evidence to establish clear efficacy and/or a favorable risk/benefit ratio. From this perspective, the increasing off-label use of antidepressants is concerning and well documented (39).

For example, an American retrospective study using data from the National Ambulatory Medical Care Surveys found that the increase in antidepressants usage is partly due to prescriptions in the absence of a psychiatric disorder, particularly in primary care. (40). Similarly, a large population-based Spanish cohort study of nearly one million patients partly attributed the increase in antidepressant prescriptions to off-label use (41). Moreover, a Canadian observational study of 100,000 subjects from 2017 found that almost 30% had off-label antidepressant use with no indication for such therapy (42). A Canadian-American cohort study of 46,021 patients from 2016 found a high risk of adverse drug reactions with off-label vs on-label use ofprescription drugs, includingantidepressants (30). Almost all use of amitriptyline (95.3%) and trazodone (94.1%) was off label and 53.0% and 94.1% use was not supported by strong scientific evidence, respectively. Drug withdrawal due to adverse reactions occurred in 4.8% of amitriptyline and 6.6% of trazodone users.Additionally, a large population-based Spanish cohort study of nearly one million patients

attributed the increase in antidepressant prescriptions predominantly to off-label use and over-prescribing (i.e. continuation without regular re-evaluation, clear indication, or shared decision-making) (41). A

Although off-label use is therefore not inappropriate per se, it should be regularly reviewed, especially its long-term use among vulnerable people with increased risk of adverse effects, such as older people.

Long-term use of antidepressants

The **long-term use** of antidepressants (often defined as the use for more than two years) has become a growing concern in recent years. Numerous studies, including a retrospective analysis of UK prescribing data from 2016 have shown that long-term prescriptions are predominantly driving the increase in antidepressant use (43-46). While clinical practice guidelines generally recommend continuation of antidepressant treatment for at least 6 to 12 months after remission to prevent relapse in acute depressive episodes (2, 31), they also support longer durations - e.g., up to two years or more - for patients at high risk of recurrence (such as those with two or more severe episodes in the past five years). However, a UK based cohort study from 2020 suggest that in a substantial proportion of cases, actual prescribing practices deviate from these recommendations, leading to extended treatment periods without clear clinical justification (NICE) (47). One contributing factor appears to be the continued renewal of prescriptions without adequately reviewing the necessity or indications for ongoing therapy, which is also true for primary care (48). A Scottish cross-sectional study from 2008 found that about a third of patients in remission had no clear indication for continuing antidepressant treatment and that 30-50% of patients on antidepressants could discontinue treatment without risking relapse (49).It is important to note, that the use of antidepressants must be evaluated differently depending on the treatment phase - such as acute therapy, continuation therapy, or relapse prevention (50). This distinction is essential for guideline-concordant indication and prescribing. The aim of this work is not to provide a general assessment of antidepressant treatment, but rather to identify situations in which a reevaluation of medication may be appropriate in the primary care setting. Such indications are intended to prompt an individualized risk-benefit assessment that also considers aspects of relapse prevention and long-term prophylaxis (cf. German National Disease Management Guideline [NVL] Unipolar Depression, 2022: continuation therapy recommended for at least 6 months after remission; relapse prevention in patients with ≥3 episodes or high relapse risk) (2).

High-risk use of antidepressants

High-risk prescribing of antidepressants refers to their use in the presence of risk factors that heighten the chances of adverse drug reactions (1). Risk factors include co-medication (drug-drug interactions), comorbidities (drug-disease reactions), and advanced age (drug-age reactions). As people age, the number of diseases often increases (multimorbidity), leading to a rise

in the number of medications prescribed (polypharmacy). This combination increases the probability of antidepressant high-risk use particularly in older patients (51-54). Depending on the antidepressant used, co-prescription of antidepressants with anticholinergic, serotonergic, QT-interval prolonging properties, fall risk or bleeding risk increasing drugs bears the risk of serious adverse drug reactions (see also **Table 1** on page 18).

The term ‘overprescribing’ in this dissertation refers exclusively to those cases in which antidepressants are continued in primary care without regular re-evaluation, a clear indication, or shared decision-making. This should not be equated with a clinically justified continuation of treatment in the form of maintenance therapy or relapse prevention, as explicitly recommended by clinical guidelines in cases of recurrent depressive episodes.

Deprescribing in primary care: current state

Definition of deprescribing

Deprescribing has emerged as a key strategy to reduce the inappropriate use of polypharmacy (most commonly defined as the simultaneous use of five or more drugs), which the WHO has declared a priority for patient safety (55). The concept of deprescribing was first defined in 2003 as “[…] the systematic, medically supervised process of discontinuing an inappropriate medication in the context of an individual’s values, preferences, goals of care, and life expectancy” (56). It follows four key steps: reviewing all current medications, identifying medications to be ceased, substituted or reduced, planning a deprescribing regimen in partnership with the patient and frequently reviewing and supporting the patient (56). A more recent and now widely accepted shorter definition is that “Deprescribing is a planned and supervised process of dose reduction or stopping of medication(s) that may be causing harm or are no longer providing benefit.” (57). Both definitions highlight that deprescribing is not simply a means to reduce the number of drugs taken for its own sake but that it includes careful and individualised balancing of drug benefits and risks in order to improve a patient’s quality of life.

Limited implementation of antidepressant deprescribing

While deprescribing interventions have successfully been applied to psychotropic medications, including antidepressants (58-61), there deprescribing antidepressants is rarely practiced systematically, especially in primary care (32, 48, 59, 62, 63). Common barriers to deprescribing are uncertainty, lack of evidence as well as lack of specific guidance on when and how to discontinue medication. Although GPs recognize the importance and are willing to support it, many feel uncertain about applying it to individual patients despite being comfortable managing medication reviews in older populations. This inertia (i.e. failure to act, despite the awareness of necessity) raises questions towards factors (facilitators and barriers) that influence implementation (64, 65).

More research is needed to address this inertia and to develop effective strategies for deprescribing. This includes supporting GPs not only in identifying patients who may benefit from deprescribing (aligning with Woodworth's fourth principle of deprescribing) but also in addressing their perspectives on medication safety (61, 66-69).

Primary care as starting point

GPs are ideally positioned to lead efforts in improving health care, including deprescribing interventions. As gatekeepers they are the first point of contact for patients; GPs often have strong, trusting relationships with their patients and are increasingly responsible for managing chronic conditions in aging populations. Additionally, GPs play a central role in care coordination within healthcare systems, both in Germany and globally (70). However, investments and additional support are needed to develop suitable interventions that support guideline-based medication reviews, including structured decision-making on whether continued antidepressant use remains appropriate.

In this context, antidepressant treatment requires careful consideration of the specific treatment phase - such as acute therapy, continuation (maintenance), or relapse prevention. Rather than proposing a general pharmacotherapy guideline, this work aims to identify situations in everyday general practice where a re-evaluation of long-term antidepressant use may be required. Such evaluations should be grounded in a patient-centred, phase-specific risk-benefit analysis and embedded within a process of shared decision-making.

Overall aims and objectives

Consistent with the UK's Medical Research Council's (MRC) guidance on the development and evaluation of complex interventions, the aim of this doctoral thesis was to develop a an intervention to support general practitioners in identifying clinical situations where ongoing antidepressant treatment may no longer be appropriate based on current guidelines or evidence, and where deprescribing might be considered as a consequence. The specific objectives were:

(1) to identify and prioritize implementation factors (barriers and facilitators) that influence general practitioners ability to critically re-evaluate ongoing antidepressant prescriptions, including the option of deprescribing where appropriate;
(2) to systematically identify and summarise clinical guidance on when re-evaluation of antidepressant therapy may be indicated, and to identify warnings and any mentioning on adverse drug events. This would then inform the creation of an indicator set containing criteria when re-evaluation of ongoging antidepressant therapy may be warrented;
(3) to develop a study protocol for piloting the intervention to evaluate for its effectivity, acceptance and feasibility in preparation for a future randomised controlled trial.

The subsequent chapter provides a detailed explanation of the overarching MRC framework, along with specific aspects of the intervention's development, with **Figure 3** on page 26 offering an overview of the development process.

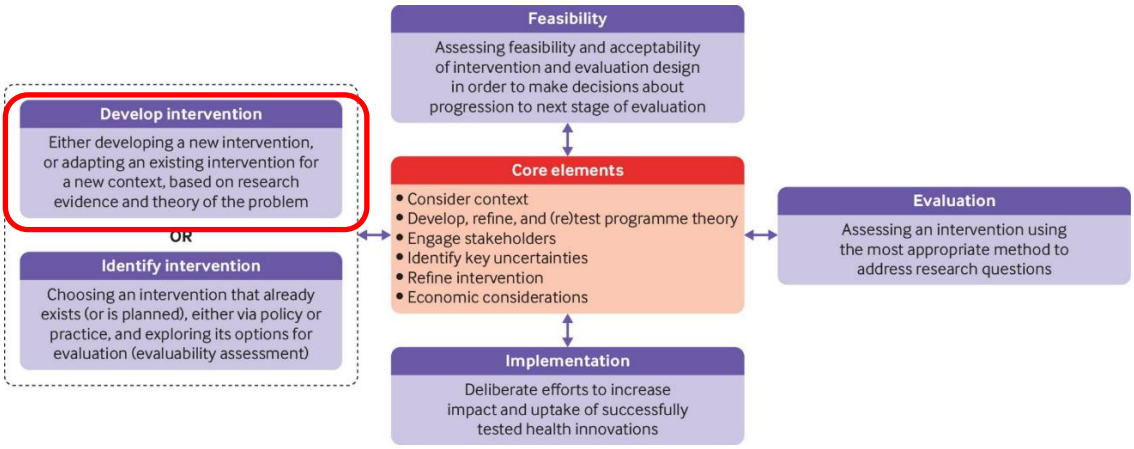
Overall research design

The study design of this doctoral thesis was based on the UK Medical Research (MRC) Framework for developing and evaluating complex interventions. Unlike highly standardized, single-component interventions, such as drug prescriptions with defined doses in randomized placebo-controlled trials, complex interventions are characterized by multiple interacting components, are typically delivered at various levels and require flexibility to adapt to specific healthcare contexts. Supporting the implementation of antidepressant deprescribing fits the criteria of a complex intervention, as it requires multiple components to address barriers in routine clinical practice and influence the behavior of both healthcare professionals and patients.

The MRC framework has been widely used to guide researchers in the systematic development of interventions, enhancing their potential for implementation in routine clinical practice and ultimately improving patient care. The framework organizes complex intervention research into four phases: development or identification of the intervention, feasibility, evaluation, and implementation (see **Figure 2**).

To enhance the quality of the intervention development, we included complement recommendations of the "Guidance on how to develop complex interventions to improve health and healthcare" (71). Within the scope of this doctoral thesis, we focused on the development phase and finished with the development of a protocol for a feasibility study (pilot study)

Figure 2: MRC framework for developing and evaluating complex interventions (72)

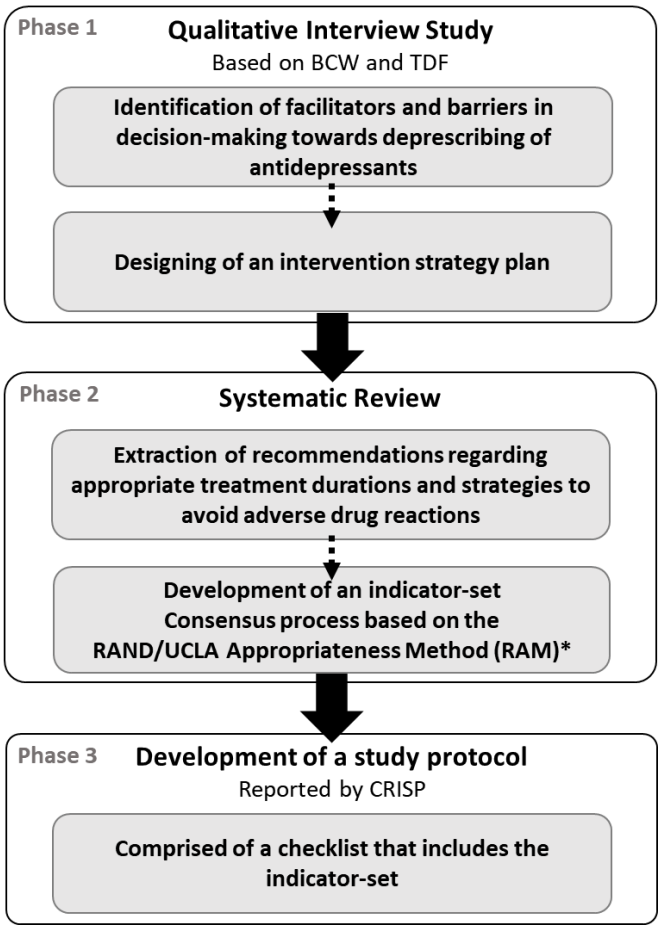


Source: Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. Bmj. 2021;374:n2061.

The intervention development process consisted of three phases, as illustrated in **Figure 3**. It was guided by a combination of the Behavioural Change Wheel (BCW) framework (73) and the Theoretical Domains Framework (TDF) (74). To ensure quality and transparency, we also incorporated various guidelines and checklists (e.g., COREQ-32).

The intervention's content, format and delivery were informed by an interview study (phase 1, described in chapter 2) and evidence from Clinical Practice Guidelines (phase 2, described in chapter 3). For the development of the intervention's study protocol (phase 3, described in chapter 4), we applied the CONSORT statement and the Consensus Reporting Items for Studies in Primary Care (CRISP) which has been invented in 2023.

Figure 3: Intervention developing process



*The indicators-set which was used to create a checklist has been developed by Brisnik et al. (1). BCW: Behaviour-Change-Wheel. TDF: Theoretical Domains Framework. CRISP: Consensus Reporting Items for Studies in Primary Care

Chapter 2: Barriers and Facilitators to Antidepressant Deprescribing - A Qualitative Interview Study

Background

Antidepressants are increasingly used long-term, often off-label and outside the recommendations of clinical practice guidelines (CPGs) (40, 41). CPGs serve as the cornerstone for therapeutic decision-making, offering guidance on when to initiate treatment and identifying scenarios where antidepressant use may pose risks for adverse drug reactions (ADRs). However, CPGs may lack specific and comprehensive recommendations on when and how to attempt deprescribing.

In Germany, and internationally, patients with depression or anxiety- and panic disorders are frequently treated in primary care settings (40, 44, 75). To facilitate antidepressant deprescribing, it is essential to understand how GPs manage uncertainties related to when and how to discontinue antidepressants as well as other barriers and facilitators that influence this process.

More recent studies have focused on influencing factors within older adults or in residential care facilities. One exploratory qualitative study from 2021 examined facilitators and barriers of deprescribing antidepressants focusing on primary care in Ireland and without limitation to age. The study advocated for further studies and suggested that formal practice protocol and guidance for deprescribing, access to evidence-based interventions and patient information and education could improve appropriate antidepressant discontinuation (76). An Australian study from 2021 explored the views of GPs on discontinuation, also without age restrictions (77). However, a limitation was that the study was restricted to GPs in more urban areas.

While numerous interview studies on facilitators and barriers to antidepressant deprescribing have been conducted internationally, it is essential to conduct a similar study in Germany due to the context-dependent nature of deprescribing practices. The German healthcare system is distinct in its structure, including its financing model and the role that GPs play in medication management (78, 79). Additionally, regulatory frameworks in Germany differ from those in other countries, creating distinct challenges and opportunities for antidepressant deprescribing (80, 81). Factors like medication reimbursement, support services, and GP-patient relationships shape unique barriers and facilitators that require setting specific investigation. Cultural attitudes toward mental health, medication use, and deprescribing also vary across countries, influencing the willingness of both patients and general practitioners to discontinue treatment. These nuances are critical in shaping deprescribing practices and must be understood within the specific context of Germany.

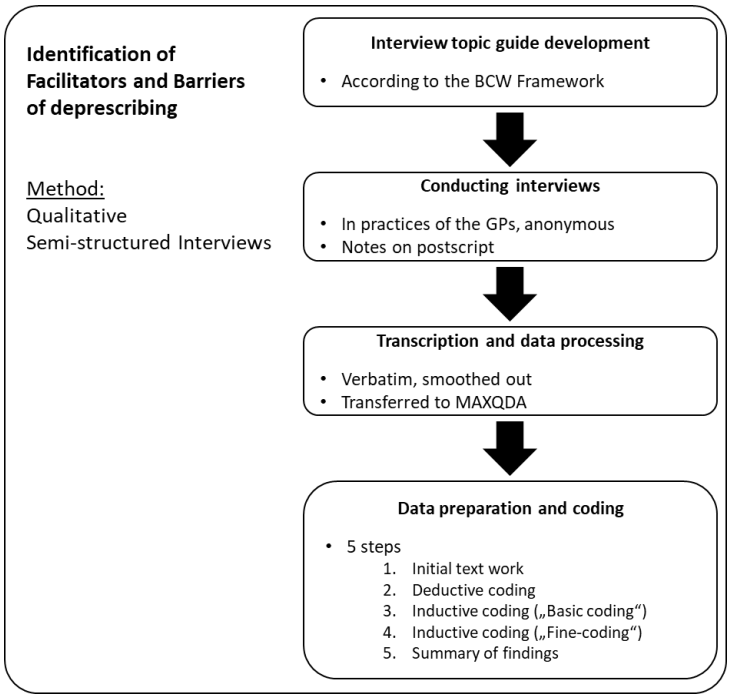
To our knowledge, no study exists in Germany that specifically explored GP’s knowledge, attitude, and decision-making on when to discontinue antidepressants. Thus, conducting an interview study in Germany would provide crucial insights into local barriers and facilitators, which are essential for developing effective, context-specific interventions (82-84).

The primary goal of our interview study was to gain a comprehensive understanding of the implementation factors - both barriers and facilitators - that influence antidepressant deprescribing. Additionally, we aimed to explore how GPs approach the decision-making process when evaluating the need for discontinuation.

Methods

We first developed the interview topic guide, followed by data collection via semi-structured interviews, verbatim interview transcription, and qualitative analysis of interview transcripts. To ensure transparency, we reported the methods and findings of the qualitative study using the COREQ-32 checklist (Appendix **Table 23** on page 109). Ethical approval was obtained from the research ethics committee of the LMU Klinikum (Project No.: 23-0880).

Figure 4: Identification of Facilitators and Barriers of Deprescribing



Interview topic guide development

An interview topic guide was used to structure the investigated topic. It was developed based on various frameworks as detailed below.

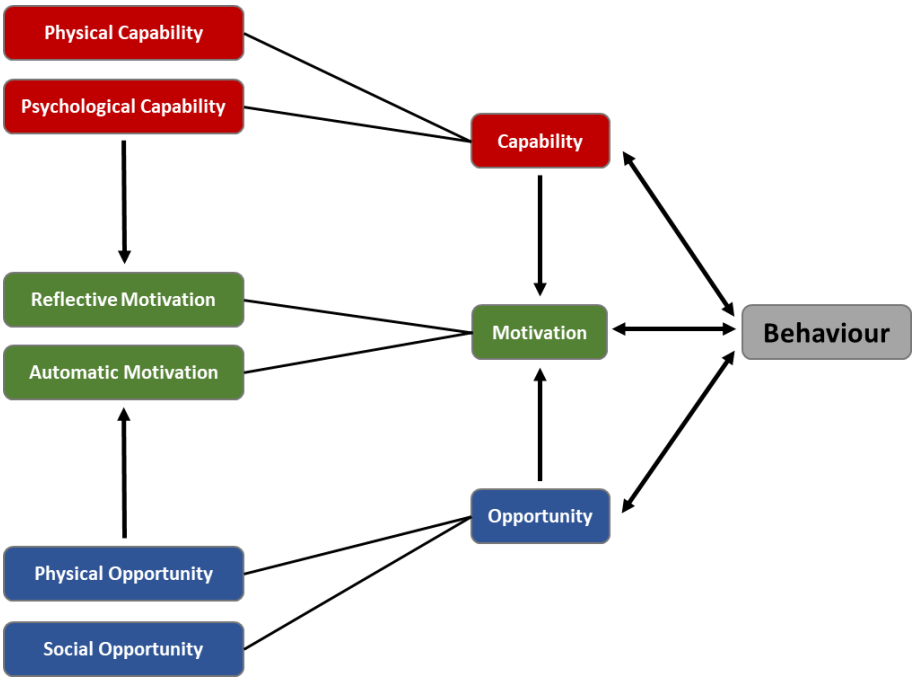
Theoretical framework

The Behavior Change Wheel (BCW) is a comprehensive framework used to develop behavior change interventions. At its core is the COM-B model, which identifies three key drivers of behavior: Capability, Opportunity, and Motivation. These components help understand what influences behavior and provide a foundation for designing targeted interventions. The BCW expands on the COM-B model by linking it to intervention functions (such as education, training, or incentives)

and policy categories that can help implement the changes. The Theoretical Domains Framework (TDF) further supports this approach by offering a more detailed breakdown of the psychological and social factors that influence behavior, allowing for a more structured categorization of these influences within the COM-B framework. Together, the BCW, COM-B, and TDF offer a systematic approach to identifying and addressing the specific barriers and facilitators of behavior change.

In this study, we used the COM-B model to identify and characterize key implementation factors, or "behavioral drivers," influencing antidepressant deprescribing. To systematically categorize the interview content, we applied the TDF. This combination allowed for a deeper understanding of the behavioral influences (i.e., facilitators and barriers) uncovered during the interviews. The interview questions were designed to align with the TDF, and where possible, subtopics were introduced and supported with prompts to clarify the themes, ensuring clearer understanding and more accurate responses. Topics were developed through literature review and discussions among the study team.

Figure 5: COM-B model, adapted from Michie et al., 2014 (73)



- **Capability**: This refers to an individual's psychological and physical ability to perform a behaviour. It encompasses knowledge and skills.
- **Opportunity**: These are the external factors that make the behaviour possible or prompt it. It includes physical opportunities provided by the environment and social opportunities afforded by cultural norms.
- **Motivation**: This encompasses all the brain processes that energize and direct behaviour, including habitual processes, emotional responses, and analytical decision-making.
- **Behaviour**: Capability, opportunity and motivation influence each other and form and result in a behaviour.

The Theoretical Domains Framework (TDF) is used to understand the determinants of behaviour change. Developed in 2005 and refined later, the TDF integrates constructs from multiple behaviour change theories, providing a consolidated structure for identifying the influences on behaviour. It is widely used in implementation science and health psychology to design and evaluate behaviour change interventions (74). Within the BCW Framework, the COM-B model can be linked to the TDF to better understand behaviour and identify necessary changes, serving as an interim step towards specifying suitable intervention functions. The TDF consists of 14 domains (cognitive skills, physical skills, knowledge, memory/attention/decision process, behavioural regulation, goals, intentions, beliefs about consequences, beliefs about capabilities, optimism, social/professional role and identity, reinforcement, emotions, social influences, environmental context and resources) as shown in **Figure 11** (appendix on page 115).

Development, pre-test and refinement of the interview guide

In January 2024 a pre-test interview was conducted in a general practice (REPROVE_HI.01.01) lasting approximately 40 minutes, within the target range of 30 - 45 minutes. The interview guide was refined based on feedback from the GP (see post-script in the appendix on page 132) and subsequent discussions within the research team.

Participants

Inclusion and exclusion criteria

We aimed to include 20 GPs in our study. To be eligible, GPs needed to meet the following criteria: practice located in the state of Bavaria, treat patients covered by the German public Health Insurance (GKV). The exclusion criterion was: current participation in research projects on the topic of medication therapy safety (Arzneimitteltherapiesicherheit) or geriatric medicine.

Sampling frame

The rationale for applying a qualitative approach was to obtain a broad view of potential barriers and facilitators of antidepressant deprescribing across different general practice settings. We therefore purposively sampled GPs for heterogeneity in terms of sex and years of professional experience. Male and female GPs may have different approaches, beliefs, and experiences regarding antidepressant deprescribing, and more experienced GPs may have encountered various patient cases and developed distinct strategies for re-evaluation of ongoing antidepressant therapy and where apporpriate deprescribing, while those with less experience might hold different views or face unique challenges. To obtain a comprehensive understanding across these GP groups, we therefore split our sample into four strata (groups): (A) female and up to 20 years of

professional experience, (B) female and more than 20 years of experience, (C) male and up to 20 years of experience and (D) male and more than 20 years of experience.

Recruitment

Recruitment was conducted via telephone and e-mail using the practice network of the Institute of General Practice and Family Medicine at the University Hospital of Munich list as well as using general practitioner online registries (jameda and doctolib).

Interview conduct

Interviews were conducted at the GPs' practices to provide a familiar and comfortable environment. Most interviews took place during lunch breaks or after office hours. The interviews were conducted by Jochen Vukas (J.V.). After initial greetings and familiarisation, the interview process began with an introduction to the study and its procedures. Participants were informed about data protection regulations, intended uses, and the anonymization process. Any questions were addressed, and data protection was secured through consent forms. Furthermore, participants were encouraged to respond openly, emphasizing that all answers were valuable and there were no wrong responses. The recording device was then activated, and the interviews commenced.

The interview guide served as a flexible point of orientation, aligned with a natural flow of conversation. In addition to the prepared open and closed questions from the guide, spontaneous follow-up questions, prompts, and requests for examples were used to enhance understanding.

To further engage interviewees, the interviewer (J.V.) adopted the role of a “co-expert”. The approach of an “interviewer as a layperson”, typical for exploratory-qualitative methods, is generally not suitable for expert interviews, as experts are more willing to provide information to other experts or quasi-experts than with non-experts.

After the interviews, feedback from the general practitioners regarding the process was collected, and interviewers’ reflections were noted on a postscript sheet (see appendix **Figure 13**). Interviews were conducted between January and April 2024.

Transcription and data processing

The interviews were recorded as mp3/mp4. All recordings were transferred to the study laptop, anonymised and uploaded onto the webpage of a transcription service (‘Transkriptions Spezialist’). Access was secured by two-factor authentication via password and FreeOTP confirmation code. Transcription rules were as follows: scientific rule; verbatim; smoothing of repetitions, stuttering and other minor errors; no further explicit anonymization as interviews were already conducted anonymously. Word elisions, dialects, and punctuation were smoothed out, but longer

pauses and incomprehensible words were represented in the transcript. As phonetic transcription would be too detailed and had led to overload with unnecessary information, those words were not transcribed. No names or person-related data was mentioned in the interviews. After transcription, rtf-documents were then downloaded back to the study laptop and processed with the qualitative data software MAXQDA Analytics Pro, version 24.2.0. Audio files were linked to the respective transcripts to allow for direct interview-inside during coding and analysis.

Data preparation and coding

After transcription, the interviews were allocated to one of the strata A-D (see “Sampling frame”, page 29-230). As illustrated in **Figure 4**, the process of data preparation and coding was conducted in five steps.

In step 1, the interviewer began with the initial text work. Sociodemographic variables of the participants were entered into the software for later analysis. The first three transcripts were read to check for deviations from the recorded audio and for familiarisation with the content. The coding tree was generated according to the topic guide. For each transcript, segments were summarized and saved as memos, with broader segments coded as either facilitator or barrier for antidepressant deprescribing or conducting medication reviews. Case summaries were created and saved in-document memos. Coding followed the proposal of Rädiker and Kuckartz (85).

In step 2, the coding tree was deductively generated. Overarching codes were facilitators and barriers. For each of these, an identical subset of codes was created as follows: Main codes were set for each component of the COM-B framework (capability, opportunity, motivation). Subcodes were generated by mapping the TDF domains to the COM-B components as done for the topic guide. Main codes and underlying subcodes (TDF domains) were colourized for future analytic reasons. Descriptions for the codes were stored using the code memo function, which, together with the code label and a forthcoming coding example, form the code definition.

In step 3, interviews were further coded, and new subcodes were inductively generated from the material, which could be assigned as underlying subcodes to the existing subcodes. The code memos were expanded with coding examples and finalized. Occasionally, the link between the transcript and the audio recording was used to hear statements in the original sound or to correct phrases or words marked by the transcript service as “not understood”.

In step 4, another round of inductive coding was performed until saturation was reached. Subcodes that were similar and difficult to distinguish from each other, were combined. The final coding tree is provided in the appendix on page 133.

In step 5, we synthesized and analysed the coded data. To identify the most frequently mentioned barriers and facilitators, we ranked the subthemes (codes) based on the number of general practitioners who provided at least one statement within each subtheme (see **Table 3** on page 35). Furthermore, we identified commonalities and differences between the strata by conducting a

comparative analysis utilizing the 'complex code frequencies' analysis tool in MAXQDA. Subsequently, we transferred the codes and associated statements of the participants into a matrix. We then meticulously reviewed the statements to explore commonalities and differences. Additionally, we calculated the average number of statements per participant for each subtheme across the four groups (A-D) to account for the varying number of participants in each group. We hypothesized that a higher average number of statements for a subtheme indicates greater importance of that subtheme.

Results

Characteristics of participants

A total of 20 general practitioners were included (11 female, 9 male). **Table 2** shows their characteristics. Participants were recruited from the city of Munich (n=8) and surrounding regions in the south-west of Bavaria (towns: n=5, small towns: n=4, village: n=3). The youngest participant was 33 years old, the oldest 64. Professional experience ranged from 8 to 37 years. Of the 20 participants, 12 worked in practices with more than one general practitioner. Eight general practitioners (4 female, 4 male) had previous experience of participating in clinical studies. Group A consisted of three participants, Group B included eight participants, Group C comprised five participants, and Group D consisted of four general practitioners. One participant dropped out due to personal reasons, and was subsequently replaced through additional recruitment. All participants received detailed information about the study and procedures, and provided written informed consent prior to participation.

Table 2: Characteristics of participants

No.	Participant ID	Group[1]	Gender	Age	Years of Professional Experience	Region[2]	Single Practice	Study Experience	Interview Duration in Minutes
1	REPROVE_HI.01.01	D	Male	57	27	City	No	No	39
2	REPROVE_HI.01.02	B	Female	56	29	City	Yes	Yes	43
3	REPROVE_HI.01.03	D	Male	51	25	Small town	No	Yes	47
4	REPROVE_HI.01.04	C	Male	33	8	City	No	No	52
5	REPROVE_HI.01.06	B	Female	59	29	City	No	Yes	37
6	REPROVE_HI.01.07	C	Male	46	17	City	Yes	No	39
7	REPROVE_HI.01.08	B	Female	59	32	City	No	No	40
8	REPROVE_HI.01.09	B	Female	62	34	City	Yes	No	28
9	REPROVE_HI.01.10	B	Female	58	29	City	No	No	28
10	REPROVE_HI.02.01	C	Male	37	10	Small town	No	Yes	54
11	REPROVE_HI.02.02	C	Male	36	8	Town	No	No	39
12	REPROVE_HI.03.01	B	Female	55	30	Town	Yes	Yes	26
13	REPROVE_HI.04.01	A	Female	46	20	Town	Yes	No	42
14	REPROVE_HI.04.02	A	Female	48	18	Village	Yes	No	25
15	REPROVE_HI.05.01	D	Male	64	37	Small town	No	Yes	27
16	REPROVE_HI.05.02	A	Female	46	18	Town	No	No	26
17	REPROVE_HI.06.01	B	Female	54	27	Town	Yes	No	63
18	REPROVE_ps_01	D	Male	58	30	Small town	No	Yes	22
19	REPROVE_ps_02	B	Female	56	30	Village	No	Yes	23
20	REPROVE_ps_03	C	Male	38	9	Village	Yes	No	16

[1]Group A (up to 20 years, female). Group B (more than 20 years, female). Group C (up to 20 years, male). Group D (more than 20 years, male)
[2]Differentation by populational size. City: >100,000. Town: ≤100,000. Small town: ≤10,000. Village: ≤1,000

Analysis of coding

Barriers to antidepressant deprescribing

Most codes related to antidepressant deprescribing barriers were attributed to the following TDF domains (see **Table 3**) *environmental context and resources, social influences, and beliefs about capabilities*. Within the *environmental context and resources* domain, statements predominantly related to lack of time, lack of practical tools and inadequate guidelines. Within the domain *social influences*, the lack of engagement from medical specialists other than general practitioners were noted and their lack of collaboration or awareness towards deprescribing were mentioned. Uncertainties about when and how to attempt or conduct deprescribing were often highlighted within the domain *beliefs about capabilities.*

Table 3: Barriers: Number of general practitioners mentioning subthemes

TDF domain		Subtheme (code)	Group (strata)				All groups
			A	B	C	D	
COM-B domain: Psychological Capability							
2	Knowledge	Lack of knowedge to CPGs	2	3	3	1	9
4	Memory, attention and decision processes	Lack of established routine	1	6	4	3	13
COM-B domain: Reflective Motivation							
9	Beliefs about capabilities	Uncertainties regarding the decision to deprescribe	2	4	1	2	9
9	Beliefs about capabilities	Uncertainties if originally prescribed by general practitioners from other disciplines	1	5	1	2	9
COM-B domain: Automatic Motivation							
14	Negative reinforcement	Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary	0	5	2	2	9
COM-B domain: Social Opportunity							
7	Social influences	Lack of engagement by general practitioners from other disciplines (outpatient care setting)	1	7	3	2	13
7	Social influences	Involvement of other general practitioners in patients treatment	2	3	3	2	10
7	Social influences	Lack of collaboration/awareness regarding medication safety by hospital general practitioners	1	4	2	2	9

COM-B domain: Physical Opportunity							
6	Environmental context and resources	Lack of time	3	7	5	2	17
6	Environmental context and resources	Lack of practical tools	2	4	3	3	12
6	Environmental context and resources	Lack or inadequacy of guidelines	0	6	2	2	10
6	Environmental context and resources	Financial and economic deficiencies/disadvantages	1	2	3	3	9

(A) female and up to 20 years of professional experience, (B) female and more than 20 years of experience, (C) male and up to 20 years of experience and (D) male and more than 20 years of experience

The following section provides a detailed explanation of the most frequently mentioned subthemes related to the COM-B components and the TDF domains. Additionally, selected quotes are presented as examples. **Table 4** on page 39 summarizes the results. All subthemes were grouped into overarching themes to identify the main focal points of the statements. The resulting themes were: Guidance and decision, interdisciplinarity, time, reward and acknowledgement. It became apparent that most barriers were related to the theme “Guidance and decision”. This supports us in the subsequent search for a suitable intervention strategy plan.

COM-B domain: Psychological Capability

Time scarcity affects both mindset and the daily routines, leaving little room mental and temporal space for reviewing medication plans. Medication reviews are not systematically integrated into daily practice. Consequently, deprescribing following a prior medication review often occurs in an unsystematic or opportunistic manner

> *"In my practice, it is not systematic. Usually, it happens let’s say, by chance or when the patient comes in with a specific concern."* (REPROVE_ps_03)

COM-B domain: Reflective Motivation

Furthermore, general practitioners are uncertain about when to consider deprescribing and are concerned about how patients will respond. Deprescribing of antidepressants were described as being more difficult to deprescribe than other drugs prescribed for prevention and without effects on patient’s mental health.

> *"It is actually a daily issue, and I would appreciate having more confidence in this area. Perhaps a greater sense of security as well, that, often, we rely on our intuition to determine the dosage, yes? It’s also, finding the right dosage, to be honest, involves a lot of experience, but*

it is also often a gut feeling about what to prescribe and how much. Sometimes, I wish I had a bit more certainty." (REPROVE_HI.01.08)

"With antidepressants, it's just that I don't know how the patient will react. Because the entire psyche is involved, I think it's simply more difficult. With a statin, they won't notice if they stop taking it or not." (REPROVE_HI.05.01)

COM-B domain: Automatic Motivation

General practitioners criticize existing tools (such as PRISCUS, FORTA, etc.) and clinical guidelines for being confusing, complex, and time-consuming, rendering them unsuitable for systematic use in daily practice. Some general practitioners had previously attempted to work with these tools and guidelines, but eventually abandoned their use.

"I admit, I do not refer to them often because they are too lengthy and not very user-friendly." (REPROVE_HI.01.07)

“PRISCUS. But I don't check it regularly. […] Because, of course, I potentially know this – anticholinergic medication, not too many benzodiazepines… So, I am generally aware of which medications these are. And with older patients and those with multimorbidity on multiple medications, I always check if there's any possibility to discontinue something. But not explicitly, like using the list and saying: "This and that is dangerous." Because then it turns out that half of it […] is dangerous.” (REPROVE_ps_02)

COM-B domain: Social Opportunity

General practitioners feel that colleagues from other disciplines and from hospitals do not adequately engage in medication safety and deprescribing. The interviewed general practitioners observed that patients returning from hospitals had medication plans changed - added, stopped or modified - without any explanations to GPs or patients. Some general practitioners felt frustrated and left alone with the challenge of managing pharmacotherapy.

"Because when I sign off on the plans and distribute them, I never know if they are truly accurate. Because, various specialists, someone is always making changes, and no one commits to using this medication plan - at least not the specialists. So, we are left with the medication plan." (REPROVE_HI.01.08)

COM-B domain: Physical Opportunity

General practitioners face heavy workloads and as a result, lack of time is a critical factor negatively influencing their behaviour regarding medication safety and deprescribing. Time constraints further hinder the establishment of integrated deprescribing routine or maintaining a "deprescribing" mindset in daily practice.

> *"Medication plans often include up to 15 different medications. It is nearly impossible for me to review these comprehensively with the patient within the constraints of a typical consultation."* (REPROVE_HI.01.04)

> *"Not really. We review it periodically and discuss it during team meetings. However, I do not work with the list [PRISCUS] directly on an ad hoc basis because it is simply too cumbersome."* (REPROVE_HI.05.01)

In addition to lacking recognition from policymakers, GPs felt undervalued financially, which deterred their investment in deprescribing efforts:

> *"And then I just have to say, it's all about sitting down and reviewing plans. If I know I get 2 euros per quarter for a chronic patient, and the health insurance gets 90 euros for the review, then I have to say, I'm the one getting the short end of the stick. There's no appreciation for our work. There is none."* (REPROVE_HI.05.01)

Table 4: Barriers of deprescribing and example quotes

TDF domain	Theme	Subtheme	Sample quotes
COM-B domain: Psychological Capability			
Memory, attention and decision processes	*Guidance and decision*	Lack of established routine	"In my practice, it is not systematic. Usually, it happens lets say, by chance or when the patient comes in with a specific concern." (REPROVE_ps_03)
COM-B domain: Reflective Motivation			
Beliefs about capabilities	*Guidance and decision*	Uncertainties regarding the decision to deprescribe	"It is actually a daily issue, and I would appreciate having more confidence in this area. Perhaps a greater sense of security as well, that, often, we rely on our intuition to determine the dosage, yes? It's also, finding the right dosage, to be honest, involves a lot of experience, but it is also often a gut feeling about what to prescribe and how much. Sometimes, I wish I had a bit more certainty." (REPROVE_HI.01.08)
	Interdisciplinarity	Uncertainties if originally prescribed by general practitioners from other disciplines	"I would definitely say so. So, if I had prescribed it myself, lets say, I would feel significantly more confident and independent in deciding to discontinue it." (REPROVE_HI.01.07)
COM-B domain: Automatic Motivation			
Negative reinforcement	*Guidance and decision*	Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary	"I admit, I do not refer to them often because they are too lengthy and not very user-friendly." (REPROVE_HI.01.07)
COM-B domain: Social Opportunity			
Social influences	*Interdisciplinarity*	Lack of engagement by general practitioners from other disciplines (outpatient care setting)	"Because when I sign off on the plans and distribute them, I never know if they are truly accurate. Because, various specialists, someone is always making changes, and no one commits to using this medication plan - at least not the specialists. So, we are left with the medication plan." (REPROVE_HI.01.08)
		Lack of collaboration/awareness regarding medication safety by hospital general practitioners	"I mean, when I create a new medication plan for an elderly patient with, say, twelve medications, and he goes to the hospital, they change everything. The patients come back without knowing what he is taking, and it becomes incredibly time-consuming. And also with, yeah, in the hospital they do not review all the new medications thoroughly with the patient." (REPROVE_HI.01.08)
COM-B domain: Physical Opportunity			
Environmental context and resources	*Time*	Lack of time	"Medication plans often include up to 15 different medications. It is nearly impossible for me to review these comprehensively with the patient within the constraints of a typical consultation." (REPROVE_HI.01.04)
	Guidance and decision	Lack of practical tools	"Not really. We review it periodically and discuss it during team meetings. However, I do not work with the list [PRISCUS] directly on an ad hoc basis because it is simply too cumbersome." (REPROVE_HI.05.01)
		Lack or inadequacy of guidelines	"The main issue is how to prescribe the medications. There is no mention of how to reduce or discontinue them. Additionally, a major weakness of guidelines is that they are often designed for monocausal diseases." (REPROVE_HI.01.02)
	Reward and acknolegement	Financial and economic deficiencies/disadvantages	"And the other component is that you usually do not get compensated if you thoroughly reviewing the medication plan." (REPROVE_HI.02.01)

Facilitators to antidepressant deprescribing

Most subthemes were linked to the following TDF domains: *social influences*, *environmental context and* resources, and *beliefs about capabilities.* Statements with *social influences* included support by pharmacists, trustful relationship with patients, and the patients' own wish to discontinue antidepressant therapy. In the *environmental context and resources* domain, most statements pertained to the following subthemes: integrated/individualized practice-management software and digital/online tools. In terms of *beliefs about capabilities*, many statements addressed the importance and benefits of deprescribing/intervention as motivating factors, as well as general practitioners' belief in their own capabilities for deprescribing.

Notably, integrated software, shared decision-making (for both deciding when to discontinue and during dose tapering), and GPs belief in their central role in deprescribing were the most frequently coded segments linked to facilitating factors. This is likely due to some of the 20 interviewed general practitioners discussing these topics multiple times, indicating their importance.

It became apparent, that general practitioners identified several areas as facilitating factors, many articulated in the subjunctive mode, indicating aspirations for the future.

COM-B domain: Psychological Capability

Effective communication skills with patients were found to be essential and supportive as was fostering a good relationship to patients and their involvement in decision-making.

> *"Yes, because the patient can listen. They can read. Everyone knows that doctor visits are an agitation for many elderly patients. And in this agitation, they are so out of sorts that they don't even remember their name or their children's birthdays. So, you really have to consider this. I also perform a dementia test. I ask ten times if they are feeling well, if today is a good day. And if it isn't a good day, we reschedule."* (REPROVE_HI_01.02)

COM-B domain: Reflective Motivation

We identified optimism and a positive attitude regarding medication safety and deprescribing as important facilitators. All general practitioners asserted that deprescribing and interventions in this area are important and potentially beneficial for patients.

> *"In principle, I always find it good when we can explore options that allow us to give patients as few medications as possible."* (REPROVE_HI.06.01)

> *"Medication safety is an extremely important issue because many patients in general practice suffer from polypharmacy, quote-unquote, and interactions are checked far too infrequently. Additionally, many patients for sure suffer from unrecognized adverse drug reactions."*

(REPROVE_HI.02.02)

Table 5: Facilitators: Number of general practitioners mentioning subthemes

TDF domain		Subtheme (code)	Group (strata)				All groups
			A (3)	B (8)	C (5)	D (4)	
COM-B domain: Psychological Capability							
1	Mental skills	Communication with patients/patient involvement	3	8	3	3	17
2	Knowledge	Shared decision making (when/how to deprescribe)	3	7	4	4	18
4	Memory, attention and decision processes	Established working routine	3	8	5	4	20
COM-B domain: Reflective Motivation							
11	Beliefs about consequences	Deprescribing/Interventions are important	2	4	5	4	15
11	Beliefs about consequences	Belief in own capability towards deprescribing	2	7	3	3	15
9	Beliefs about capabilities	Belief that deprescribing antidepressants is easier than with drugs (process, tapering)	1	6	2	2	11
COM-B domain: Automatic Motivation							
14	Reinforcement	Positive experience with deprescribing	2	5	2	3	12
COM-B domain: Physical Opportunity							
6	Environmental context and resources	Integrated/individualized practice-management-software	2	7	5	2	16
6	Environmental context and resources	Digital/online tool	3	3	5	2	13
COM-B domain: Social Opportunity							
7	Social influences	Support by pharmacies	3	6	2	1	12
7	Social influences	Good patients' compliance and relationship with patients	1	4	1	2	8
7	Social influences	Patients desire to discontinue antidepressant	2	5	4	3	14

(A) female and up to 20 years of professional experience, (B) female and more than 20 years of experience, (C) male and up to 20 years of experience and (D) male and more than 20 years of experience

COM-B domain: Automatic Motivation

General practitioners mentioned that their software lacks adequate components and expressed a desire for enhanced functionality. Conversely, facilitating factors were an integrated, intelligent and patient-individualized clinical decision support software or digital tools.

> *"Ultimately, I think the software could be designed to be more intelligent. So that it provides more useful alerts, not unnecessary ones, ok? For example, it could give alerts for new prescriptions or, like, integrate lab values with medications. It should be possible to, like, to develop such an intelligent software that better filters medications and adverse drug reactions and thereby helps to better filter, that one maybe remembers that better, ok?"* (REPROVE_ps_02)

COM-B domain: Social Opportunity

Most general practitioners stated that pharmacists should be involved in medication safety. Collaboration would also be beneficial and helpful.

"Yes, that is the interesting part, because pharmacies, at least in our case, very often conduct interaction checks. And pharmacies often know more than we do regarding the patient's medication. Because they also gather medications prescribed by specialists, and then interaction feedback quickly comes from the pharmacy, for example. Or feedback like, 'Hey, they have been taking this for very very long,' when it comes to hypnotics and sedative medications. 'You should perhaps discuss it with the general practitioner.' And that works very well here."

(REPROVE_HI.03.01)

COM-B domain: Physical Opportunity

Some GPs found existing software alerts helpful in detecting potential drug interactions, with warnings classified by severity (yellow, orange, and red), although they retain the option to proceed with prescribing (and refrain from deprescribing) if necessary.

> *"So, it is like this: I have a digital practice, which means my medication tool in the software warns me when I prescribe things that have interactions. There are different levels of warnings from yellow, orange, to red, and I can still prescribe if I choose to. But I am alerted to these interactions. This is actually one of the main tools I have."* (REPROVE_HI.01.10)

Table 6: Facilitators of deprescribing and quotes

TDF domain	Theme	Subtheme	Sample quotes
COM-B domain: Psychological Capability			
Mental skills	*Relationship* *Guidance and decision*	Communication with patient/patient involvement	"I speak in clear sentences. I then ask if they have understood. I repeat often. And very frequently, I work with my own self-designed recommendations." (REPROVE_HI.01.02)
Knowledge		Shared decision making (when/how to describe)	"They usually tell me, 'Yes, I have already thought about that,' and then explain to me why now is a good time. Or we discuss when a good time might be. So, it's more of a safeguard. Then we think about how to proceed. Sometimes we postpone the decision, and I say, 'Well, it might not be the right time yet, I'll ask you again later.' That's how it goes. Yes." (REPROVE_HI.01.10)
COM-B domain: Reflective Motivation			
Beliefs about consequences	*Guidance and decision*	Benefit of deprescribing/interventions	"Nevertheless, deprescribing is fundamentally good. The saying, 'Every medication less is a good medication,' is something, I do, I often say in various places and truly believe in." (REPROVE_HI.01.03)
		Belief in own capability towards deprescribing	"And, as I said, you can relatively easily discontinue psychotropic drugs and diuretics, you know, it is, as I said, relatively straightforward." (REPROVE_HI.01.02)
COM-B domain: Automatic Motivation			
Reinforcement	*Guidance and decision*	Positive experience with deprescribing	"It has always worked so far. I do it reluctantly, for example, in winter, during the darker months when patients are more likely to be in low spirits. Spring is actually a very, very good time to start or to try it." (REPROVE_HI.03.01)
COM-B domain: Physical Opportunity			
Environmental context and rescources	*Guidance and decision*	Integrated/personalized practice managment software	“Essentially, for me, it would be / So if I just go into my system, into the / into the medication plan, there / the potential interactions already light up there, in the plan, meaning in the compilation of the medications. I immediately get a / I don't have to do an interaction check laboriously and then read through all the lists. Instead, it directly / shows the / the two medications that might cause an issue, with a potential adverse drug reaction and a suggestion for reduction. I would find that kind of digital solution fantastic." (REPROVE_HI.01.08)
		Digital/online tool	"So, it is like this: I have a digital practice, which means my medication tool in the software warns me when I prescribe things that have interactions. There are different levels of warnings from yellow, orange, to red, and I can still prescribe if I choose to. But I am alerted to these interactions. This is actually one of the main tools I have." REPROVE_HI.01.10)
COM-B domain: Social Opportunity			
Social influences	*Guidance and decision*	Patients desire to discontinue antidepressant	"Yes, well it’s, it happens that patients frequently bring it up actively." (REPROVE_HI.01.04)
	Relationship	Good patients’ compliance and relationship with patients	"So, the individual trust in the person? Yes, of course, it is beneficial. If I know that I can rely on them to tell me the truth, whether intentionally or unintentionally, it is certainly a support for me." (REPROVE_HI.01.09)
	Interdisciplinarity *Guidance and decision* *Relationship*	Support by pharmacies	"Yes, that is the interesting part, because pharmacies, at least in our case, very often conduct interaction checks. And pharmacies often know more than we do regarding the patient's medication. Because they also gather medications prescribed by specialists, and then interaction feedback quickly comes from the pharmacy, for example. Or feedback like, 'Hey, they have been taking this for very very long,' when it comes to hypnotics and sedative medications. 'You should perhaps discuss it with the general practitioner.' And that works very well here." (REPROVE_HI.03.01)

Comparison of GPs perspectives by strata

This section explores the differences in behaviors and attitudes regarding the consequent re-evaluation and potential deprescribing of antidepressants, based on the sex and years of professional experience of general practitioners (GPs). We divided the sample into four groups: female GPs with up to 20 years of experience (Group A), female GPs with more than 20 years of experience (Group B), male GPs with up to 20 years of experience (Group C), and male GPs with more than 20 years of experience (Group D). We analyzed these groups with respect to their capability, motivation, and opportunity to deprescribe antidepressants and gave quotes as examples.

Group A: Female, up to 20 years of experience

Female GPs with less than 20 years of experience reported concerns regarding their knowledge, especially when it came to deprescribing guidelines. All GPs found time management to be challenging. These GPs emphasized the importance of communication with patients. Their motivation to deprescribe was hindered by uncertainty and hesitation, particularly regarding their capability to manage the process independently. They showed a preference for digital tools to aid their practice, but had fewer positive experiences with deprescribing overall, potentially reflecting their limited exposure to this aspect of patient care. They also placed a high value on interdisciplinary collaboration, although they reported fewer concerns about the lack of engagement from other practitioners than their more experienced counterparts.

Example quote:

B: "*That would be cool if there was something like that as an app or software. Because I think it's easier. Then you just click through. If a box is checked somewhere, then a new window opens and says, okay, done. So, that would be great.*"

I: "So, digital, as software?"

B: "*Digital. Exactly. That would be great. And what I have noticed is that if I followed this approach, I wouldn't prescribe antidepressants anymore."* REPROVE_ HI.04.02

Group B: Female, more than 20 years of experience

Female GPs with over 20 years of experience demonstrated more confidence in their knowledge and capabilities, though they frequently reported barriers related to the complexity and practical limitation of guidelines and found existing tools to be burdensome. They highlighted the challenges they faced with interdisciplinary collaboration, particularly in coordinating care with other physicians, and expressed higher expectations for engagement from colleagues. Their motivation to deprescribe was supported by positive experiences. Time constraints were little less problematic for this group compared to less experienced GPs. They emphasized the importance of integrated clinical decision support software.

Example quote:

"*Because many guidelines, they all know them. It's just about how to prescribe the medications. And how to reduce or discontinue them, there's not a word about that. Then, a weakness of guidelines, they are often designed for monocausal diseases.*" REPROVE_ HI.01.02

"*Well, in what sense does time play a role? My time doesn't really matter, because I take the time, as I find it important.*" REPROVE_ HI.01.02

Group C: Male, up to 20 years of experience

Male GPs with fewer than 20 years of experience reported similar knowledge limitations and especially heavy time management challenges as their female counterparts in Group A. However, they displayed a stronger interest in digital tools to help manage these barriers, reflecting a tech-savvy approach to deprescribing. They were less concerned about deprescribing overall, suggesting greater confidence in their ability to manage this aspect of patient care. Nevertheless, they faced notable challenges with workload and the practical tools available to support deprescribing. Economic concerns were also more prominent for this group, indicating that financial considerations played a significant role in their decision-making. Socially, Group C placed less emphasis on pharmacy support, showing a preference for managing deprescribing independently.

Example quote:

"*But I do feel that this responsibility tends to lie more with general practitioners. That we have the patient's context, you could say—with multiple issues, somehow. So, I do think that we are probably the ones most likely to discontinue medications in context. […] But I do feel that it is generally getting better with digital work, because changes can be entered quickly.*" REPROVE_ HI.01.04

"*Of course, if there were compensation for corresponding measures, it could certainly be an incentive, yes.*" REPROVE_ HI.01.07

Group D: Male, more than 20 years of experience

Male GPs with more than 20 years of experience exhibited the highest levels of confidence in their ability to deprescribe, with fewer concerns about their knowledge or the complexity of guidelines. They reported being more adaptable and capable of managing the process without significant difficulties. Established routines were not a major issue for this group, and they placed strong emphasis on communication with patients and shared decision-making. Their motivation to deprescribe was reinforced by positive experiences, though they noted that the practical tools available to them could be improved. This group encountered fewer time constraints than less experienced GPs, suggesting that workload management improves with experience. Economic concerns were more relevant for these GPs, indicating that financial factors influenced their approach to deprescribing. Socially, they were less dependent on pharmacy support, reflecting a self-reliant approach to managing deprescribing, though they expressed strong concerns about a lack of collaboration from hospitals and from other physicians, particularly regarding medication safety.

Example quote:

"*And yes, I think, of course, it might be quite nice if, for example, in a program like the practice management software, a window would pop up after a year, saying 'Medication review, psychotropics, or something.' That would be an option.*" REPROVE_ HI.01.01

"*Because the specialists always prescribe their medications, just pile them on, and the hospitals do the same.*" REPROVE_ HI.05.01

"*Hospital discharge letters are a goldmine for discontinuing medications.*" REPROVE_ ps_01

Group-specific conclusions

In conclusion, **group A** (female GPs with less than 20 years of experience) faced challenges in terms of knowledge limitations, time management, and confidence. They relied on external resources like pharmacies and showed a preference for digital tools to support their practice. **Group B** (female GPs with more than 20 years of experience) encountered more interdisciplinary barriers and frustrations with guideline complexity, though they remained confident in their capabilities. **Group C** (male GPs with less than 20 years of experience) embraced technology and digital tools to overcome their challenges, but economic concerns played a larger role in their practice. Finally, **group D** (male GPs with more than 20 years of experience) demonstrated high levels of confidence and adaptability, though they still faced some difficulties with the practical tools available for medication reviews and conducting deprescribing of antidepressants. This group was more self-reliant, placing less emphasis on external support such as pharmacies, and facing challenges towards collaboration with hospitals and other physicians.

Discussion

Summary of findings

This doctoral thesis addresses a gap in the German healthcare landscape by examining general practitioners' (GPs) knowledge, attitudes, and decision-making processes regarding the discontinuation of antidepressants. Prior to this study, no research in Germany had specifically focused on these aspects, making the findings particularly important. The study aimed to understand the barriers and facilitators that influence GPs' decision-making when re-evaluating ongoing antidepressant use, including the option of deprescribing. Through semi-structured interviews, the research explored how GPs assess the need to discontinue antidepressants and what factors influence their decisions.

A key finding was the shared emphasis on medication safety across all GPs, regardless of experience or gender. Many expressed a strong interest in improving care quality through computerized programs and saw research and continuous education essential for making informed decisions about deprescribing. However, there were mixed views on the use of guidelines and tools, such as the PRISCUS list, which some found too complex to apply in everyday practice.

In terms of deprescribing practices, GPs generally favored gradual tapering when discontinuing antidepressants. They highlighted the importance of involving patients in decision-making, with shared decision-making viewed as essential for successful outcomes. GPs also felt they held the primary responsibility for medication safety, reinforcing the need for strong patient relationships to facilitate collaborative decision-making.

However, several barriers hindered effective deprescribing and prior medication reviews. Time constraints were a major challenge, particularly for less experienced GPs, who found it difficult to balance workload with deprescribing efforts. Additionally, there was frustration over the lack of interdisciplinary collaboration, especially with specialists and hospital physicians. GPs felt these colleagues often overlooked medication safety, leaving primary care practitioners to address issues like polypharmacy. The complexity of guidelines and the absence of practical deprescribing tools also made the process more difficult.

On the other hand, several facilitators were identified. Many GPs saw digital tools integrated into practice software as a potential game-changer, particularly if they provided automated warnings and reminders. Regular training and quality circles were also seen as important for keeping up with deprescribing practices. Pharmacist support was another facilitator, with GPs recognizing the role pharmacists play in monitoring medication safety through checks on drug interactions.

GPs expressed a strong desire for an integrated medication management and deprescribing tool that could be incorporated into their practice management software. Such a tool would offer personalized warnings, automated prompts, and help filter medications based on patient-specific data. Improved digital infrastructure across healthcare settings was also seen as crucial for enhancing deprescribing processes.

In conclusion, while GPs in Germany are committed to deprescribing antidepressants, they face considerable barriers, particularly related to time, interdisciplinary collaboration, and practical

tools. However, their interest in digital solutions and pharmacist support presents promising facilitators that could enhance their ability to deprescribe effectively. These findings provide important insights for developing targeted interventions that address the specific challenges faced by GPs, improving the safety and quality of antidepressant use.

Building on these findings, the interviews also revealed a clear demand for structured support in identifying patients who may benefit from deprescribing. The indicator-based tool, developed in a separate project (cf. Brisnik et al., 2024), directly responds to this need and reflects the priorities expressed by the general practitioners who participated in this study.

Comparison with literature

Numerous studies conducted in various settings have examined the barriers and facilitators to deprescribing antidepressants, providing valuable insights into this complex process. This section aims to contextualize the findings of our study by comparing and contrasting them with existing literature. By exploring the barriers and facilitators identified through the COM-B framework, we can better understand how these factors influence general practitioners' decision-making regarding antidepressant discontinuation.

COM-B domain: Psychological Capability

Time constraints emerged as a significant barrier to deprescribing, as GPs often lacked the necessary time to implement or maintain routines in medication review and concommitant deprescribing if indicated. This finding aligns with previous studies that have shown that a heavy workload, short consultation times, and the absence of established deprescribing practices lead to continued prescribing habits (33). However, a notable facilitator in this domain was the strong communication skills that many GPs demonstrated, which helped build trust with patients. Effective communication was crucial in educating patients about the benefits of discontinuing antidepressants and involving them in shared decision-making. This proactive approach to patient engagement helped counterbalance the psychological barriers by fostering patient understanding and cooperation (86).

COM-B domain: Reflective Motivation

A significant barrier identified was the uncertainty surrounding the right timing for the attempt of deprescribing antidepressants, particularly when patients had a history of withdrawal symptoms or relapse. This uncertainty, also highlighted in prior literature, often prompted GPs to adopt a cautious stance in their deprescribing decisions, relying more on intuition than clear guidelines (33, 87, 88). The lack of specific criteria for deprescribing left GPs uncertain about when it was safe to discontinue treatment. However, shared decision-making and effective patient communication emerged as strong facilitators in this domain. GPs recognized the importance of guiding patients through a planned and safe tapering process instead of allowing unsupervised discontinuation.

COM-B domain: Social Opportunity

Collaboration and communication challenges with colleagues from other disciplines and hospitals were identified as significant barriers. GPs expressed feelings of isolation, particularly as the number of patients experiencing polypharmacy increased. This finding resonates with existing literature, which points out that specialists often focus on their own treatment protocols without considering the broader medication regimen of patients, further complicating the deprescribing process (33, 70, 89). Conversely, some participants noted the role of pharmacies in supporting medication safety by identifying potentially inappropriate medications (PIMs). Although there were mixed feelings regarding this collaboration, in alignment with other studies (90-92) most GPs acknowledged that integrating pharmacists into the deprescribing process could ultimately enhance patient outcomes.

COM-B domain: Physical Opportunity

While previous studies have identified the complexity of deprescribing as a barrier (93), our findings revealed that GPs did not perceive the deprescribing process itself as particularly time-consuming or complicated. Instead, they cited the frequency of medical reviews and patient contacts as contributing factors to their heavy workloads, which ultimately limited their capacity to address deprescribing. Interestingly, the context of healthcare systems varied between countries; for instance, GPs in the Netherlands reported having more time for medication reviews issues compared to their counterparts in Germany (94). Additionally, our participants highlighted the lack of financial incentives as a barrier to their motivation for the engagement in medication review, including deprescribing where appropriate. Unlike pharmacists, who receive compensation for medication reviews, GPs felt undervalued, leading to a perception of inequity.

Despite being aware of existing decision aids like FORTA and PRISCUS, GPs viewed these tools as overly complex and impractical for daily use, different to findings from other studies (95). Furthermore, as observed in previous studies (96), general practitioners in our research identified a lack of perceived impact on deprescribing from their practice software, attributing this to the excessive number of alerts generated. Participants expressed a desire for integrated and user-friendly digital tools that could support structured medication review and help identify patients for whom discontinuation of antidepressant therapy might be clinically appropriate. Furthermore, GPs reported a lack of comprehensive clinical practice guidelines for deprescribing, with existing guidelines often perceived as too time-consuming to apply effectively in their daily work.

In summary, this study's findings largely support existing literature regarding the barriers and facilitators to antidepressant deprescribing. Consistent with previous studies, we found that time constraints, uncertainty in decision-making, and collaboration challenges with specialists significantly hinder the deprescribing process. However, our study also highlights unique insights, such as the particular burden of financial incentives and workload management among GPs in Germany. Additionally, while GPs recognized the importance of effective communication and shared decision-making as facilitators, there remains a gap in the proactive involvement of patients in discussions about deprescribing. These nuanced differences underscore the need for tailored

interventions that consider the specific contexts and challenges faced by general practitioners in different healthcare systems.

Strengths and limitations

Strengths

To our knowledge this was the first interview study exploring facilitators and barriers towards antidepressants deprescribing and preceding medication reviews from the perspective of general practitioners in Germany. We achieved diversity in demographic and geographic variables within the GPs sample, ensuring that multiple perspectives were represented, thus enriching the study's insights.

We see a strength by the use of a mixed theory model namely the COM-B and TDF framework to guide the interviews the coding process, thus providing insightful knowledge on the perspective of GPs towards deprescribing antidepressants. This allowed us to systematically identify relevant facilitators and barriers associated with deprescribing of antidepressants and to further continue developing an intervention within the same widely accepted and comparable models or frameworks.

Our study mostly confirms findings of other studies. It adds value by confirming existing data, thus increasing robustness of knowledge that future clinical trials have vigorous data to build on. Our study reveals some differences to other studies showing that context factors (type of health system, financial aspects, etc.) are highly relevant when planning deprescribing interventions.

Limitations

Despite its strengths, the study has several limitations. First, it was conducted with a limited number of GP practices in Bavaria and cannot be extrapolated to all GPs in Germany. Additionally, the findings may not be transferable to other countries with different health care systems. As an example, in Germany GPs do not experience financial rewards for regular medication reviews and deprescribing efforts, thus motivation for conducting a medical review might be lower compared to other countries where GPs are reimbursed by capitation fees, rather than fee for service. Additionally, a barrier that has been identified in the interview study was the lack of time in terms of heavy workload which might be less of a barrier in other countries where GPs experience greater support from other health care professionals, such as practice pharmacists (97). Additionally, GPs in Germany have a higher number of patient contacts per week compared to other countries (94), implying that time to engage in deprescribing may even be more limited in the German health care system.

Another limiting factor is the selection bias due to motivation of general practitioners to participate in the study. Although we purposively sampled for heterogeneity in terms of sex, professional experience and location, eight participants had previously taken part in research. Although not all of these studies focused on deprescribing, the motivation to engage in deprescribing may have been above average in our sample.

Finally, since the interview aimed to explore barriers to conduct medication review and deprescribing antidepressants, the questions may have unintentionally led participants toward expected responses. To minimize this interviewer bias, we conducted a pilot interview with detailed feedback to identify any unintended question directions and engaged in discussions within the study team to further refine our approach.

Implications

This study provides important insights into the barriers and facilitators affecting general practitioners (GPs) in Germany regarding the deprescribing of antidepressants. It highlights the significant challenges faced by GPs, such as time constraints, uncertainty in determining the right timing for deprescribing, and difficulties in interdisciplinary collaboration. Despite these obstacles, the study also emphasizes the importance of effective communication skills and shared decision-making, which can enhance patient engagement in the deprescribing process. The findings underline the need for tailored interventions that consider the specific contexts of the German healthcare system, as well as the potential for integrated digital tools and better training to support GPs in their deprescribing efforts.

Further research could expand the geographic scope of studies to include diverse healthcare settings and to investigate how different financial incentives can impact deprescribing motivations among GPs. Additionally, exploring the role of interdisciplinary support structures and longitudinal studies on the evolving barriers and facilitators could further inform strategies to improve regular assessments of antidepressant therapy and evaluate for potential deprescribing practices. On the practical side, there is a pressing need for awareness of existing guidelines, enhanced training in communication skills, and advocacy for policy reforms that recognize the value of deprescribing in primary care. By addressing these areas, stakeholders can foster a more effective and supportive environment for the safe discontinuation of antidepressants, ultimately improving patient care outcomes.

Conclusions

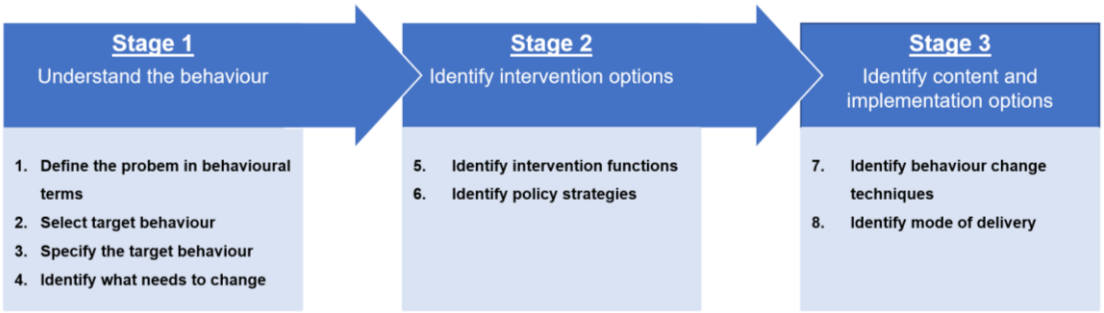
The interview identified facilitators and barriers regarding medication reviews and deprescribing of antidepressants. It revealed barriers especially concerning criteria or situations when to discontinue therapy (decision-making). By exploring perspectives of general practitioners in Germany, it contributes real-world knowledge to existing literature on that topic and provides in behavioural terms factors that hinder deprescribing. Future interventional studies should consider these factors to increase the efficient identification of potentially inadequate medication (PIM), thus increasing medication safety and patients' quality of life.

Utilising the study findings to develop an intervention

Behaviour change intervention design process

By integrating the COM-B model with the Theoretical Domains Framework (TDF), we adopted a systematic approach to identify the facilitators and barriers to deprescribing in general practice. According to the Behaviour Change Wheel (BCW) framework, these insights can be transformed into an actionable intervention strategy that promotes the target behavior - namely, the appropriate function of intervention supported by specific techniques and modes of delivery. The development of the intervention strategy consists of three stages, each encompassing several steps, as illustrated in **Figure 6**. In the final stage of the intervention design process, we synthesized all elements into a cohesive intervention strategy plan.

Figure 6: Behaviour change intervention design process, based on Mitchie et al., 2014 (73), own illustration



1. Define the problem: describe what is the problem in behavioural terms
2. Deprescribing may be an appropriate response in cases where ongoing antidepressant use is no longer indicated. Thus, the behavioural focus is the critical re-evaluation of ongoing antidepressant treatment to ensure guideline-concordant prescribing.Select target behaviour: what is the main behaviour that need to targeted? Consider other behaviours that are present in the context of a main behaviour.
3. Specify the target behaviour: who, what, when, where, how often, with whom?
4. Identify what needs to change and understand the determinants of the behaviour: what needs to change in the person and/or the environment in order to achieve the desired change in behaviour?
5. Select appropriate intervention functions: Choose from the nine intervention functions in the BCW that address the identified TDF domains.
6. Choose supporting policy categories: Identify the policy categories that will best support the intervention functions. Not applicable
7. Identify behaviour change techniques (BCT): which BCT best serves the identified intervention function? Link intervention functions to appropriate BCTs.
8. Select the mode of delivery: Integrate the selected intervention functions and policy categories by developing practical methods and channels for implementation (mode of delivery).

During the interviews, we mapped the most frequently mentioned subthemes (codes) to the COM-B model and TDF domains, thoroughly examining the facilitators and barriers related to deprescribing. Employing an iterative approach based on the BCW framework, we developed our intervention strategy by first mapping the selected subthemes to TDF domains and linking these to specific IFs. Next, we identified the appropriate behaviour change techniques (BCTs) that best support these IFs, followed by determining the mode of delivery for implementing these BCTs in

practice. Throughout this process, we carefully considered all potential IFs and BCTs to ensure no promising options were overlooked. Through all steps, we applied the APEASE-criteria (see **Table 26** on page 120) that provided a structured approach in assessing the suitability of different IFs, BCTs and modes of delivery. Through the whole process of linking, mapping and selection of items we eventually identified certain IFs and BCTs that would most probably be helpful in helping GPs to overcome barriers as shown on **Table 7**.

Prioritization of behaviour change techniques

We prioritized the final BCT considering several criteria:

- Likelihood of impact on target behaviour;
- Likelihood of implementation in daily practice;
- Likelihood of positive impact on other behaviours favouring medication safety;
- Measurability of BCT for later evaluation of effectiveness of the intervention.

Appropriate BCTs (see **Table 7**) have been discussed in the study team in several rounds until consent has been reached. We decided in favour of the theoretical BCT "*Adding objects to the environment"* and discussed possible specific content of the BCT. Several reasons advocated our decision. The BCT

- had potential for high impact on the target behaviour (when effective as decision-aid);
- had high potential for being used in daily practice (when easy to apply);
- had potential on influencing other behaviours associated to medication safety and deprescribing of antidepressants (and possibly other drugs) such as increased certainty of GPs towards deprescribing (if success comes with the BCT, i.e., if opportunity is increased, capability and motivation would most probably be increased, thus having a positive impact on behaviour);
- covered several intervention functions, thus raising the chance to have positive impact on target and other behaviours and decreasing effort of GPs and the practice team.
- might positively influence several subthemes: lack of practical tools; uncertainties regarding the decision to deprescribe; uncertainties if originally prescribed by physicians from other disciplines; guidelines, tools and aids are to complex, time-consuming, not read and not necessary.

Table 7: Result of linking and mapping of subtheme, COM, TDF, IF, BCT

Selected subtheme	TDF Domain	Intervention function	BCT
Psychological Capability (mental skills)			
Lack of established routine	Memory, attention and decision processes	Environmental restructuring Enablement	*Adding objects to the environment* Prompts/cues Social support (unspecified) Social support (practical) Goal setting (behaviour) Goal setting (outcome) *Adding objects to the environment* Problem solving Action planning Self-monitoring of behaviour Review behaviour goal(s) Review outcome goal(s) Identity associated with changed behaviour
Physical Opportunity			
Lack of practical tools	Environmental context and resources	Environmental restructuring Enablement	*Adding objects to the environment* *Adding objects to the environment*
Reflective Motivation			
Uncertainties regarding the decision to deprescribe	Beliefs about capabilities	Education Enablement	Information about social and environmental consequences Information about health consequences Feedback on behaviour Feedback on outcome(s) of the behaviour Self-monitoring of behaviour Social support (unspecified) Social support (practical) Goal setting (behaviour) Goal setting (outcome) *Adding objects to the environment* Action planning Self-monitoring of behaviour Review behaviour goal(s) Review outcome goal(s)
Uncertainties if originally prescribed by physicians from other disciplines	Beliefs about capabilities	Education Enablement	Information about social and environmental consequences Information about health consequences Feedback on behaviour Feedback on outcome(s) of the behaviour Prompts/cues Self-monitoring of behaviour Social support (unspecified) Social support (practical) Goal setting (behaviour) Goal setting (outcome) *Adding objects to the environment* Problem solving Action planning Self-monitoring of behaviour Review behaviour goal(s) Review outcome goal(s)

Automatic Motivation			
Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary	Negative reinforcement	Training Environmental restructuring	Demonstration of the behaviour Instruction on how to perform a behaviour Feedback on the behaviour Feedback on outcome(s) of behaviour Self-monitoring of behaviour Behavioural practice/rehearsal *Adding objects to the environment* Prompts/cues

The specific content of the selected Behavior Change Technique was determined through discussions within the study team. Specific content examples for the BCT "Adding objects to the environment" are provided in **Table 31** (appendix on page 128). Ultimately, we selected two components to serve as the content for the chosen BCT:

Component 1: A *checklist* serving as a decision aid to support general practitioners (GPs) in the structured re-evaluation of long-term antidepressant use, with deprescribing considered as a potential outcome, forms the core component of the intervention.

Component 2: An *empowerment brochure* that serves as an additional resource. This brochure provides patients with pertinent information prior to their consultations with GPs, equipping them with a solid knowledge base. This approach promotes shared decision-making, enhances patient involvement, and improves medication knowledge.

Final draft of the intervention strategy plan

As done in previous steps, APEASE criteria needed to be applied to modes of delivery in order to get the most promising one. Modes are categorized as being "face-to-face" or "distance". Distance as category seemed not relevant to us as we aimed to strengthen the capacity of GPs to conduct medication reviews and support deprescribing where clinically indicated. However, we applied the APEASE criteria to evaluate each mode of delivery. We selected 'individual' (face-to-face) as the most proper mode of delivery. **Table 29** on page 126 shows possible modes of delivery.

In the final step of the intervention design process, we synthesized all identified and selected elements into a cohesive intervention strategy plan. In conclusion, the study team reached a consensus on the plan as shown on **Table 8**. The intervention was designed to consist of a checklist that functions as a decision aid for effectively identifying patients for whom the discontinuation of an antidepressant may be considered. This would be complemented by a brochure to enhance medication knowledge and promote patient involvement.

Table 8: Final draft of the intervention strategy plan

Intervention functions	**COM-B component (TDF domain) served by intervention functions**	**BCTs to deliver intervention functions**	**Intervention strategy**
Enablement Environmental restructuring	Physical Opportunity (Environmental context and resources) Reflective motivation (Beliefs about capabilities)	Adding objects to the environment	(1) The intervention will be delivered by GPs who will use a checklist to effectively support the structured review of long-term antidepressant prescriptions. This review aims to help identify cases where continued use may no longer be clinically indicated. If used routinely, the tool may increase confidence in making evidence-based, patient-centred decisions - including, where appropriate, the consideration of deprescribing. (2) The intervention will be supported by a patient empowerment brochure to enhance patient involvement.

Reflections on the intervention design process

Selection of the Behaviour Change Technique

The intervention design process is a blend of evidence and expert opinion. Alongside established guiding principles and rules, exchange within the expert team plays a crucial role. With the identified Behaviour Change Techniques (BCTs), a diverse array of options is now available to facilitate behaviour change and address the identified barriers. This flexibility allows for tailored interventions that can effectively promote positive changes in behaviour, ultimately enhancing the likelihood of successful outcomes in the context of deprescribing. Therefore, there is ultimately no definitive right or wrong in choosing intervention functions and behaviour change techniques and in designing an intervention strategy plan. More importantly, it is crucial to follow a framework to systematically structure the development process. The intervention strategy plan presented here is just one of many potential strategies to influence the desired behaviour change in GPs. Other researchers may choose differently based on their specific context and objectives.

We have decided to choose only one single BCT (Adding objects to the environment) comprising two components (checklist, brochure). In a scientific context, as recommended by Mitchie et al. (73), it is crucial to choose a single BCT with varying content at the end of the intervention design process rather than implementing multiple BCTs simultaneously. This has several advantages:

Clarity and Focus: Selecting a single BCT allows for a clear definition of the intervention and enables concentration on the specific behavioral changes to be achieved. Implementing multiple BCTs at once can lead to confusion and complicate the evaluation of the intervention.

Evaluation and Effectiveness: Evaluating the effectiveness of an intervention becomes simpler when it is based on a single BCT. This facilitates a more precise measurement of the impact on the specific behavior, as the underlying technique can be distinctly identified.

Resource Efficiency: The implementation and management of resources are more efficient when the design focuses on a single technique. This reduces the effort required for training, execution, and monitoring.

Theoretical Consistency: The application of a single BCT ensures that the intervention is theoretically consistent and based on a clear understanding of the psychological mechanisms that promote behavioral change. This aids in the practical implementation of the intervention.

Utilizing the BCW framework

We have chosen to use the Behaviour Change Wheel (BCW) framework for our intervention design process despite some potential shortcomings. While some argue that the BCW might be too broad and lacks empirical validation across various contexts (98), we believe its flexibility allows for diverse applications tailored to specific behavioral issues. Critics also mentioned the framework's complexity, which could complicate implementation for practitioners who may not be familiar with its theoretical foundations (99). However, we see this complexity as a means to ensure a thorough and structured approach, ultimately leading to a more robust intervention. Additionally, while concerns about the BCW's prescriptive nature exist (99), we find that it fosters meaningful discussions about behaviour change, enhancing collaboration among stakeholders. Furthermore, within the BCW framework, the Theoretical Domains Framework (TDF) serves as a valuable conceptual foundation for identifying implementation challenges (barriers and facilitators of deprescribing), crafting an intervention aimed at improving healthcare practices, and gaining insights into behaviour change processes (100). Thus, the BCW framework serves as a valuable tool in bridging the gap between theory and practice, supporting our goal of systematically developing an effective and contextually relevant intervention in facilitating deprescribing antidepressants. It facilitates the continuous development of an intervention, allowing for refinement during subsequent pilot studies and ultimately preparing for a final randomized controlled trial.

To summarize, applying the BCW Framework in combination with the TDF Framework allowed us to systematically identify intervention components focused on the behaviour of GPs that needed to be changed to facilitate effective decision-making with regards to deprescribing of antidepressants. The intervention strategy plan served as the bases for the development of a deprescribing intervention especially created for general practices. Eventually, its effectiveness, acceptance and feasibility need to be tested through a pilot study.

Chapter 3: Identification of Potential Deprescribing Indications for Antidepressants – a Systematic Review

Background

The interview study reported in chapter 2 highlighted that recognising opportunities for antidepressant deprescribing (i.e. the first step in the deprescribing process) in routine practice was key to more widespread implementation. Consequently, we concluded that implementing alerts based on explicit criteria could be a potentially effective strategy to address this issue. Although integrating such alerts into electronic health records for automatic generation within GPs' workflows was beyond the scope of this research project, it became clear that this would be a necessary step in the future. Regardless of the eventual mode of delivery, the development of clear, evidence-based criteria was an essential first step.

Various instruments have previously been developed to assist prescribers identify potentially inappropriate medication (so called PIM lists). Although some of these lists also include antidepressants, they are typically limited to recommending their avoidance in older people. A few instruments also consider limited comorbidities or co-medication, but no existing instrument systematically provides potential deprescribing indications for antidepressants. Such criteria sets should consider both potential overuse (i.e. use of antidepressants for longer periods than indicated) and potential high-risk use (i.e. use of antidepressants in the presence of risk factors that increase the risk of adverse drug reactions).

Adverse effects of antidepressants

Antidepressants are associated with a range of adverse effects due to their pharmacological actions, which vary by drug class. Understanding these mechanisms is critical when considering deprescribing strategies and are therefore briefly introduced here.

Tricyclic antidepressants (TCAs) inhibit the reuptake of serotonin and norepinephrine but also antagonize muscarinic, histamine, and adrenergic receptors, causing a wide range of adverse effects. Anticholinergic effects, such as dry mouth, constipation, and cognitive impairment, result from muscarinic receptor blockade. Cardiovascular toxicity, including arrhythmias, is caused by sodium and calcium ion channel interference. TCAs also cause sedation and weight gain through histamine H1 receptor antagonism and increase the risk of orthostatic hypotension and seizures.

Selective serotonin reuptake inhibitors (SSRIs) increase serotonin levels by inhibiting its reuptake, but this mechanism also causes adverse effects. Gastrointestinal disturbances arise from increased serotonin in the gut, while sexual dysfunction is linked to serotonin’s effects on dopamine. SSRIs also impair platelet aggregation, increasing the risk of bleeding, and in elderly patients, can cause hyponatraemia by promoting inappropriate secretion of antidiuretic hormone (ADH). In some cases, excess serotonin can lead to serotonin syndrome, a life-threatening condition marked by agitation and hyperreflexia. Some SSRIs, like citalopram, also prolong the QT interval, raising the risk of cardiac arrhythmias.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) act similarly to SSRIs but also increase norepinephrine levels, leading to elevated blood pressure and potential cardiovascular risks. This norepinephrine increase can also cause insomnia, sweating, and hyperarousal. SNRIs share adverse effects like sexual dysfunction and serotonin syndrome with SSRIs.

Monoamine oxidase inhibitors (MAOIs) block the enzyme that breaks down serotonin, norepinephrine, and dopamine, increasing these neurotransmitters. However, this mechanism also raises the risk of hypertensive crisis when combined with dietary tyramine and serotonin syndrome when used with other serotonergic drugs. Orthostatic hypotension and weight gain are common due to disrupted baroreflexes and histamine receptor effects.

Atypical antidepressants, such as bupropion and mirtazapine, have unique profiles. Bupropion, a norepinephrine-dopamine reuptake inhibitor, lowers the seizure threshold and can cause insomnia and agitation. Mirtazapine, which increases norepinephrine and serotonin release by antagonizing alpha-2 adrenergic receptors, leads to significant sedation and weight gain due to histamine H1 antagonism.

Serotonin antagonists and reuptake inhibitors (SARIs), such as trazodone, block serotonin 5-HT2 receptors and weakly inhibit serotonin reuptake. While effective for insomnia, SARIs cause sedation through histamine H1 antagonism and can lead to orthostatic hypotension due to alpha-adrenergic receptor blockade. Rarely, SARIs are associated with priapism, a painful and prolonged erection.

In summary, the mechanisms by which antidepressants exert their therapeutic effects are closely linked to their adverse effects, often through interactions with neurotransmitter pathways, receptor blockade, and ion channel modulation. Understanding these effects is essential for managing antidepressant therapy and considering deprescribing in patients where the risks may outweigh the benefits.

Aims and objectives

Similar to the development of evidence based clinical practice guidelines, the development of explicit deprescribing criteria usually follows a two-stage process: a systematic literature review followed by a consensus process with experts. This section of the doctoral thesis contributed the literature review, providing a foundation for the consensus process, which was part of a fellow PhD student's project within the POKAL-Kolleg.

The aim of this systematic review was to identify clinical situations, as identified by clinical practice guidelines, that may act as triggers for critically reviewing the continuation of antidepressant treatment. The specific objectives were (1) to compare recommendations across different guidelines regarding therapy durations and safety concerns, and (2) to assess how extensively guidelines provide information on when antidepressant deprescribing should be considered in managing various psychiatric disorders.

Methods

Study design

We conducted a systematic guideline review following the PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is a guideline designed to enhance the reporting quality and comparability of systematic reviews and meta-analyses. It provides a structured framework to ensure that researchers clearly articulate the rationale, methodology, results, and conclusions of their work, thereby promoting transparency and reproducibility in research. We conducted a comprehensive literature search to identify clinical practice guidelines (CPGs) from Germany and other high-income countries. Eligible guidelines were those that addressed the use of antidepressants in the management of common mental disorders. Data were extracted and analysed to examine whether and how included guidelines identified potential deprescribing indications for antidepressants. We assessed the quality of guidelines using established tools and synthesised findings to identify key patterns, strengths, and gaps across the guidelines.

Eligibility criteria

Inclusion and exclusion criteria were established using the PICAR framework, which was specifically designed for the evaluation of clinical practice guidelines (101). The acronym represents its items: Population, Intervention, Comparator, Actionable recommendations, and Rationale. A summary of the eligibility criteria is presented in **Table 9**, providing a clear outline of the parameters guiding the selection process for this systematic review.

Our focus pertained to guidelines published by national authorities as well as both national and international organizations specializing in general practice, psychiatry, and geriatrics. The objective was to identify CPGs with significant clinical and international relevance. For this purpose, we aimed to compare CPGs from Germany, with those from selected English-speaking and high-income countries, namely the United Kingdom, the USA, Canada, Australia, and New Zealand. Consensus papers and statements were excluded from our search.

To ensure the guidelines' relevance and currency, only those published within the last ten years (2013-2023) were included, selecting the latest version of each guideline. We specifically selected CPGs for the treatment of depression as well as anxiety- and panic disorders. Our inclusion criteria encompassed all severity levels of these disorders.

As potential deprescribing indications, we considered any explicit or implicit description of clinical situations where antidepressant use was characterised as potential high-risk prescribing (i.e. use of antidepressants in the presence of risk factors that increase the risk of adverse drug reactions), irrespective of whether such descriptions were part of formal (consented) recommendations or provided in accompanying text. We disregarded guideline content that merely informed readers of possible adverse reactions associated with antidepressant use without highlighting risk factors that may alter clinical decision making.

Table 9: PICAR criteria for inclusion of CPGs

Population & clinical indication	Patients with depression, anxiety- and panic disorders age: 18+ years Any symptom severity
Interventions	Antidepressant treatment for above mentioned disorders
Comparators, comparisons and content	*Comparisons:* Between clinical practice guidelines *Key content*: Prescribing, High-risk prescribing, deprescribing (any warning or mentioning on stopping or reducing an antidepressant). Statements on adverse drug reactions without emphasising risk factors that could influence clinical decision-making will not be extracted.
Attributes of eligible CPGs	*Language*: German, English *Year of publication*: 2013-2023 *Publishing region*: Germany and selected English-speaking countries (England, Canada, USA, Australia, New Zealand), high-income countries *Version*: Latest versions only *System of rating evidence*: Any *Scope*: Primary focus on treatment with antidepressants (on two diagnoses: depression, anxiety- and panic disorder) *Recommendations*: Implicit or explicit recommendations on discontinuation, warnings on high-risk prescribing of antidepressants.
Recommendation characteristics	*Duration of treatment*: No restrictions *Levels of confidence*: No restrictions *Interventions*: No restrictions *Locating recommendations*: any (e.g. within CPG texts, tables, graphs)

CPG – clinical practice guideline

Search strategy

We searched online through the following guideline registries and websites:

Table 10: Searched online Registries and websites

Country	**Registry**
Germany	• Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
UK	• ECRI Guidelines Trust®, guidelines.co.uk (redirected to medscape.co.uk) • Guidelines International Network Library (Scotland)
USA	• National Guideline Clearinghouse (NGC, closed and now Agency for Healthcare Research and Quality (AHRQ)) • American College of General practitioners Best Practice guidelines (ACP)
Canada	• Canadian Medical Association Infobase (CMAI)
Australia/ New Zealand	• New Zealand Guidelines Group (NZGG) • National Health and Medical Research Council (NHMRC) • New Zealand Guidelines Group (NZGG)
Country	**Website of professional organization or authorities**
UK	• National Institue for Health and Care Excellence (NICE) • British Association for Psychopharmacology (BAP) • Health Service Executive (HSE) • Irish College of General Practitioners (ICGP)
USA	• American Psychological Association (APA) • Institute for Clinical Systems Improvement (ICSI) • American Association for Geriatric Psychiatry (AAGP) • Department of Veterans Affairs Department of Defense (VaDoD)
Canada	• Canadian Network for Mood and Anxiety Treatments (CANMAT) • Canadian Coalition for Seniors' Mental Health (CCSMH) • Canadian Psychiatric Association (CPA)
Australia/ New Zealand	• Royal College of Psychiatrists: Faculty of Old Age (RCPSYCH) • Royal Australian and New Zealand College of Psychiatrists (RANZCP)

Guideline selection

For the selection of CPGs (see **Figure 7**), two researchers (JV, VB) independently screened titles and, where available, abstracts of the identified publications. Duplicates were removed. Guidelines without full text were excluded. We then excluded records that did not meet eligibility criteria, including superseded guidelines, non-guideline documents, those not targeting antidepressant use in the management of targeted common mental disorders. For unclear records or disagreement on inclusion, eligibility was discussed and solved by agreement. If further disagreement occurred, a third member of the research group was consulted (TD).

Quality assessment

The quality of the identified guidelines was assessed using the 2016 validated Mini Checklist (MiChe, see appendix **Figure 14**) (102-106). This validated tool was specifically developed for the evaluation of guidelines and has demonstrated a high level of agreement with the AGREE II instrument in terms of quality assessment of guidelines (103, 107). We chose this checklist not only for its feasibility but also because it incorporates practical aspects relevant to general practitioners. The checklist comprises eight items: intelligibility, target audience, background (including purpose and patient target group), conflict of interest, literature search, recommendations and evidence, management options, and date of publication. Each item was rated independently as "yes," "to some extent," or "no." The overall assessment was conducted using a 7-point Likert-type scale, ranging from 1 (very poor) to 7 (very good). Additionally, the final question on the MiChe, "Would you recommend others use the guideline?" was answered with "yes," "yes, with certain reservations," or "no." As part of the assessment using the Mini Checklist (MiChe), all guidelines were reviewed to determine whether they contained clear and comprehensible information (methodology, evidence description) regarding item 5 - Levels of Evidence (LoE) and item 6 - Grades of Evidence (GoE). To facilitate the clear presentation of evidence levels, those items were additionally recorded as either present (√) or absent (-).

Data extraction

After the final selection of CPGs, the two researchers (JV, VB) reviewed the documents and extracted relevant data using a standardized MS Excel sheet, organized by diagnosis (depression, anxiety and panic disorder). The data extracted included: country of origin, name of issuing organization, title, year of publication, drug-drug interactions, drug-disease interactions, drug-age interactions, and statements related to the duration, cessation, discontinuation, or switching of therapy, as well as any references to limited evidence for efficacy or benefit. We focused exclusively on extracting data from the CPGs and did not investigate the documents referenced within these guidelines.

Data synthesis and analysis

After extracting all data, we created a matrix of statements for each of the following groups: drug-drug interactions, drug-disease interactions and drug-age interactions, for all types of antidepressants. Within these groups, we aimed for creating a brief overview of warnings. In order to get a comprehensive and concurrently robust overview, we categorised statements into (1) contraindicated as being strongest recommendation, (2) avoid, (3) use with caution and (4) warning information without specific recommendations. The categories are defined as follows:

(1) Contraindicated

The CPG states that therapy with the addressed antidepressant is contraindicated.

Words in guideline: contraindicated.

Symbol in the matrix: ↑↑↑

(2) Avoid

The CPG states that therapy with the addressed antidepressant should be avoided.

Words in guideline: avoid, not recommended, should not be prescribed, discontinuation, choose drug xy, reduce dose

Symbol in the matrix: ↑↑

(3) Caution

The CPG states that therapy with the addressed antidepressant should be used with caution.

Words in guideline: monitor, caution with drug xy, max. dose of drug xy

Symbol in the matrix: ↑

(4) Information

The CPG states that therapy with the addressed antidepressant could probably have negative implications on the individual's health status.

Words in guideline: e.g. increased risk of GI-bleeding, associated with hyponatraemia, orthostatic hypotension.

Symbol in the matrix: ↔

After construction of the matrices and data extraction, we then calculated the number of statements (absolute and relative) of CPGs for each category.

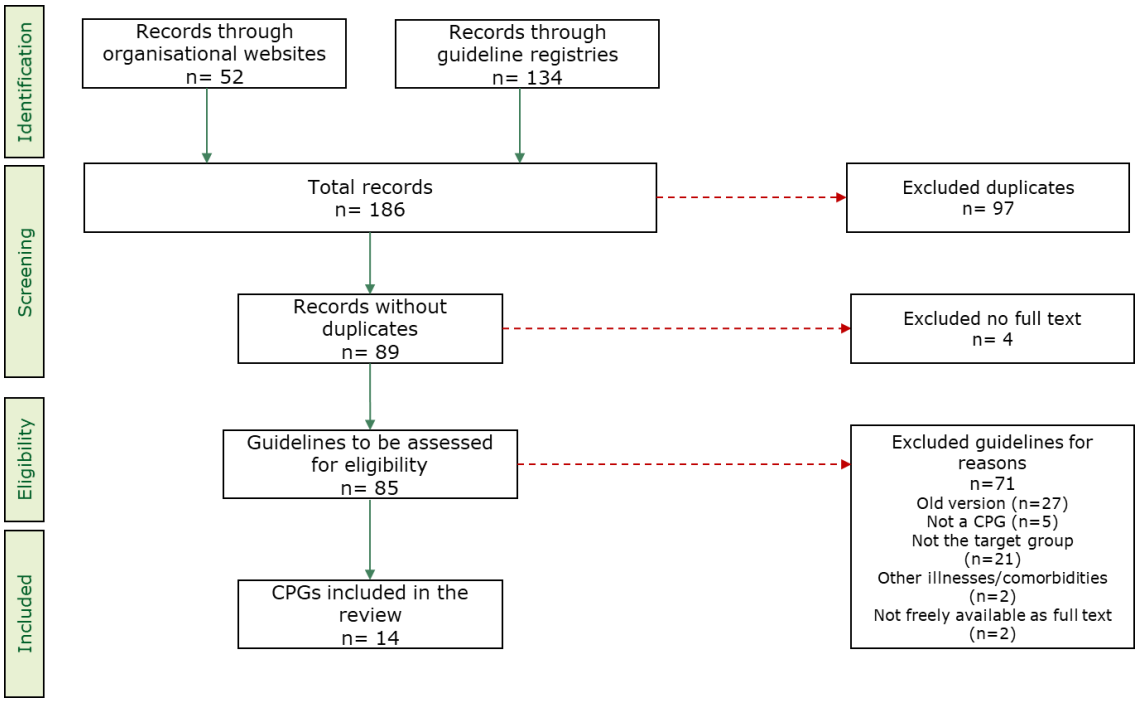
Results

Figure 7 shows that the literature search identified a total of 186 records. Of these, 97 were duplicates, 4 records were without full text, and 71 records for excluded for various reasons. Finally, we included a total of 14 guidelines.

Characteristics of guidelines

Eligible CPGs were either published or updated within the last 10 years (2013-2023). The target populations primarily consisted of adults aged 18 and older, with some guidelines specifically designed for individuals not exceeding 65 years of age. Some guidelines (e.g. NICE) did not include all relevant information within the document itself but instead referred to supplementary or older versions of the clinical practice guidelines for more detailed information. This was outside the scope of this review, as we aimed to focus on recommendations that are readily accessible within guidelines. Regarding the guidelines for depression, one was from Germany, two from the UK, three from the USA, two from Canada, and one from Australia/New Zealand. For the guidelines on anxiety and panic disorders, one originated from Germany, two from the UK, and one each from Canada and Australia/New Zealand. The guidelines from Australia and New Zealand were jointly developed by The Royal Australian and New Zealand College of Psychiatrists (RANZCP).

Figure 7: Study Selection according to PRISMA



Quality assessment

The identified guidelines were published or updated between 2013 and 2023. Utilizing the Mini Checklist, all 14 clinical practice guidelines (CPGs) were deemed recommendable for practical application. Item number 8 exhibited the most variability, as 9 CPGs did not provide information on the expiration date. Additionally, "Conflict of Interest" (item 4) displayed inconsistencies, with some guidelines offering information on conflicts that was either not readily accessible or entirely absent. Certain guidelines referred to supplementary documents or other guidelines, complicating the process for readers seeking information on levels of evidence and grading of recommendations (e.g., NICE). Furthermore, some guidelines (e.g. anxiety- and panic disorders, RANZCP), were funded by pharmaceutical companies, which raised critical concerns regarding potential bias.

Among the CPGs pertaining to the management of depression, 6 out of 9 provided clear and specific information regarding the level of evidence (LoE), while 8 out of 9 contained clear and specific information on the grade of recommendation (GoR). Despite some shortcomings, all CPGs received an overall rating of "good to very good" (6 out of 7 points).

In the context of CPGs for anxiety- and panic disorders, 4 out of 5 included explicit information on both LoE and GoR. Overall, 3 out of 5 guidelines were rated as “good to very good,” with the German CPG being the only one awarded full points.

A summary of the results of the quality assessment based on MiChe are presented in **Table 11** (depression) and **Table 12** (anxiety- and panic disorders). For more details on the rating see **Figure 14** and **Table 33** in the appendix.

Table 11: Characteristics and quality assessment of CPGs (depression)

Country	Organisation	Title	Year[1]	Age of target group	LoE	GoR	MiChe-Score
Depression							
Germany	Nationale Versorgungsleitlinien	NVL Unipolare Depression	2022	Adults > 18 years	√	√	6
England	National Institue for Health and Care Excellence (NICE)	Depression in adults: treatment and management	2022	People aged ≥ 18 years	(√)	(√)	6
	British Association for Psychopharmacology (BAP)	Evidence-based guidelines for treating depressive disorders with antidepressants	2014	not specified	√	√	6
USA	American Psychological Association (APA)	APA Clinical practice guideline for the treatment of depression	2019	Children > 6 years, adolescents, general adults, older adults	-	√	6
	Institute for Clinical Systems Improvement (ICSI)	Adult Depression in Primary Care Guideline	2013	Adults ≥ 18 years	√	√	6
	Department of Veterans Affairs Department of Defense (VA/DoD)	VA/DoD Clinical practice guideline for the management of major depressive disorder	2016	Adults ≥ 18 years	√	√	6
Canada	Canadian Network for Mood and Anxiety Treatments (CANMAT)	Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments	2016	Adults	√	√	6
	Canadian Coalition for Seniors' Mental Health (CCSMH)	Canadian Guidelines on Prevention, Assessment and Treatment of Depression Among Older Adults	2021	Adults > 65 years	√	√	6
Australia / New Zealand	Royal Australian and New Zealand College of Psychiatrists (RANZCP)	The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	2020	Adults	-	√	6

[1]Year of publication or last update; LoE: level of evidence; GoR: grade of recommendation; √: present and explained in the CPG; (√): not present in the CPG, but referral to external document; -: not present in CPG; MiChe-Score: 1 (very poor) – 7 (very good) see **Table 33: Detailed quality assessment results (MiChe)**

Table 12: Characteristics and quality assessment of CPGs (anxiety- and panic disorders)

Country	Organisation	Title	Year[1]	Age of target group	LoE	GoR	MiChe-Score
Anxiety- and panic disorders							
Germany	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)	S3-Leitlinie Behandlung von Angststörungen Version 2	2021	Adults ≥ 18 years	√	√	7
England	British Association for Psychopharmacology (BAP)	Evidence-based guidelines for the pharmacological treatment of anxiety disorder	2014	Adults 18-65 years	√	√	6
	National Institue for Health and Care Excellence (NICE)	Generalised anxiety disorder and panic disorder in adults: management	2020	Adults ≥ 18 years	(√)	(√)	6
Canada	Canadian Psychiatric Association (CPA)	Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders	2014	Children to elderly	√	√	6
Australia / New Zealand	Royal Australian and New Zealand College of Psychiatrists (RANZCP)	Clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder	2018	Adults 18-65 years	√	√	6

[1]Year of publication or last update; LoE: level of evidence; GoR: grade of recommendation; √: present and explained in the CPG; (√): not present in the CPG, but referral to external document; -: not present in CPG; MiChe-Score: 1 (very poor) – 7 (very good) see **Table 33: Detailed quality assessment results (MiChe)**

Potential deprescribing indications

Table 13 summarizes the information on potential deprescribing indications extracted from the guidelines. Overall, we identified 68 drug-drug interactions, 72 drug-disease interactions, and 33 drug-age interactions as starting points for potential deprescribing indications. Out of the total of those 173 potential deprescribing indications extracted, 27 (16%) were categorized as contraindicated (highlighted by ↑↑↑), 56 (32%) as to be avoided (↑↑), 38 (22%) as be treated with caution (↑), and 52 deprescribing indications (30%) were considered as information without a clear recommendation (↔). Details for each group of interaction (drug-drug, drug-disease, drug-age) can be found on tables 14-18.

Table 13: Number of extracted potential deprescribing indications across all categories (all ADs[1])

	Category					
Interactions	**Contraindicated** ↑↑↑	**Avoid** ↑↑	**Caution** ↑	**Information** ↔	**Sum interactions**	
Drug-Drug	5	12	13	38	68	39%
Drug-Disease	21	35	12	4	72	42%
Drug-Age	1	9	13	10	33	19%
Sum category	27 16%	56 32%	38 22%	52 30%	**173**	100%

[1] AD - Antidepressants

Tricyclic antidepressants

Overall, we identified 37 potential deprescribing indications for tricyclic antidepressants (TCAs) from all guidelines, of which 12 drug-drug, 20 drug-disease, and 5 were drug-age interactions.

Table 14: Number of extracted potential deprescribing indications (TCA)

	Category					
	Contraindicated ↑↑↑	**Avoid** ↑↑	**Caution** ↑	**Information** ↔	**Sum interactions**	
TCA						
Drug-Drug	1	3	2	6	12	32%
Drug-Disease	6	13	1	0	20	54%
Drug-Age	0	4	0	1	5	14%
Sum category	7	20	3	7	**37**	
	19%	54%	8%	19%		100%

Drug-drug interactions

The majority of warnings were emphasized in European countries, with 11 out of 12 guidelines highlighting concerns related to serotonin syndrome, which received the most prominent and severe warnings, particularly in clinical practice guidelines (CPGs) for depression. In contrast, only one mention of “caution” was noted in one non-European country (ISCI, USA). Overall, serotonin syndrome is the most frequently discussed interaction, reflecting consistent concerns across guidelines. However, there is considerable heterogeneity in the risk assessment among the CPGs. These findings indicate a need for more standardized guidance on tricyclic antidepressant (TCA) interactions to promote safer prescribing practices.

Drug-disease interactions

For tricyclic antidepressants (TCAs), guidelines commonly recommend contraindications or avoidance, particularly in patients with cardiovascular conditions. Notably, the use of TCAs in patients with high cardiovascular risk, arrhythmia, or ischemic heart disease is highlighted in *four guidelines* (from Germany, the UK, and the USA), with strong recommendations indicating contraindication (↑↑) or avoidance (↑↑↑). Additionally, conditions such as dementia, urinary retention, ileus, pyloric stenosis, and narrow-angle glaucoma predominantly feature contraindications (↑↑↑) or recommendations for avoidance (↑↑) in the German guideline for depression. The BAP (UK) also noted several interactions and advised against TCA use. Overall, the strength of recommendations for TCAs appears to be relatively consistent across guidelines. However, Canadian guidelines did not include any such warnings.

Drug-age interactions

For tricyclic antidepressants (TCAs), guideline coverage is limited, with only *five guidelines* addressing interactions. Nortriptyline is specifically highlighted in *four guidelines* (from the UK, USA, and Germany), all recommending avoidance (↑↑), suggesting potential concerns regarding its use. Amitriptyline is mentioned in *one guideline* for anxiety (BAP, UK), which also recommends avoiding its use (↑↑). While *three guidelines* for depression advocate for the avoidance of TCAs, the *two guidelines* for anxiety- and panic disorders either recommend avoidance or provide only informational warnings about adverse drug reactions (ADRs). Notably, despite the presence of warnings in some clinical practice guidelines (CPGs), the guideline specifically addressing patients over 65 years of age (CCSMH, Canada) contained no warnings or information on drug-age interactions. These findings underscore significant inconsistencies across the guidelines.

Selective serotonin reuptake inhibitors

Overall, we identified 58 potential deprescribing indications for selective serotonin reuptake inhibitors (SSRIs) from all guidelines, of which 22 drug-drug, 18 drug-disease and 18 were drug-age interactions.

Table 15: Number of extracted potential deprescribing indications (SSRI)

	Category					
	Contraindicated ↑↑↑	**Avoid** ↑↑	**Caution** ↑	**Information** ↔		**Sum interactions**
SSRI						
Drug-Drug	0	4	4	14	22	38%
Drug-Disease	1	11	3	3	18	31%
Drug-Age	1	3	8	6	18	31%
Sum category	2	18	15	23	**58**	
	3%	31%	26%	40%		100%

Drug drug interactions

The combination of SSRIs with antiplatelets, anticoagulants, or NSAIDs is considered potentially risky for gastrointestinal bleeding in *seven guidelines*, including those in Germany (NVL), the United Kingdom (NICE), Canada (CANMAT), Australia/New Zealand (RANZCP), and the United States (VA/DoD). The NICE guidelines specifically recommend avoiding this combination, while other sources provide only general information. Regarding the use of (Es)citalopram with QTc-prolonging drugs, the NICE guidelines advise against the combination due to an increased risk of Torsade de Pointes, whereas the German NVL guidelines classify it as potentially problematic

without a strict avoidance recommendation. The risk of hyponatraemia with concurrent use of SSRIs and diuretics is highlighted in both Canadian and German guidelines, suggesting caution. Several guidelines, including NVL, NICE, CANMAT, and RANZCP, address the danger of serotonin syndrome when SSRIs are used alongside serotonergic agents, with NICE recommending avoidance of this combination. There is also mention of interactions with CYP450-metabolized drugs in *three guidelines*, though no specific recommendations are provided. The presence of numerous general recommendations without strong warnings suggests that many guidelines prefer to provide broad advice on SSRI use rather than specific guidance on individual drugs.

Drug-disease interactions

Regarding selective serotonin reuptake inhibitors (SSRIs), the risk of prolonged QTc is highlighted in *two guidelines* (UK and USA) advising caution (↑↑), and three guidelines (Germany, UK, USA) specifically regard their use in patients with congenital long QT syndrome as a contraindication (↑↑↑). Bleeding risk is discussed in *two guidelines* (UK and Australia/New Zealand), with one (UK) recommending avoidance (↑↑) and another (Australia/New Zealand) providing general information (↔). Risks related to hyponatraemia are mentioned in *one Canadian guideline* with a specific caution for older adults. Caution is also noted for hepatic impairment, with citalopram and other SSRIs being flagged in *three guidelines* (UK, USA, Canada) for patients with liver issues.

Drug-age interactions

The selective serotonin reuptake inhibitors (SSRIs) show considerable variability across the guidelines, with a total of *11 mentions across both depression and anxiety recommendations* (7/4). Paroxetine receives the strongest warnings, with *three guidelines* (UK, USA, and Canada) advising against its use or recommending caution (↑↑↑ or ↑↑), suggesting concerns about side effects or risks. Citalopram is mentioned *five times*, with four mentions for depression and one for anxiety. Recommendations vary, ranging from cautious use (↑) to general information (↔), indicating some variation in how the drug is assessed across different guidelines. Escitalopram is covered *three times*, with two recommendations for depression and one for anxiety, typically suggesting cautious use. Fluoxetine is mentioned once with a cautionary recommendation (↑↑), indicating more limited discussion of this SSRI compared to others.

Serotonin-norepinephrine reuptake inhibitors

Overall, we identified 24 potential deprescribing indications for serotonin-norepinephrine reuptake inhibitors (SNRIs) from 12 guidelines, of which 11 drug-drug, 11 drug-disease and 2 were drug-age inter-actions.

Table 16: Number of extracted potential deprescribing indications (SNRI)

	Category					
	Contraindicated ↑↑↑	**Avoid** ↑↑	**Caution** ↑	**Information** ↔		**Sum interactions**
SNRI						
Drug-Drug	0	3	3	5	11	46%
Drug-Disease	3	4	4	0	11	46%
Drug-Age	0	0	2	0	2	8%
Sum category	3	7	9	5	**24**	
	13%	29%	38%	21%		100%

Drug-drug interactions

For serotonin-norepinephrine reuptake inhibitors (SNRIs), the risk of gastrointestinal bleeding associated with concurrent use of antiplatelet agents, anticoagulants, or non-steroidal anti-inflammatory drugs (NSAIDs) is noted in four guidelines, with the BAP (UK) specifically advising against such combinations. Additionally, the risk of serotonin syndrome when SNRIs are combined with serotonergic agents is acknowledged by four guidelines, with the BAP (UK) recommending avoidance of these combinations (avoid, ↑↑).

Duloxetine is flagged only by the CANMAT guidelines (Canada) for potential serious interactions when used with CYP1A2 inhibitors such as cimetidine or ticlopidine, emphasizing the need for caution. While most warnings are found in the clinical practice guidelines (CPGs) for depression, only three statements regarding SNRIs were identified in CPGs for anxiety and panic disorders, with the BAP (UK) recommending avoidance of SNRIs in combination with serotonergic drugs due to the risk of serotonin syndrome. Overall, there is considerable variability in recommendations and warnings across the guidelines, with no warnings found in CPGs from the USA.

Drug-disease interactions

For serotonin-norepinephrine reuptake inhibitors (SNRIs), bleeding tendencies are prominently highlighted, with *two guidelines* (Germany and the UK) issuing a contraindication (↑↑↑) or advising avoidance (↑↑) respectively, particularly for patients with an increased risk of bleeding or existing

bleeding disorders. Concerns about QTc prolongation result in strong recommendations against their use (↑↑↑) in *one guideline* (Germany). Venlafaxine is specifically noted for its risks in patients with uncontrolled hypertension or arrhythmia, prompting caution in *two European guidelines*. In the case of duloxetine, both hepatic and renal impairments are significant concerns, leading *two guidelines* (USA and UK) to recommend caution and advise that its use is best avoided (↑↑). Consistent with findings for other antidepressants, the strongest warnings (contraindication) were issued by the German guideline (NVL). Notably, no warnings were identified in the Australian/ New Zealand guidelines.

Drug-age interactions

For serotonin-norepinephrine reuptake inhibitors (SNRIs), there are only two mentions in *two different guidelines* for depression (CCSMH, RANZCP), both with recommendation to avoid antidepressants (↑↑), suggesting less emphasis on this class across the guidelines. We did not find any statement in CPGs for anxiety- and panic disorders.

Monoamine oxidase inhibitors

Overall, we identified 24 potential deprescribing indications for monoamine oxidase inhibitors (MAOIs) from 7 guidelines, of which 12 drug-drug, 11 drug-disease and 1 were drug-age interactions.

Table 17: Number of extracted potential deprescribing indications (MAOI)

	Category					
	Contraindicated ↑↑↑	**Avoid** ↑↑	**Caution** ↑	**Information** ↔	**Sum interactions**	
MAOI						
Drug-Drug	4	1	1	6	12	50%
Drug-Disease	5	3	2	1	11	46%
Drug-Age	0	1	0	0	1	4%
Sum category	9	5	3	7	**24**	
	38%	21%	13%	29%		100%

Drug-drug interactions

The majority of interactions were identified in guidelines pertaining to depression, particularly within European guidelines such as NVL (Germany), NICE, and BAP (both UK), albeit with notable heterogeneity. In terms of ADRs, most warnings are associated with serotonin syndrome (8/12), hypertensive crisis emerged as the second most relevant adverse drug reaction (3/12) mentioned across three guidelines. For hyponatraemia, only a single recommendation to avoid this risk is provided by NICE.

Drug-disease interactions

The recommendations regarding monoamine oxidase inhibitors (MAOIs) are fairly consistent across all guidelines with strong warnings for depression, with the majority classified as “contraindications” (five mentions) or “avoid” (three mentions), particularly in guidelines from the Veterans Affairs/Department of Defense (VA/DoD, USA) and NVL (Germany). In contrast, guidelines for anxiety- and panic disorders include only one warning to avoid MAOIs, as noted by the BAP (UK). Notably, the guidelines from Australia and New Zealand (RANZCP) contain no such warnings.

Drug-age interactions

With respect to drug-age interactions, only the CCSMH guideline from Canada advises against the use of this medication in individuals aged 65 years and older.

Other antidepressants

Overall, we identified 10 potential deprescribing indications for antidepressants grouped into "other AD" (other antidepressants) from 7 guidelines, of which 11 drug-drug, 12 drug-disease and 7 were drug-age inter-actions.

Table 18: Number of extracted potential deprescribing indications (other ADs, incl. NaSSA)

	Category					
	Contraindicated ↑↑↑	Avoid ↑↑	Caution ↑	Information ↔		Sum interactions
Other Ads (incl. NASSA[1])						
Drug-Drug	0	1	3	7	11	37%
Drug-Disease	6	4	2	0	12	40%
Drug-Age	0	1	3	3	7	23%
Sum category	6	6	8	10	**30**	
	20%	20%	27%	33%		100%

[1]NaSSA - Noradrenergic and Specific Serotonergic Antidepressants

Drug-drug interactions

With other antidepressants, such as trazodone, combinations with sedative drugs or α2-receptor blockers are considered potentially problematic, particularly regarding the risk of orthostatic hypotension. Bupropion presents potential risks for seizures and interactions with monoamine oxidase inhibitors (MAOIs) and dopaminergic agents; however, specific recommendations addressing these risks are lacking. The NICE guidelines note the risk of hyponatraemia associated with the concurrent use of antidepressants and diuretics. Additionally, interactions between fluoxetine or paroxetine and drugs metabolized by CYP450, as well as between agomelatine and CYP1A2 inhibitors and vilazodone and CYP3A4 inhibitors, are regarded as potentially hazardous, with CANMAT guidelines highlighting these concerns.

Overall, there were only three recommendations to either avoid or exercise caution with antidepressant use. The NVL guideline from Germany contained the most statements, albeit categorized with the least stringent warnings ("information," ↔). In general, warnings were scarce, and strong recommendations were rarely found for antidepressants other than tricyclics, SSRIs, SNRIs, or MAOIs. Notably, no warnings were identified in the clinical practice guidelines (CPGs) for anxiety and panic disorders.

Drug-disease interactions

Other antidepressants, such as bupropion, tianeptine, and agomelatine, present specific risks outlined in the guidelines. The use of bupropion is particularly cautioned against in patients with seizure disorders (e.g., epilepsy) or severe hypertension, with three guidelines (Germany, USA, Australia/New Zealand) recommending against its use, classifying it as a contraindication (↑↑↑). Tianeptine is flagged for its potential risk of dependence, while the use of agomelatine is heavily cautioned in cases of hepatic impairment, leading to a contraindication (↑↑↑) as noted in two guidelines (Germany and the UK). Aside from two warnings (Germany and the UK), the majority of warnings originate from guidelines focused on depression, with the most significant and strongest warnings (contraindication, ↑↑↑) coming from the NVL guideline in Germany.

Drug-age interactions

Agomelatine is mentioned only once in the guidelines for depression (UK), where it is recommended to use with caution (↑↑). The limited discussion surrounding other specific antidepressants shows the variability in guidance across different drug classes. In total, there are only seven mentions across six guidelines, reflecting a lack of comprehensive guidance on these medications.

In terms of total recommendations across all antidepressant classes, Germany, the UK, and Canada show the most frequent mentions, with the UK offering a mix of specific recommendations and general information (4/1 for BAP and 5/2 for CCSMH). In contrast, the USA and Australia/New Zealand guidelines show fewer mentions, typically providing strong recommendations for certain drugs rather than broad guidance. This variability highlights differences in how antidepressant use is addressed across countries, reflecting differing levels of specificity and caution in the guidance provided.

Table 19: Drug-drug interactions

Antidepressant + interacting drugs		Adverse drug reaction (ADR)	Depression									Anxiety/Panic				
			Germany	UK		USA			Canada		AUS & NZ	Germany	UK		Canada	AUS & NZ
			NVL	NICE	BAP	APA	ISCI	VA/DoD	CAN-MAT	CCSMH[1]	RANZCP	AWMF	BAP	NICE	CPA	RANZCP
TCA	+ anticholinergic drugs	Anticholinergic effects	↔									↔				
	+ antihypertensive drugs	Orthostatic hypotension*			↑↑							↔				
	+ serotonergic drugs	Serotonin Syndrome	↑↑↑	↑↑			↑						↔			
	+ sedating psychotropic drugs	Sedation										↔				
	+ QTc prolonging drugs	Torsade de Pointes*	↔													
	+ diuretics[1]	Hyponatraemia		↑[1]												
	+ antiarrhythmics class 1A	Ventric. Arrhythmia, IHD[3]											↑↑			
SSRI	+ antiplatelets/anticoagulants/NSAID	(GI)-Bleeding	↔		↑↑				↔	↔[1]		↔		↔	↔	↔[1]
	(Es)citalopram + QTc prolonging drugs	Torsade de Pointes*	↔		↑↑											
	+ diuretics	Hyponatraemia		↑[1]						↑[1]						
	+ antiepileptics	Hyponatraemia										↔				
	+ serotonergic drugs	Serotonin Syndrome	↔	↑↑			↑		↔				↑	↑↑		
	+ drugs metabolized through CYP P450	*							↔				↔			↔
SNRI	+ antiplatelets/anticoagulants/NSAID	(GI)-Bleeding	↔		↑↑							↔			↔	
	+ diuretics	Hyponatraemia		↑[1]						↑[1]						
	+ serotonergic drugs	Serotonin Syndrome	↔	↑↑					↔				↑			
	Duloxetine + CYP1A2 inhibitors: e.g., cimetidine, ticlopidine, ciprofloxacin	*							↑↑							
MAOI	+ serotonergic drugs	Serotonin Syndrome	↔	↑↑	↔			↑↑↑	↔				↔			↑↑↑
	+ sympathomimetic drugs	Hypertensive crisis			↔			↑↑↑	↔							
	+ diuretics	Hyponatraemia		↑[1]												
	Tranylcypromine + Fluoxetine	Serotonin Syndrome	↑↑↑													

Total number of recommendations / Information
0/2
1/1
3/1
0/1
0/1
1/0
1/0
1/7
1/1
2/0
0/1
4/2
0/3
1/3
2/0
2/2
1/0
3/4
1/2
1/0
1/0

NASSA	+ serotonergic drugs	Serotonin Syndrome*	↔																0/1
	+ diuretics[1]	Hyponatraemia		↑															1/0
Other ADs	Trazodone + sedating drugs	Orthostatic hypotension	↔																0/1
	Trazodone + α2-Receptor blocking agents	Orthostatic hypotension	↔																0/1
	Bupropion + Convulsant	Risk of seizure	↔																0/1
	Bupropion + MAOI	*	↔																0/1
	Bupropion + dopaminergic substances	*	↔																0/1
	+ diuretics	Hyponatraemia		↑[1]															1/0
	Fluoxetine/Paroxetine + CYP 450 metabolized drugs	Increased risk for adverse effects	↔																0/1
	Agomelatine + CYP1A2 inhibitors: cimetidine, ticlopidine, ciprofloxacin	*							↑↑										1/0
	Vilazodone + CYP3A4 inhibitors: e.g., ketoconazole	*							↑										1/0
Total number of recommendations/information per guideline:			**2/15**	**14/0**	**4/2**	**0/0**	**2/0**	**2/0**	**3/6**	**2/1**	**0/0**	**0/6**	**3/3**	**1/1**	**0/2**	**1/2**			

*ADR not specifically named in the guideline; [1]in older adults; [2]NASSA (Noradrenergic and Specific Serotonergic Antidepressants): mianserin, mirtazapine; [3]IHD: ischaemic heart disease; TCA: Tricyclic Antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors ; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; MAOI: Monoamine Oxidase Inhibitors; AD: antidepressant

Recommendations			**Information**
Contraindicated (CI) ↑↑↑ (n=5)	Avoid (A) ↑↑ (n=12)	Caution (C) ↑ (n=13)	Information (I) ↔ (n=38)

Table 20: Drug-disease interactions

Antidepressant	Comorbidity	Depression									Anxiety/Panic				Total number of recommendations / information
		Germany	UK		USA			Canada		AUS & NZ	Germany	UK		Canada	AUS & NZ	
		NVL	NICE	BAP	APA	ISCI	VA/DoD	CANMAT	CCSMH	RANZCP	AWMF	BAP	NICE	CPA	RANZCP	
TCA	at high risk of# cardiovascular disease (ischemic heart disease)			↑↑		↑						↑↑				3/0
	Arrhythmia			↑↑								↑↑				2/0
	Heart failure			↑↑												1/0
	(Severe) cardiac disease (incl. conduction abnormalities and arrhythmias	↑↑↑										↑↑				2/0
	Dementia and Delir	↑↑↑														1/0
	Cognitive impairment									↑↑						1/0
	Urinary retention/prostatic hyperplasia	↑↑↑														1/0
	Ileus	↑↑↑														1/0
	Pyloric stenosis	↑↑↑														1/0
	Narrow-angle glaucoma	↑↑↑														1/0
	Hepatic or renal impairment						↑↑									1/0
	Suicidality / Patients at risk for suicide	↑↑	↑↑				↑↑					↑↑				4/0
Clomipramine, maprotiline	Epilepsy										↑↑					1/0

SSRI	(Es)citalopram	Prolonged QTc (>500ms)		↑↑	↑↑								2/0
	(Es)citalopram	Preexisting/Congenital long QT-Syndrome	↑↑↑	↑↑	↑↑								3/0
		Cardiac risk factors, e.g., Hypokalaemia/ hypomagnesaemia		↑↑						↑↑			2/0
		Bleeding disorder/bleeding/risk of bleeding#		↑↑			↔					↔[1]	1/2
		Hyponatraemia						↑[1]					1/0
	Citalopram	Hepatic impairment		↑		↑↑			↑				3/0
	Fluoxetine			↑↑									1/0
	Sertraline			↑↑									1/0
	(Es)citalopram	Renal impairment				↑↑							1/0
	Paroxetine	Cognitive impairment							↔[1]				0/1
SNRI		Bleeding disorder		↑↑									1/0
		Increased tendency for bleeding#	↑↑↑										1/0
		Hyponatraemia						↑[1]					1/0
		Severe hepatic impairment	↑↑↑										1/0
		Known QT-prolongation	↑↑↑										1/0
	Venlafaxine	(Uncontrolled) Hypertension		↑						↑			2/0
	Venlafaxine	Arrhythmia risk#		↑									1/0
	Duloxetine	Hepatic impairment/at risk of#				↑↑				↑↑			2/0
	Duloxetine	Renal impairment				↑↑							1/0
MAOI	Isocarboxazid	Hepatic impairment				↑↑↑							1/0
	Phenelzine	Hepatic impairment				↑↑↑							1/0
	Tranylcypromine	Hepatic impairment	↑↑↑			↑							2/0
	Tranylcypromine	Severe hypertension/ pheochromocytoma, aneurysm with risk of rupturing	↑↑↑										1/0
	Isocarboxazid	Renal impairment				↑↑							1/0
	Phenelzine	Renal impairment				↑↑↑							1/0
	Phenelzine	Suicidality / Patients at risk for suicide								↑↑			1/0
	Any	Suicidality / Patients at risk for suicide	↑↑										1/0
	Sympathomimetic agents	Can precipitate hypertensive crisis				↔							0/1
	Tranylcypromine	Renal impairment				↑							1/0

Other ADs	Bupropion	Seizure disorder/epilepsy	↑↑↑					↑↑					↑↑							3/0
	Bupropion	Eating disorder						↑↑												1/0
	Bupropion	Severe hypertension	↑↑↑																	1/0
	Bupropion	Hepatic impairment						↑												1/0
	Tianeptine	Dependence disorder	↑↑↑																	1/0
	Agomelatine	Hepatic impairment	↑↑↑		↑↑↑										↑					3/0
	Nefazodone	Hepatic impairment						↑↑												1/0
	Mianserin, Mirtazapine (NASSA)	Hepatic impairment	↑↑↑																	1/0
Total number of recommendations/information per guideline:			19/0		1/0	14/0	0/0	3/0	16/1	0/1	2/0	1/1	3/0		9/0	0/0	0/0	0/1		

*ADR not specifically named in the guideline; [1]in older adults, [#]unspecified – at risk population; [2]NASSA (Noradrenergic and Specific Serotonergic Antidepressants): mianserin, mirtazapine; [3]IHD: ischaemic heart disease; TCA: Tricyclic Antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; MAOI: Monoamine Oxidase Inhibitors; AD: antidepressant

Recommendations			**Information**
Contraindicated (CI) ↑↑↑ (n=21)	Avoid (A) ↑↑ (n=35)	Caution (C) ↑ (n=12)	Information (I) ↔ (n=4)

Table 21: Drug-age interactions

Antidepressant		Depression									Anxiety/Panic					Total number of recommendations / information
		Germany	UK		USA			Canada		AUS & NZ	Germany	UK		Canada	AUS & NZ	
		NVL	NICE	BAP	APA	ISCI	VA/DoD	CANMAT	CCSMH	RANZCP	AWMF	BAP	NICE	CPA	RANZCP	
TCA	Any										↔					0/1
	Nortriptyline				↑↑	↑↑	↑↑									3/0
	Amitriptyline											↑↑				1/0
SSRI	Any			↔				↔	↑	↑			↔[3]		↔	2/4
	Paroxetine				↑↑↑		↑↑		↑↑							3/0
	Citalopram			↑		↑			↔	↑	↑					4/1
	Escitalopram			↑					↔		↑					2/1
	Fluoxetine								↑↑							1/0
SNRI	Any								↑	↑						2/0
MAOI	Any								↑↑							1/0
Other AD	Agomelatine			↑↑												1/0
Any AD			↑	↑	↔							↑		↔	↔	3/3
Total number of recommendations/information per guideline:		0/0	1/0	4/1	2/1	2/0	2/0	0/1	5/2	3/0	2/1	2/0	0/1	0/1	0/2	

[3]IHD: ischaemic heart disease; TCA: Tricyclic Antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; MAOI: Monoamine Oxidase Inhibitors; AD: antidepressant

Recommendations			Information
Contraindicated (CI) ↑↑↑ (n=1)	Avoid (A) ↑↑ (n=9)	Caution (C) ↑ (n=13)	Information (I) ↔ (n=10)

Discussion

Summary of findings

The findings of this review highlight substantial variability across international clinical practice guidelines (CPGs) in addressing drug-drug, drug-disease, and drug-age interactions in antidepressant prescribing.

We found 173 interactions, which provided us with potential deprescribing indications. In terms of drug-drug interactions, European guidelines provided the most detailed recommendations while those from the USA, Canada, and New Zealand/Australia offered significantly fewer. A notable consistency was found across German, UK, and USA guidelines concerning the risk of serotonin syndrome when combining tricyclic antidepressants (TCAs) with serotonergic drugs. However, for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), there were broad variations across countries regarding risks such as gastrointestinal bleeding, serotonin syndrome, and cardiovascular complications like QT prolongation. These differences underscore the need for more standardized and harmonized guidelines to enhance safety in antidepressant use across regions.

Similarly, drug-disease interaction guidance showed significant variation. While guidelines from Germany, UK and USA provided the most comprehensive recommendations for managing comorbidities such as cardiovascular risks, hepatic impairment, and suicidality, Australian/New Zealand and Canadian guidelines were less specific, often offering general advice. TCAs and monoamine oxidase inhibitors (MAOIs) were consistently flagged for cardiovascular concerns, while SSRIs and SNRIs showed more variability in addressing risks related to bleeding and liver function.

Drug-age interactions, particularly in older adults, were less thoroughly addressed. UK, USA, and Canadian guidelines offered more recommendations than those from Germany and Australia/New Zealand, but gaps remain in providing clear deprescribing guidance. Most of the warnings and recommendations focused on TCAs and MAOIs, highlighting the need for more consistent deprescribing criteria and monitoring practices across international guidelines.

Across all guidelines we found 11 clear statements on when to *stop* antidepressant therapy. Most of the selected guidelines (n=11 out of 14) lacked specific recommendations on when specifically to deprescribe antidepressants. Recommendations on when to avoid or monitor antidepressants were mentioned in all guidelines, but varied and were not consistent.

Comparison with literature

The recommendations for tricyclic antidepressants (TCAs) in this review consistently emphasize concerns about cardiovascular risks and anticholinergic adverse drug reactions. Cardiovascular risks, such as QT prolongation and associated arrhythmias, are frequently highlighted in guidelines from the UK, USA, and Australia/New Zealand. These findings align with systematic reviews

like Vieweg et al. (2012), which underscore the association between TCAs and QT prolongation (108). A meta-analysis by Reilly et al. (2000) also found that TCAs pose a higher QT prolongation risk than other antidepressants, especially in patients with cardiac conditions (109). The risk of serotonin syndrome is consistently discussed in the CPGs, particularly when TCAs are used with other serotonergic agents, which is supported by Boyer and Shannon (2005), who emphasize the life-threatening potential of this syndrome (110). Anticholinergic adverse drug reactions, including dry mouth, constipation, and cognitive impairment, are noted as significant risks, especially for patients with dementia, reflecting concerns from reviews like Rudolph et al. (111).

Selective serotonin reuptake inhibitors (SSRIs) present distinct risks, including serotonin syndrome and QT prolongation. The CPGs emphasize caution with citalopram and escitalopram, particularly at higher doses, which aligns with findings by McClelland et al. (2016) and others who note the dose-dependent QT risks (112-114). Our findings also underscore bleeding risks associated with SSRIs, especially when combined with anticoagulants or NSAIDs. This concern is supported by a meta-analysis from Anglin et al. (2014) as well as numerous other studies which report an increased risk of gastrointestinal bleeding (23, 115, 116). Hyponatraemia is frequently noted in the CPGs as an adverse effect of SSRIs in older patients, with support from evidence by Jacob and Spinler (117) and Viramontes et al. (118).

For serotonin-norepinephrine reuptake inhibitors (SNRIs), the CPGs note risks like serotonin syndrome and bleeding, especially with venlafaxine, with literature like De Abajo (119) and Erken et al. confirming this risk (120). According to Jasiak et al., as with SSRIs, the use of SNRIs appears to be associated with QTc prolongation. (121). Hyponatraemia represents a notable risk linked to the use of SNRIs, particularly in the elderly population, as underscored by Movig et al.(122).

Monoamine oxidase inhibitors (MAOIs) are less frequently addressed in the CPGs but still carry significant risks, particularly serotonin syndrome and complications in patients with hepatic or renal impairment. These risks are supported by findings from Preskorn (123) and Boyer and Shannon (110). Other antidepressants, such as bupropion and agomelatine, are linked to specific concerns, including seizure risks with bupropion and hepatic impairment with agomelatine, consistent with recommendations from various guidelines and reviews.

The guidelines' general recommendations call for individualized risk assessments, considering comorbidities and concurrent medications. This approach aligns with systematic reviews like Cipriani et al. (2009), which advocate for weighing the benefit-risk balance for each patient (124). Overall, the CPGs and international literature consistently highlight risks such as serotonin syndrome, QT prolongation, bleeding, and hyponatraemia across different antidepressant classes. TCAs are more often associated with cardiovascular and anticholinergic risks, while SSRIs and SNRIs are linked to bleeding and metabolic disturbances. MAOIs present significant concerns related to serotonin syndrome, requiring caution in patients with hepatic or renal impairment.

We found very few systematic reviews that specifically compared CPGs related to antidepressants. However, a notable review by Langford et al. reported similar findings, highlighting the variability in recommendations across guidelines, and advocated for the development of a co-designed template or best practice guide to improve clarity and consistency in deprescribing strategies (125).

In the literature, we identified reviews focusing on tapering or withdrawal symptoms of antidepressants (126, 127) as well as recommendations regarding antidepressant use during pregnancy or the peripartum period (128, 129).

Strengths and limitations

Strengths

Comprehensive Range of Interactions Covered: The tables offered a detailed overview of multiple antidepressant classes (TCAs, SSRIs, SNRIs, MAOIs, and other antidepressants) and their associated adverse drug reactions, thus covering a broad scope. This extensive range enables a more *holistic understanding* of the potential risks across different antidepressant types. *Consistency in Highlighting Common Risks:* The data consistently addressed major risks, including serotonin syndrome, QT prolongation, bleeding, and hyponatraemia, reflecting a *robust approach* to identifying widely recognized adverse effects that are frequently discussed across different clinical practice guidelines (CPGs). By including guidelines from various countries (e.g., Germany, UK, USA, Canada, Australia/New Zealand), the tables offered a *comparative approach* that sheds light on differences in clinical recommendations, potentially highlighting areas where *harmonization* could improve practice. The tables pinpointed unique risks for specific antidepressants, such as QT prolongation with citalopram or seizure risks with bupropion, *adding depth* to the analysis by focusing on the distinct properties of individual medications.

In sum, the review provides a *comprehensive overview* of multiple antidepressant classes and common risks such as serotonin syndrome and QT prolongation. Including guidelines from various countries adds an *international dimension*, pointing out where harmonization might enhance clinical practice.

Limitations

The data revealed considerable *variability* in how different countries and guidelines address specific risks. This may reflect differences in healthcare systems, local practices, or regulatory environments rather than purely *evidence-based conclusions*, potentially limiting the applicability across different clinical settings. The tables mainly focused on well-established risks, without considering *emerging concerns* or newly identified adverse effects. This may *overlook recent evidence* or evolving clinical insights that could influence future guideline recommendations. Well-established risks associated with antidepressants include serotonin syndrome, weight gain, sexual dysfunction, and increased suicide risk, particularly among younger patients. In contrast, evolving clinical insights, such as potential long-term cognitive effects and alterations to the gut microbiome, underscore the need for guidelines to comprehensively address both established and newly identified adverse effects. Not all guidelines relied on the same *level of evidence* in making recommendations. Some may have been based on *expert consensus* rather than high-quality clinical trials, introducing potential *bias* in how risks are presented or prioritized. For example, the American Psychiatric Association (APA) Guidelines incorporate both high-quality trials and expert consensus, which can introduce personal biases in interpreting risks, particularly in under-researched areas. In contrast, NICE Guidelines from the UK emphasize high-quality clinical

trials and systematic reviews, reducing bias, but may become outdated if newer studies are not included.

The variability in recommendations largely reflects differences in healthcare systems and guideline processes, rather than being purely evidence-based. This means that the variations in clinical guideline recommendations are not solely based on scientific evidence but also reflect differences in healthcare systems and the processes used for guideline development. For instance, economic factors and local practices may influence recommendations in one country, while the latest research may take precedence in another. This underscores the fact that guidelines are tailored to the specific context of the respective healthcare systems, which may as well account for their heterogeneity.

Conclusions

This systematic review of clinical practice guidelines on antidepressant prescribing and deprescribing reveals significant variability across countries and guideline authorities. Key findings include substantial differences in the number and type of recommendations related to drug-drug, drug-disease, and drug-age interactions for different antidepressant classes. This may serve as a compelling argument for future efforts to harmonize guidelines across different countries.

We discovered a significantly higher number of recommendations for contraindications and avoidance within the category of drug-disease interactions compared to the other two categories. This insight is particularly valuable for establishing criteria within guidelines that may initiate considerations for discontinuing antidepressant therapy.

The analysis also indicated a general lack of specific recommendations for drug-age interactions, with most guidelines primarily offering general information rather than clear guidance on when to avoid or monitor antidepressants in older adults. Overall, this review provides a useful comparative framework for understanding the risks associated with different antidepressants and across various guidelines.

Future studies and guideline updates should address the identified inconsistencies and gaps across different regions by harmonizing recommendations. It is essential for clinical practice guidelines to not only focus on initiating antidepressant therapy but also to provide clear and evidence-based recommendations on when and how to safely discontinue treatment. Incorporating deprescribing criteria into clinical practice guidelines, especially for patients with complex comorbidities or older adults, would help clinicians identify appropriate situations for discontinuation and ensure a more comprehensive approach to managing antidepressant therapy. This would promote safer prescribing practices and support patient-centred care by optimizing both the initiation and cessation of antidepressant treatment.

The current systematic review identified clinical situations, as identified by CPGs, that may act as triggers for critically reviewing the continuation of antidepressant treatment. It served as a foundation for a consensus process conducted by a fellow PhD student within the POKAL-Kolleg, aimed at developing an indicator-set to. Within the scope of this doctoral thesis, the indicator-set has ultimately been transformed into a checklist, to function as core component of an intervention that assists GPs in facilitating decision-making related to the deprescribing of antidepressants.

Chapter 4: Development of a Study Protocol

Background

According to the MRC framework for the development and evaluation of complex interventions, such interventions require pilot testing before being formally evaluated for effectiveness and safety in randomized controlled trials. The aims of pilot studies vary depending on what is already known about the intervention components, but common goals include ensuring that the components are feasible and acceptable to users (health care professionals and/or patients), as well as confirming the plausibility of the desired benefits or the absence of adverse effects.

Based on the interview findings in chapter 2, an intervention strategy was drafted, and in chapter 3, a systematic guideline review was conducted to inform the development of one of its components - a set of explicit criteria listing potential deprescribing indications for antidepressants. These criteria were further developed by a fellow doctoral student through an expert consensus process. The resulting criteria set, named REPROVE ("Sc**R**eening-tool zur Id**E**ntifikation **P**otenzieller Über- und Risikove**R**s**O**rgung mit Antidepressi**V**a in der hausärztlich**E**n Praxis"), is shown in **Table 34** and **Table 35** in the appendix. It includes 62 criteria, of which 37 identify potential high-risk prescribing, and 25 focus on potential overprescribing of antidepressants.

Before moving to a formal evaluation of the intervention strategy proposed in chapter 2, two key uncertainties about the REPROVE tool required testing. First, while REPROVE is designed to identify potential deprescribing indications for antidepressants, there is uncertainty about its actual performance in identifying patients with deprescribing opportunities in real-world general practice settings. Second, although the most convenient use of REPROVE would be through integration with electronic health records (EHR), this presents technical challenges in Germany due to the large variety of EHR systems used in general practices and the lack of standardized application programming interfaces (APIs). Therefore, if REPROVE is to be used as part of an intervention strategy in the near future, paper-based solutions would likely be required—though the acceptability of such a method to potential users remains uncertain.

Aims and objectives

The overarching aim of this research is to develop and evaluate the feasibility and effectiveness of the REPROVE tool for identifying deprescribing opportunities for antidepressants in general practice, while assessing its practical implementation in both paper-based and digital formats to ensure its usability and acceptability in real-world clinical settings. The specific objectives were

(1) To evaluate the performance of the REPROVE tool in identifying patients with actual deprescribing opportunities for antidepressants in a general practice setting, which would then prompt a consultation and discussion (shared-decision) on the continuation oder discontinuation of ongoing antidepressant therapy.

(2) To assess the feasibility and acceptability of implementing the REPROVE tool in a paper-based format, given the current technical limitations of integrating it with electronic health records (EHR) in Germany.

Methods

Reporting framework

We adapted the "CONSORT 2010 Statement: Extension to Randomized Pilot and Feasibility Trials" (130) to standardize, improve quality, and ensure comprehensive reporting of our pilot study. This ensures clarity, reproducibility, and transparency in study design and outcomes, facilitating the identification of challenges and improving feasibility assessments. For primary care research, we supplemented the CONSORT statement with the 2023 CRISP Checklist (131), a guideline developed to address the unique needs of primary care settings. Integrating both CONSORT and CRISP guarantees a high-quality and well-documented protocol for piloting the deprescribing intervention.

Study design

This is a feasibility/pilot study conducted as a single-arm prospective intervention study. The participating general practitioners will select individuals from their patient pool who meet the inclusion criteria and will carry out the intervention after completing prior training. The follow-up will be two months. For an overview of the study procedure, please see **Figure 8** below.

Study team

The study team will include Professor Dr. Tobias Dreischulte as study director. Jochen Vukas will be conducting the study. Further research members might be announced upon need. See COREQ-32 in the appendix on page 109 for further details on members of the study team.

Study participants

Inclusion and exclusion criteria for study participation: General practitioners

For logistical reasons, only general practitioners in Bavaria who care for at least 1,000 patients are eligible to participate in the study. Practices currently involved in other studies on medication therapy safety (AMTS) will be excluded.

Inclusion and exclusion criteria for study participation: Patients

The pilot study targets all patients aged 40 years and older who are actively treated in outpatient general practice care and are taking at least three medications, including at least one antidepressant. Additional exclusion criteria are listed in **Table 22**.

Table 22: Inclusion and exclusion criteria for general practitioners (GPs) and patients

Inclusion criteria: GPs	Exclusion criteria: GPs
• Region of Bavaria • Care for patients who are also in public health insurance system • Care of ≥ 1.000 patients per quarter	• Participation at research projects whithin medication safety or geriatric medicine
Inclusion criteria: Patients	**Exclusion criteria: Patients**
• age ≥40 years • overall ≥3 drugs • including ≥1 antidepressants • ability to sign informed consent	• Participation at research projects whithin medication safety or geriatric medicine • According to the physician, the patient is not able to meet the requirements of the study (to be specified in Appendix 3). • Deprescribing is not indicated according to the physician's assessment (to be specified in Appendix 7).

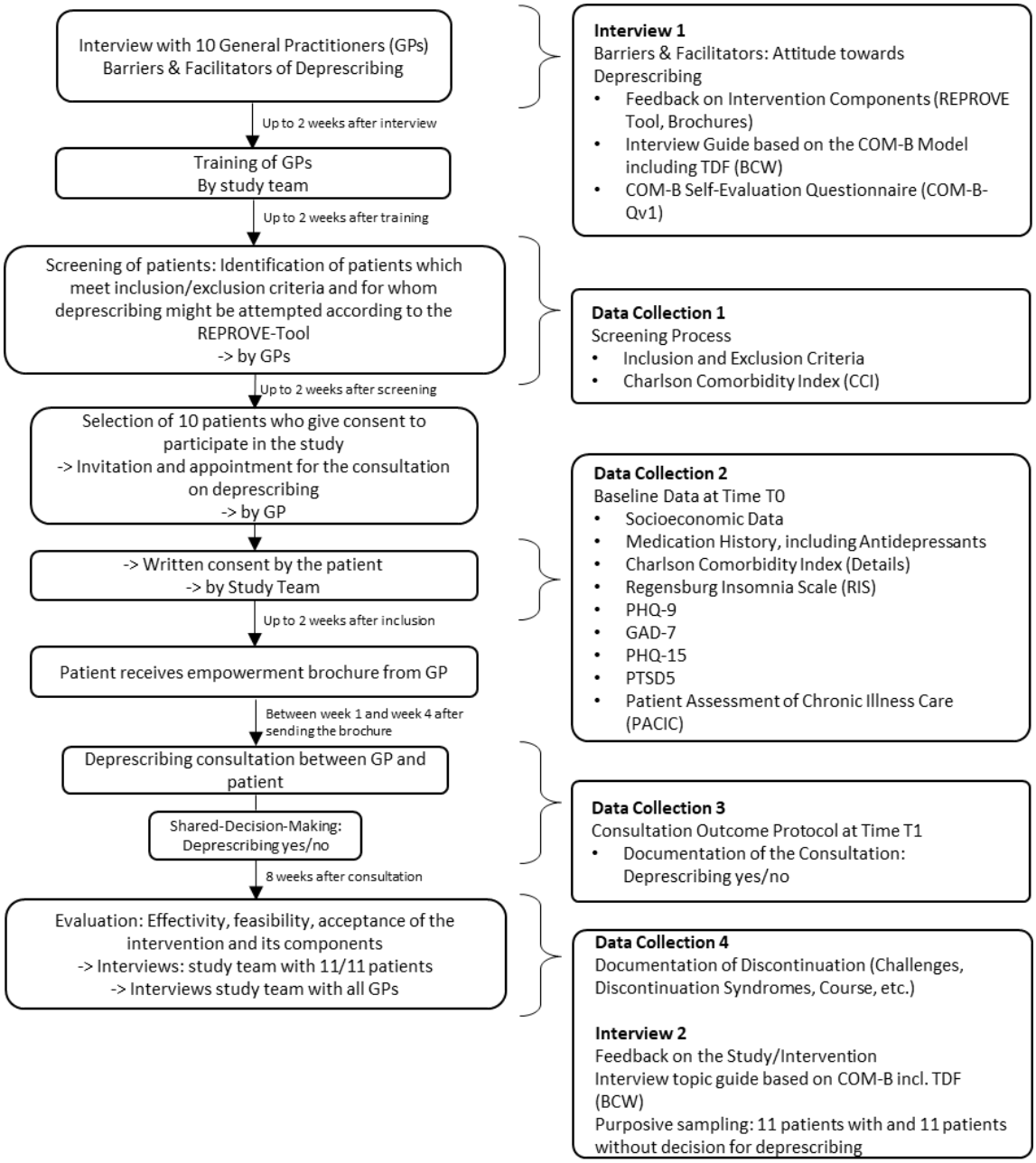
Recruitment and training of general practitioners

General practitioners within a 200 km radius of Munich who meet the inclusion/exclusion criteria (see **Table 22** above) will be contacted incrementally (via email and/or telephone) until six general practitioners from six different practices are recruited. The aim is to recruit practices in both urban and rural areas. Interested practices will receive a study information and an invitation for a personal meeting to address any questions. General practitioners who do not respond will receive up to two reminder emails. By signing the consent form, the general practitioners confirm their participation in the study. As the study aims to assist GPs in facilitating effective deprescribing decisions, practice nurses are not actively included in the study. However, GPs are permitted to delegate any tasks to their practice employees at their discretion. Participating general practitioners will receive training on the study's content and procedures during a visit by the study team.

Screening for patients

Six general practitioners will initially identify up to 35 patients aged 40 years or older who have been taking antidepressants and three or more medications for 12 months or longer using their practice management system (n = up to 200 patients). All identified patients will be screened for potential overprescription and risks associated with antidepressants using the REPROVE tool. Baseline data, such as age, gender, indication for the antidepressant, and certain chronic diseases (to determine the Charlson Comorbidity Index), will be collected to characterize the overall screened patient population. Additionally, the criteria met by the REPROVE tool will be documented for each patient. For patients identified as having overprescription or risk prescription of antidepressants, exclusion criteria will be checked and documented by the general practitioners. The data collected during the screening process will be provided to the study team anonymously. Patient consent is not required at this stage.

Figure 8: Pilot study, overview



PHQ-9 - Patient Health Questionnaire-9; GAD-7 - Generalized Anxiety Disorder-7; PHQ-15 - Patient Health Questionnaire-15; PTSD5 - Post-Traumatic Stress Disorder-5

REPROVE Tool

The core component of the study is a checklist containing 62 indicators of high-risk or overmedication. This indicator set was developed by Brisnik in 2024 using the RAND/UCLA Appropriateness Method, involving experts in general practice, psychiatry, geriatrics, and pharmacy. For this pilot study, the indicators have been categorized by drug class (SSRI, SNRI, TCA, etc.) and by diagnoses (depression, anxiety, insomnia) to facilitate the checklist's use. If an indicator applies to a patient, this should prompt a review of the continued use of the antidepressant.. Discontinuation should only be considered where clinically appropriate and based on guideline-informed, shared decision-making processes.

Selection and recruitment of patients

Each general practitioner will invite up to ten patients with deprescribing potential to participate in the study and will provide patient information if they are interested (n = 60 patients). All patients will have sufficient time (at least 24 hours) to consider their participation and the opportunity to ask questions. By signing the consent form, patients confirm their participation.

Invitation to consultation and empowerment brochures

Patients who consent to participate will be invited to a personal conversation with their general practitioner to discuss the continuation of their antidepressant therapy. Prior to the conversation, they will receive one or two information brochures outlining the benefits and risks of antidepressant therapy. These brochures aim to (a) correct potential misconceptions about the benefits and risks of antidepressants, (b) explain the potential benefits of deprescribing antidepressants, and (c) address concerns regarding deprescribing.

After study inclusion, additional sociodemographic data, past and current therapies, depressive episodes, and criteria met by the REPROVE tool will be collected in Part 1 of the survey form. In Part 2, various questionnaires (including additional sociodemographic questions, and validated tools such as PHQ-9, GAD-7, PHQ-15, PTSD5, and PACIC) and the medication plan will be collected.

Consultation between general practitioners and patients

General practitioners and patients will jointly decide on deprescribing or continuing antidepressant therapy (shared decision-making). The course of the conversation and the reasons for or against deprescribing, from the perspectives of both patients and general practitioners, will be documented on a form. There will be no prescribed structure for the conversation; GPs are free to conduct it in whatever manner they find appropriate to ensure a comfortable atmosphere.

Data from the consultation will be collected by general practitioners, including the date and duration of the conversation, treatment options discussed for individual medications, and any medication changes agreed upon with patients. Additionally, data such as age, gender, antidepressant medication, and Charlson Comorbidity Index will be collected from all patients (anonymous collection).

Tapering

The focus of the study lies in measuring the efficiency of a checklist that helps identify patients with antidepressant overuse and high-risk prescriptions for whom re-evaluation is warranted, and deprescribing may be considered. The tapering process itself will not be part of the study. However, the success of discontinuing an antidepressant greatly depends on the tapering regimen. To support GPs, we offer training on deprescribing and tapering beforehand.

Second interview with general practitioners

Using a topic guide, all general practitioners will be asked through semi-structured interviews about their experiences with the REPROVE tool, as well as clinical, patient-related, and contextual factors that facilitated or hindered the deprescribing of antidepressants. General practitioners will also be asked about additional strategies that might help overcome barriers to deprescribing.

Interview with up to 22 patients

To gather feedback on the intervention, interviews will be conducted with patients. Up to 11 patients who choose to attempt discontinuation and up to 11 patients who decide against discontinuation will be interviewed. Using an interview topic guide, patients will be asked about their general attitudes toward medications and their willingness to stop certain medications. Additionally, their experiences with the intervention, including the appropriateness and potential benefits of the information brochures and the course of the consultation itself, will be explored. Patients will be asked to explain why they decided for or against deprescribing the antidepressant and what might have made the decision easier for them.

Outcomes

Primary outcome measures of the study in general practices will be reported as follows:

(a) The number and proportion of patients identified by the checklist for whom deprescribing might be beneficial.

(b) The number and proportion of patients who decided to discontinue or continue antidepressants.

We expect that 10% of patients identified by the checklist will choose to discontinue their current antidepressant therapy.

Secondary outcome measures will assess the feasibility and acceptability of the study.

Statistical analysis

The statistical analysis of quantitative data will be descriptive. Baseline characteristics of the study participants (GPs and patients) will be summarized using median (interquartile range) or mean

(standard deviation), or percentages (%). Regarding Project Objective 1 (performance of the REPROVE tool), the proportion (%) of patients with antidepressant therapy for whom (a) deprescribing potential was identified or (b) a deprescribing attempt was made will be determined.

Regarding Project Objective 2 (barriers and facilitators for deprescribing antidepressants, feedback on feasibility by GPs and patients), the qualitative interview data will be transcribed verbatim, and the transcripts will be coded and analysed using appropriate software (e.g., MAXQDA).

Risks, burdens and benefits

Risks: Patients may engage with their illness more than usual. There is also a likelihood of a potential recurrence of depressive symptoms or side effects (rebound) after or during discontinuation.

Burdens: For general practitioners, the time commitment is approximately 30 minutes per patient, plus a one-time commitment of about 3 hours (including initial conversation with the study team, training/information sessions, questionnaires, patient screening, and interviews with the study team). The total time commitment for patients is approximately 3 hours (including the information session, answering questionnaires, reading the information brochure, consultation, and interview with the study team).

Benefits: Possible reduction in medication burden and potentially undesirable drug effects through the deprescribing intervention (discontinuation/reduction of an antidepressant). Raising awareness among general practitioners and patients about medication safety (and thus the concept of deprescribing).

All clinical decisions (including any medication changes) and the assessment of an individual risk-benefit ratio are at the discretion of the general practitioner and require the patient's consent; these decisions are not determined by the study protocol.

Discussion

This pilot study protocol was systematically developed using the CONSORT 2010 Extension for Randomized Pilot and Feasibility Trials, together with the CRISP (Consensus Reporting Items for Studies in Primary Care) checklist, ensuring a comprehensive and standardized approach to primary care research. By integrating both guidelines, we aimed to enhance the quality, transparency, and rigor of the study design, establishing a robust foundation for future larger-scale trials. The combination of these frameworks underscores the importance of both feasibility and primary care-specific considerations, ensuring that the study is well-aligned with real-world clinical settings.

The study protocol provides the basis for conducting the proposed pilot study to evaluate the feasibility, performance, and acceptability of the REPROVE tool for identifying deprescribing opportunities for antidepressants in general practice. This pilot will provide critical insights into how well the tool performs in a real-world setting, while also assessing whether general practitioners find it feasible and acceptable to use in its paper-based format, given the current limitations of

electronic health record (EHR) integration in Germany. The evaluation will support refinements to the study design and intervention, thereby increasing its potential applicability in routine care.

Strengths and limitations

A notable strength of the study lies in its focus on developing a practical, evidence-based checklist aimed at helping general practitioners identify potentially inappropriate medications (PIMs). By simplifying the deprescribing decision process, the REPROVE tool aims to improve medication safety and, ultimately, patients' quality of life. However, one limitation of the current protocol is the lack of direct patient involvement in the initial design of the tool. Although the focus is on empowering general practitioners to identify deprescribing opportunities, future iterations of the intervention should include greater patient engagement to ensure that deprescribing decisions are well-aligned with patient preferences and needs. While literature suggests that patient involvement is key to optimizing care, many existing deprescribing tools have not been widely adopted due to their complexity. This study aims to address that gap by creating a more accessible tool that is both evidence-based and user-friendly for clinicians.

Another limitation is the reliance on a paper-based version of the REPROVE checklist. While this was necessary given the technical challenges of integrating the tool with diverse EHR systems in Germany, it may pose practical challenges in daily practice, potentially reducing the tool’s usability. A digital version, compatible with EHRs, would streamline its application, making it easier for practitioners to use and more likely to be adopted in routine care. The results of this pilot will provide important feedback on the acceptability of the paper-based version and help identify the necessary steps for transitioning to a digital format in the future.

Conclusion

In conclusion, this pilot study will contribute to the broader efforts to improve medication safety through deprescribing interventions in primary care. By systematically developing an intervention that integrates general practitioner perspectives and primary care-specific reporting frameworks, we aim to build a strong foundation for future research. The insights gained from this pilot study will inform the design of larger randomized controlled trials, ultimately supporting the wider implementation of deprescribing tools like REPROVE to help identify antidepressant prescriptions that may not align with current guideline recommendations or available evidence, thereby contributing to more appropriate and patient-centred antidepressant use.

Chapter 5: Overall Discussion

Overall summary

Aiming to develop a complex intervention to support general practitioners in evaluating the appropriateness of ongoing antidepressant prescriptions and potential antidepressant deprescribing, we used a systematic approach aligned with guidance from the MRC framework. As a first step, we conducted a theory-based qualitative interview study (chapter 2). The topic guide was structured around the COM-B model and the Theoretical Domains Framework, providing a comprehensive approach to identifying key facilitators and barriers to antidepressant deprescribing in the German general practice setting. The interview study identified time constraints, lack of interdisciplinary collaboration, complexity of guidelines, and the absence of practical deprescribing tools as key barriers to antidepressant evaluation. Conversely, it highlighted digital tools integrated into practice software, shared decision-making, motivated patients, and support from pharmacies as potential facilitators. Utilizing the Behaviour Change Wheel (BCW) allowed us to iteratively develop an intervention strategy, with a checklist supporting GPs in identifying cases where antidepressant treatment may warrant re-evaluationas a core component.

To inform the content of the checklist, we conducted a systematic review of clinical practice guidelines. From included guidelines, we extracted statements on risk factors for adverse drug reactions (informing the detection of potential high-risk prescribing) with specific recommendations. The systematic review identified two guidelines from Germany, four from the UK, three from the USA, three from Canada, and two from Australia/New Zealand. Our review highlighted large heterogeneity between guidelines regarding coverage of antidepressant safety issues. Across all guidelines, 68 drug-drug, 72 drug-disease and 33 drug-age interactions were identified. The results were used in a subsequent expert consensus process conducted by a fellow doctoral student, yielding the REPROVE tool with 62 validated indicators of potential high-risk and overprescribing (1), whereby the term ‘overprescribing’ refers specifically to instances in which antidepressants are continued without regular re-evaluation, without a clear clinical indication, or without shared decision-making.

In order to address key uncertainties around the implementation of the REPROVE tool in routine general practice, we designed a study protocol of a single arm feasibility and optimization study using a mixed methods approach. In preparation for a planned evaluation of an antidepressant deprescribing intervention, the study investigates the performance of the tool in identifying patients with actual deprescribing opportunities for antidepressants in a general practice setting (objective 1) and the feasibility and acceptability of implementing the REPROVE tool (objective 2). On the basis of the findings, we will be able to judge whether and how the instrument requires further optimization with regards to its content or mode of delivery, and whether and how it requires supplementation with other intervention components to enhance the implementation of antidepressant deprescribing interventions in German general practices.

Reflections on Methodological Strengths and Limitations

This project has several strengths. Firstly, the use of the MRC framework ensured a standardized approach in developing a pilot study. Building on this, further research can continue to employ the MRC framework for the standardized development of a subsequent main trial.

Secondly, the use of theoretical frameworks, specifically the BCW and TDF, was another *notable strength in guiding* the behaviour change process and providing in-depth insights into the perspectives of GPs regarding the evaluation of the appropriateness of ongoing antidepressant prescriptions and deprescribing potential. This approach allowed us to systematically identify relevant barriers and develop an intervention strategy, thereby enhancing the likelihood of successful implementation.

Another key strength was the involvement of GPs, who play a central role in utilizing the checklist to effectively identify patients for whom continued antidepressant use may no longer be indicated, and for whom discontinuation could be appropriate. Developing an implementable intervention requires a thorough understanding of the target behaviour and the context in which the behaviour needs to change.

Furthermore, achieving diversity in demographic and geographic characteristics among the GPs participating in the interview study was an additional strength, as it ensured the representation of multiple perspectives, thereby enriching the study results.

Another strength is the checklist as a core component of the intervention. This project is unique in that it tests this newly developed indicator-set in real-world settings in German general practices. Additionally, the results of the systematic review provided important evidence for the development of the indicator set.

The project has several limitations. We did not involve patients in the development of the study protocol. This decision was made because the intervention focuses on changing the behaviour of general practitioners (GPs) in identifying patients for whom deprescribing might be *appropriate*. Thus, GPs are central to the intervention. However, according to our protocol, patients will be interviewed following the consultation and, if applicable, after tapering. This approach *enables* us to collect feedback on the process, patient involvement by GPs, and attitudes toward deprescribing antidepressants. Such feedback will aid in improving the design of a subsequent randomized controlled trial (RCT).

Additionally, the intervention was developed without the inclusion of other stakeholders (community nurses, family members, etc.). In accordance with the recommendations of Mitchie et al. (73), we constrained the complexity of the intervention. However, deprescribing is a complex process that, in real-world settings, heavily depends on the general practitioner-patient relationship and the involvement of stakeholders such as practice staff, home nurses, or family members. Therefore, the effectiveness of the checklist can be further enhanced by considering additional stakeholders and all steps of the deprescribing process in future trials.

Another limitation is that the results may not be transferable to other countries with different healthcare systems, as the facilitators and barriers identified in the interview study may vary across contexts. However, this research provides valuable insights for studies conducted in other countries and can serve as a foundation for further investigation tailored to their specific needs.

A further limiting factor involves the participating general practitioners. Approximately eight participants had previously taken part in other studies. Although not all of these studies were focused on deprescribing, a potential motivation bias could influence the interview results. However, this is inherent in recruiting general practitioners for a qualitative interview study. To mitigate this, we purposively included GPs with diverse backgrounds, ages, genders, and from different geographic regions in Southeast Bavaria (both urban and rural) to collect as varied data as possible.

For the systematic literature review, we did not include all possible countries. In some instances, guidelines were either unavailable or not freely accessible (e.g., Finland). This limitation reduces the generalizability of the results and, consequently, the checklist. Nevertheless, we included CPGs from well-known institutions, such as NICE, to ensure a comprehensive dataset from a variety of highly respected CPGs. Once the checklist is evaluated in future RCTs and found to be effective and implementable in general practice, it can be adapted for use in other countries and tailored to their specific healthcare systems.

Implication for Research and Practice

By using real-world data (interviews), theory (BCW, TDF), and evidence (systematic review), we developed an intervention strategy to support general practitioners in identifying situations where ongoing antidepressant treatment may require re-evaluation due to a lack of current indication, with deprescribing considered as one possible option. We also drafted a protocol to pilot test the intervention. The MRC Framework emphasizes the importance of an iterative process, where each phase of intervention development - from initial modelling to pilot testing - is used to refine and enhance the intervention. After the pilot phase, it is crucial to assess and adapt the intervention to ensure its practicality, feasibility, acceptance and effectiveness before advancing to a full-scale trial.

A unique feature of the intervention is the inclusion of an indicator set developed using the RAND/UCLA Appropriateness Method in a previous study. Additionally, the intervention incorporates insights from interviews with general practitioners (GPs) in Germany, addressing their need for an instrument that supports efficient identification of patients for whom ongoing antidepressant therapy may no longer be indicated, allowing for guideline-based reassessment and, if appropriate, discontinuation. Participants in our interview study expressed concerns that guidelines and interventions are often too complex and impractical for everyday use by GPs. In primary care research, interventions tested may be overly complex or time-consuming, rendering them unfeasible in practice. For example, a German intervention study failed to significantly reduce hospital admissions or the number of potentially inappropriate medications (132). Similarly, a Swiss prospective study found limited value in using a PIM-Check compared to a control group (96). Unlike other deprescribing interventions (133), the current intervention is based on an indicator set informed by evidence from a wide range of studies and guidelines within the RAND/UCLA Appropriateness Method. Furthermore, our intervention does not require extensive training or significant time commitments, making it more feasible for implementation in general practice.

The indicators presented in this dissertation are not intended to provide standalone or prescriptive rules, but to serve as prompts for clinical reflection and structured review. Any action taken must

be grounded in individual risk-benefit evaluation and adjusted according to the treatment phase. Further refinement of the indicators represents an important direction for future development.

An open question remains how the re-evaluation of antidepressant use via an instrument such as the REPROVE tool can be systematically integrated into the clinical workflow of general practitioners. One implementation strategy could involve annual medication reviews, as recommended by national and international guidelines for patients with polypharmacy (defined as the simultaneous use of five or more medications). These reviews aim to support a comprehensive assessment of therapeutic goals, the identification of medications that are no longer indicated, the detection of suboptimal or high-risk treatments, and the assessment of patients' willingness and capacity to adhere to prescribed therapies. However, such reviews are rarely implemented in general practice and typically require dedicated time outside of routine consultations.

As an alternative, antidepressant use could be re-evaluated at the end of each treatment phase as defined by the Kupfer model (50) - namely, acute treatment, continuation therapy, and relapse prevention. This would align deprescribing decisions more closely with clinical treatment planning. However, proactive scheduling of such evaluations is rarely established in primary care. The limited use of this approach may partly explain why concerns about the uncritical continuation of antidepressant treatment have emerged in recent years. Moreover, the Kupfer model does not account for the use of antidepressants beyond depression management, such as for insomnia or chronic pain. High-risk prescribing situations - e.g., due to drug-drug interactions or age-related pharmacokinetic changes - may arise at any time and are not necessarily linked to depressive phases.

In our interview study, general practitioners expressed a strong desire for digital support tools that could provide context-sensitive alerts - e.g., identifying high-risk medications or inappropriate long-term use. While such alerts would be minimally disruptive to practice workflows, shared decision-making around antidepressant deprescribing typically requires protected time for consultation, which is difficult to accommodate during routine visits given the high workload in general practice. A pragmatic approach could involve triggering alerts during regular appointments and then actively scheduling a follow-up consultation for deprescribing decisions if indicated. In such systems, the time points defined by the Kupfer model could serve as additional, phase-specific prompts to support structured treatment planning and medication re-evaluation. This would help embed the REPROVE tool within an evidence-informed and phase-aware deprescribing strategy.For future studies, we therefore suggest transforming the checklist into a digital version, either as a stand-alone tool or preferably integrated into existing software, to further minimize the time required for identifying potentially inappropriate medications (PIMs). This recommendation aligns with the MRC Framework's emphasis on enhancing intervention scalability and ensuring that tools are practical for real-world application.

While we are confident that the intervention will efficiently identify patients for whom treatment re-evaluation might reveal that discontinuation is appropriate in light of current evidence and clinical condition, challenges regarding long-term abstinence and relapse remain (134). Studies incorporating educational and motivational components for GPs, nurses, patients, and their families are needed to ensure sustained discontinuation in the long term. Alongside strategies that promote

careful re-evaluation of antidepressant prescriptions, including deprescribing when clinically justified, maintaining a restrictive approach to repeated prescribing remains an essential method for preventing potentially inappropriate medication.

We designed the intervention for use by GPs, but our interviews revealed that pharmacists could potentially play a role in supporting medication safety through collaboration with general practice. We identified several studies exploring GPs' perceptions of partnerships with pharmacists, though not specifically focusing on antidepressants (70, 135-137). As the incidence of inappropriate antidepressant prescriptions continues to rise, we believe that conducting research on antidepressant use will ultimately improve the quality of life for patients undergoing treatment. Therefore, we recommend involving pharmacists in future trials on antidepressant deprescribing, as this could highlight the benefits of regular collaboration with GPs.

Finally, in the absence of specific guidance on how best to design a feasibility and optimisation study in primary care, we combined the CONSORT statement with a recently developed checklist specifically designed for primary care studies (CRISP). In order to better support primary care researchers in developing and evaluating complex interventions in primary care, there is a need for more specific guidance on designing and conducting pilot studies in this setting.

Conclusions

This dissertation adds to the growing body of research on deprescribing interventions. It demonstrates that deprescribing antidepressants in primary care is a complex challenge, *complicated* by multiple barriers but also presenting clear opportunities for improvement. Based on qualitative interviews and a systematic review, a targeted intervention was developed to assist general practitioners in Germany in effectively identifying patients for whom a re-evaluation of treatment may suggest deprescribing as an appropriate step. Numerous studies have focused on interventions comprising different stakeholders with *complex* characteristics and limited success. In contrast, decision aids like the checklist represent a promising opportunity to increase deprescribing (86). The developed checklist aims to provide a practical and efficient tool for GPs to facilitate deprescribing.

Future research should focus on piloting and evaluating the proposed intervention to assess its feasibility, acceptability, and effectiveness. Promoting interdisciplinary collaboration and developing user-friendly digital tools are *also* important steps toward improving medication safety and implementing deprescribing strategies. Overall, this work shows that a comprehensive, context-specific approach that considers the unique demands of primary care is essential for successfully promoting antidepressant deprescribing and thereby enhancing medication safety.

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Appendix: interview-study

COREQ: 32-item checklist

Table 23: COnsolidated criteria for REporting Qualitative studies (COREQ): 32-item checklist

Number	Item	Guide questions / description	Reported on manuscript page or short description
Domain 1: research team and reflexivity			
Personal characteristics			
1	Interviewer	Which author(s) conducted the interviews?	Jochen Vukas (J.V.), Assistant doctor in residency for general practice
2	Credentials	What were the researcher's credentials? *E.g., PhD, MD*	Jochen Vukas (J.V.): Medical Doctor, BSc, Research group POKAL for medical doctors' degree (Dr. med.) Tobias Dreischulte (T.D.): pharmacist, MSc in clinical pharmacy and in pharmacovigilance and pharmacoepidemiology, PhD in clinical pharmacy, Vita Brišnik (V.B.): pharmacist, MSc in pharmacy, PhD programme Linda Sanftenberg (L.S.): Dr. rer. nat. cell biology
3	Occupation	What was their occupation at the time of the study?	J.V.: research, general practitioner scientist with focus on pharmacotherapy and depression , lecturer T.D.: Professor for clinical research, lecturer, deputy director at the institute, clinical research in pharmacy V.B.: scientist in the research group POKAL, lecturer L.S.: senior researcher, focus on vaccine hesitancy, lecturer All at the Institute of General Practice and Family Medicine, LMU Clinic, Munich
4	Gender	Was the researcher male or female?	J.V.: male, T.D.: male, V.B.: female, L.S.: female
5	Experience and training	What experience or training did the researcher have?	J.V.: 3 years experience in clinical research, author of several other studies (field: tobacco dependency, depression, medication safety), completion of several workshops on depression, scientific writing, qualitative analysis T.D.: more than 10 experience as pharmacist, since 2006 research on pharmacy, pharmacoepidemiology and pharmacovigilance, Lead of Pharmacy Research and Development at University of Dundee V.B.: pharmacist for more than 10 years, author of several studies in pharmacotherapy and medication safety L.S.: more than 10 years of experience in various research projects in healthcare service, vaccination readiness, psychological determinants influencing health behaviours
Relationship with participants			
6	Relationship established	Was a relationship established prior to study commencement?	One participant known already before study. Otherwise no relationship has been established in forehand. Intention and procedures have been explained through e-mail or telephone. All participants have been introduced to the procedure before beginning the interview (informed consent).
7	Participant knowledge of interviewer	What did the participants know about the researcher? *E.g., reason for doing the research*	The researcher J.V. introduced himself and own work during recruitment phase if requested, otherwise before beginning the interview. Participants have not been informed about other researchers involved as they were not part of interviews and direct contact.
8	Interviewer characteristics	What characteristics were reported about the interviewer? *E.g., bias, assumptions, reasons and interests in the research topic*	J.V.: Understanding, processing and analysing data may have been influenced by previous work, such as systematic review and literature research on medication safety and deprescribing. T.D., V.B. and L.S. have not been interviewers.

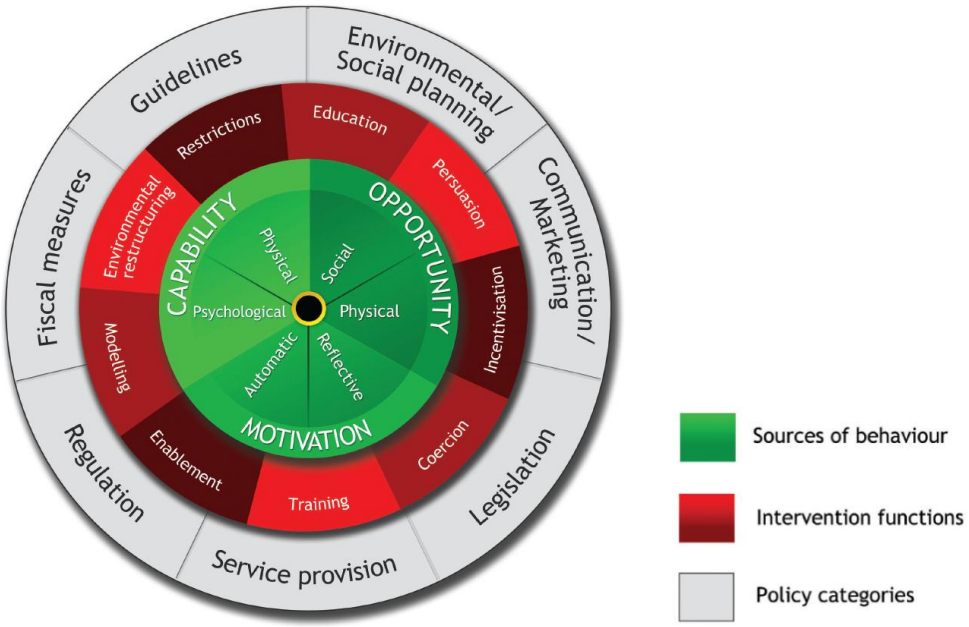
Domain 2: study design			
Theoretical framework			
9	Methodological orientation and theory	What methodological orientation was stated to underpin the study? *E.g., grounded theory, ethnography, discourse analysis*	Qualitative content analysis, deductive-inductive coding Behaviour Change Framework and components (Mitchie et al., 2014)
Participant selection			
10	Sampling	How were participants selected? *E.g., purposive, convenience, consecutive*	Purposive sampling to ensure covered categories (male, female, professional experience) (online registries: Jameda)
11	Method of approach	How were participants approached? *E.g., face-to-face, telephone, email*	Telephone, E-Mail
12	Sample size	How many participants were in the study?	20
13	Non-participation	How many people refused to participate or dropped out (with reasons)?	Refused after contact: 4 (all did not have capacity), Drop-out: none
Setting			
14	Setting of data collection	How was the data collected? *E.g., home, clinic, workplace*	Interviews all took place at the practices of the general practitioners (=workplace)
15	Presence of non-participants	Was anyone else present besides the participant and researcher?	NO
16	Description of sample	What are the important characteristics of the sample? *E.g., demographic data*	11 female, 9 male. Location of practices: 8 in Munich, 12 from countryside in south-west Bavaria. Youngest participant 33yoa, oldest participant 64yoa. Professional experience: 8-37 years. 12 participants worked in practice with more than 1 general practitioner. 8 participants with experience in clinical studies.
Data collection			
17	Interview guide	Were questions and prompts provided by the authors?	A topic guide with open and closed questions has been created. The guide was organized according to the COM-B-model with TDFs mapped to it. Topics covered (excerpt): Knowledge and experience with deprescribing, criteria for the identification of potentially inadequate medication, general practitioners' own role and relationship to external/internal colleagues and stakeholders.
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No
19	Audio/visual recording	Did the researcher use audio or visual recording to collect the data?	Audio recording, anonymous with no names/personal data being mentioned neither from interviewer nor participants Transcribed verbatim
20	Field notes	Were field notes made during/after the interview?	After the interview: notes have been written on a post-scriptum document.
21	Duration	What was the duration of the interviews?	16 minutes to 63 minutes
22	Data saturation	Was data saturation discussed?	Data saturation was reached after 14 interviews with no new (sub)themes emerged in the last 6 interviews.
23	Transcripts returned	Were transcripts returned to participants for comment/correction?	First interview: yes, in order to get feedback and to discuss appropriate changes for future interviews. Transcripts of remaining (19) interviews were not returned to participants.
Domain 3: analysis and findings			
Data analysis			
24	Number of data coders	How many data coders coded the data?	J.V.: main coder (all 20 interviews). Intracoder-reliability has been performed. (REPROVE_HI.01.01)
25	Description of the coding tree	Did authors provide a description of the coding tree?	Coding tree has been developed identical to the topic guide as both are based on the COM-B model (deductively). Codes for subthemes emerged from exploration and analysis of the data set (inductively).
26	Derivation of themes	Were themes identified in advance or derived from the data?	Main themes derived from topic guide (see 25), subthemes generated from data set.

27	Software	What software, if applicable, was used to manage the data?	MAXQDA Analytics pro, version 24.2.0
28	Participant checking	Did participants provide feedback on the findings?	No
Reporting			
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? E.*g., participant number*	Yes, including participant/interview ID
30	Data and findings consistent	Was there consistency between the data presented and the findings?	Assumably yes
31	Clarity of major themes	Were major themes clearly presented in the findings?	Major findings have been reported, e.g. barriers for carrying out a medical review including deprescribing, lack of communication by external general practitioner to support deprescribing.
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes. E.g.: The diverse attitude towards and experience with collaborative work and partnership of external colleagues from other disciplines.

Behaviour Change Wheel, Theoretical Domains Framework

The Behaviour Change Wheel (BCW) model is a comprehensive framework designed to understand and influence behaviour change. It serves as a systematic guide for identifying and designing interventions that aim to modify behaviour in various contexts, including health settings. The BCW integrates insights from multiple disciplines, offering a cohesive structure to approach behaviour change (73).

Figure 9: Behaviour Change Wheel



Core components of the COM-B model

The Hub (sources of behaviour, COM-B model)

At the centre of the wheel lies the "COM-B" model, which stands for Capability, Opportunity, and Motivation, each of which influences Behaviour.

Capability: This refers to an individual's psychological and physical ability to perform a behaviour. It encompasses knowledge and skills.

Opportunity: These are the external factors that make the behaviour possible or prompt it. It includes physical opportunities provided by the environment and social opportunities afforded by cultural norms.

Motivation: This encompasses all the brain processes that energize and direct behaviour, including habitual processes, emotional responses, and analytical decision-making.

Behaviour: Capability, opportunity and motivation influence each other and form and result in a behaviour.

The Middle Layer (intervention functions)

Surrounding the hub are nine intervention functions, which are strategies that can be employed to change behaviour.

Used within in the BCW Framework, the COM-B and TDF identify what needs to change for the desired behaviour to be achieved and therefore what to target in an intervention. Every TDF domain can be mapped to one or more intervention functions. That way, the BCW identifies nine intervention functions to choose from that may be effective in bringing about the desired change in behaviour. Intervention functions can also be described as strategies or activities used to change a desired behaviour. They represent the middle layer of the BCW and are crucial for translating theoretical insights into practical actions.

Education:	Increasing knowledge or understanding.
Persuasion:	Using communication to induce positive or negative feelings or stimulate action.
Incentivization:	Creating an expectation of reward.
Coercion:	Creating an expectation of punishment or cost.
Training:	Imparting skills.
Restriction:	Using rules to reduce the opportunity to engage in the target be haviour (or to increase the target behaviour by reducing the op portunity to engage in competing behaviours).
Environmental Restructuring:	Changing the physical or social context.
Modelling:	Providing an example for people to aspire to or imitate.
Enablement:	Increasing means or reducing barriers to increase capability or opportunity.

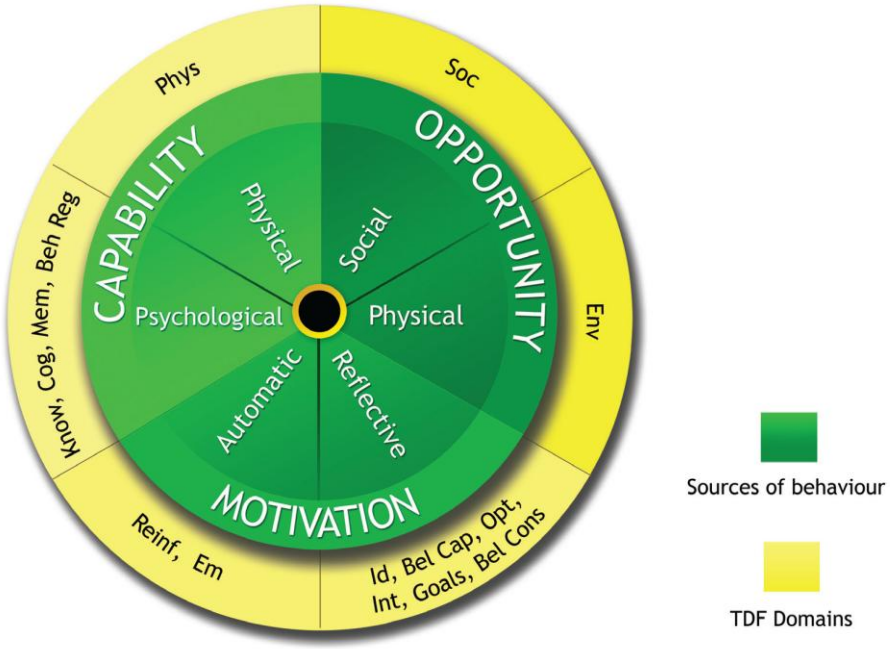
The Outer Layer (policy categories)

This layer includes seven policy categories that support the delivery of the intervention functions, most suitable for target behaviour on populational level. As we did not work on populational level, this component did not apply to our project.

Theoretical Domains Framework

The Theoretical Domains Framework (TDF) is a comprehensive framework used to understand the determinants of behaviour change. Developed in 2005 and later refined, the TDF integrates constructs from multiple behaviour change theories, providing a consolidated structure that aids in identifying the influences on behaviour. It is widely used in implementation science and health psychology to design and evaluate behaviour change interventions (74). Within the BCW Framework, COM-B can be linked to TDF to better understand a behaviour and identify what needs to change. It serves as an interim step on the way to more specifically identify suitable intervention functions. The TDF consists of 14 domains.

Figure 10: TDF domains linked to the COM-B model, from Mitchie et al. 2014



Soc - Social influences
Env - Environmental Context and Resources
Id - Social/Professional Role and Identity
Bel Cap - Beliefs about Capabilities
Opt - Optimism
Int - Intentions
Goals - Goals
Bel Cons-Beliefs about Consequences
Reinf - Reinforcement
Ern - Emotion
Know - Knowledge
Cog - Cognitive and interpersonal skills
Mem - Memory, Attention and Decision Processes
Beh Reg-Behavioural Regulation
Phys - Physical skills

Behaviour Change Techniques

Behaviour Change Techniques (BCTs) are the active components of an intervention designed to change behaviour. They are observable, replicable, and irreducible components of an intervention. The Behaviour Change Wheel (BCW) Framework identifies and categorizes these techniques to aid in the design, implementation, and evaluation of behaviour change interventions.

BCTs are the smallest components of interventions that on their own have the potential to change behaviour. Michie et al. identified 93 distinct BCTs grouped into 16 units, which are organized into a taxonomy to facilitate their use in intervention design. Each BCT is assigned to specific intervention functions. A list of all BCTs can be found in the appendix on **Table 30**, page 127. For more details on the taxonomy of the BCTs we refer to the book 'The Behaviour Change Wheel' (73).

Figure 11: Link between COM-B, TDF domains and BCTs, own illustration, adapted from Mitchie et al., 2014

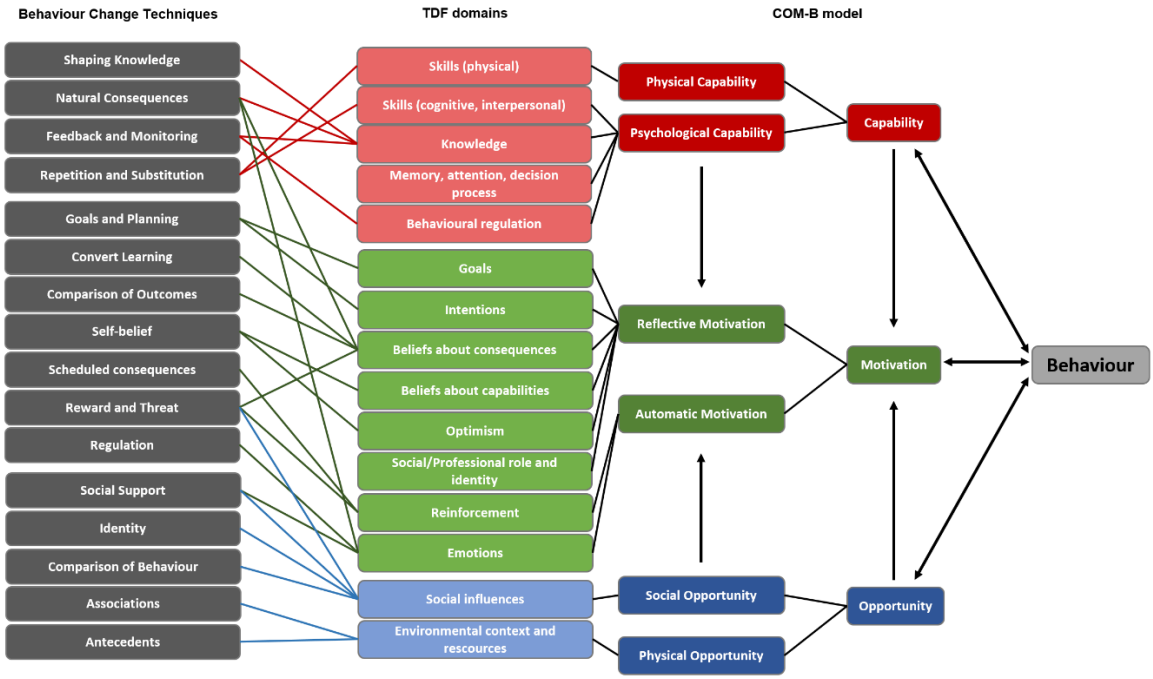


Table 24: TDF domain definitions, theoretical constructs, example questions, from Mitchie et al. 2014

Domain Definition	**Theoretical constructs represented within each domain**	***Interview questions***[c]
Knowledge An awareness of the existence of something	Knowledge (including knowledge of condition / scientific rationale); procedural knowledge; knowledge of task environment	*Do you know about x?*
Skills An ability or proficiency acquired through practice	Skills; skills development; competence; ability; interpersonal skills; practice; skill assessment	*Do you know how to do x?*
Memory, attention and decision Processes The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives	Memory; attention; attention control; decision making; cognitive overload / tiredness	*Is x something you usually do?*
Behavioural regulation Anything aimed at managing or changing objectively observed or measured actions	Self-monitoring; breaking habit; action planning	*Do you have systems that you could use for monitoring whether or not you have carried x?*
Social/professional role and identity A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	Professional identity; professional role; social identity; identity; professional boundaries; professional confidence; group identity; leadership; organisational commitment	*Is doing x compatible or in conflict with professional standards/identity?*
Beliefs about capabilities Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	Self-confidence; perceived competence; self-efficacy; perceived behavioural control; beliefs; self-esteem; empowerment; professional confidence	*How difficult or easy is it for you to do x?*
Optimism The confidence that things will happen for the best or that desired goals will be attained	Optimism; pessimism; unrealistic optimism; identity	*How confident are you that the problem of implementing x will be solved?*
Beliefs about consequences Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	Beliefs; outcome expectancies; characteristics of outcome expectancies; anticipated regret; consequents	*What do you think will happen if you do x?*
Intentions A conscious decision to perform a behaviour or a resolve to act in a certain way	Stability of intentions; stages of change model; transtheoretical model and stages of change	*Have they made a decision to do x?*
Goals Mental representations of outcomes or end states that an individual wants to achieve	Goals (distal / proximal) ; goal priority; goal / target setting; goals (autonomous / controlled); action planning; implementation intention	*How much do they want to do x?*
Reinforcement Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Rewards (proximal / distal, valued / not valued, probable / improbable); incentives; punishment; consequents; reinforcement; contingencies; sanctions	*Are there incentives to do x?*

To be continued…

Emotion A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	Fear; anxiety; affect; stress; depression; positive / negative affect; burn-out	*Does doing x evoke an emotional response?*
Environmental context and resources Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour	Environmental stressors; resources / material resources; organisational culture / climate; salient events / critical incidents; person x environment interaction; barriers and facilitators	*To what extent do physical or resource factors facilitate or hinder x?*
Social influences Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours	Social pressure; social norms; group conformity; social comparisons; group norms; social support; power; intergroup conflict; alienation; group identity; modelling	*To what extent do social influences facilitate or hinder x?*

Intervention design process: supplementary material

Stage 1: Understand the behaviour

1. *Define the problem: describe what is the problem in behavioural terms*

   Deprescribing may be an appropriate response in cases where ongoing antidepressant use is no longer indicated. Thus, the behavioural focus is the critical re-evaluation of ongoing antidepressant treatment to ensure guideline-concordant prescribing.

What behaviour	Improve deprescribing of antidepressants
Where does the behaviour occur	General practice
Who is involved in performing the behaviour	GPs, nurses, patients

2. *Select target behaviour: what is the main behaviour that need to targeted? Consider other behaviours that are present in the context of a main behaviour.*

   In the context of deprescribing, general practitioners face the challenge to effectively identifying situations in which a re-evaluation of ongoing antidepressant treatment may be warranted based on current evidence and guidelines. Several target behaviours have been discussed. To decide which candidate to choose, we applied the criteria according to the BCW framework: likelihood of impact, easiness of behaviour change, centrality of behaviour, easiness of measurement. Within our study team as target behaviour, we consented on improving GPs ability to effectively identify clinical situations in which continued antidepressant use may no longer be appropriate, and in which deprescribing may be attempted.

3. *Specify the target behaviour: who, what, when, where, how often, with whom?*

   We specified the target behaviour by describing key questions as shown in **Table 25**.

Table 25: Description of the target behaviour

Target behaviour	**Support guideline-based medication review in general practice, by identifying patients for whom continued antidepressant use may no longer be appropriate – and for whom discontinuation could be considered where clinically justified**
Who needs to perform the behaviour?	General Practitioners

What do they need to do differently to achieve the desired change?	Increase decision-making (criteria) towards deprescribing
When do they need to do it?	On regular bases, each patient-visit
Where do they need to do it?	In primary care practices
How often do they need to do it?	During appointments with patients When changes in patients' medication occur
With whom do they need to do it?	Identification: alone; decision-making: patients

4. *Identify what needs to change and understand the determinants of the behaviour: what needs to change in the person and/or the environment in order to achieve the desired change in behaviour?*

   Usage of the COM-B model helps to recognize the determinants of the target behaviour by identifying issues related to Capability, Opportunity and Motivation. The components can be further broken down into 14 domains by using the Theoretical Domains Framework (TDF) to achieve better and detailed understanding of behaviour. To analyse and understand behaviour, information needs to be collected. We performed an interview study to collect information on facilitators and barriers to the target behaviour.

Stage 2: Identify intervention options

5. *Select appropriate intervention functions: Choose from the nine intervention functions in the BCW that address the identified TDF domains.*

Certain barriers, that hinder GPs from deprescribing have been identified through the interview study. With this, the goal was to eventually offer ways (BCT-behaviour change techniques and modes of their delivery) that may be suitable to deliver the identified interventions function in order to overcome these barriers, i.e. to change general practitioners' behaviour in favour for deprescribing. During the process it was necessary to make decisions for which item (i.e. IFs, BCTs etc.) to choose to proceed to the next step. As encouraged by Mitchie et al. (73) we did so by applying APEASE criteria and conducting discussion within the study team until consent was reached.

Selection of subthemes

We used the ten most mentioned subthemes (subcodes/subcodes of subcodes) that have been identified from the interviews as being relevant barriers. Every subtheme has been generated inductively from the transcripts and is linked to an overarching TDF domain. We aimed to eventually offer the most relevant BCTs and their modes of delivery for the selected intervention function. It seemed reasonable to us that BCTs resulting from not more than ten subthemes is enough to choose from in order to draft an appropriate intervention strategy.

Mapping themes and TDF domains to intervention function

Candidate intervention functions have been selected that best fit the TDF domains which in turn were related to each of the ten subthemes. For this, we selected the ten most coded subthemes as described above and mapped them to TDF domains and to interventions functions

Selection of most appropriate intervention functions

Of all potential intervention functions ("candidates"), we chose the most relevant ones by applying the APEASE criteria. The APEASE criteria provide a structured approach to assessing the suitability of different behaviour change interventions, BCTs and modes of delivery. Developed by Susan Michie and colleagues, these criteria are part of the BCW Framework and are integral to the development and implementation of effective, efficient, and ethical behaviour change interventions. Particularly, where there is no effective evidence to inform one's choice of an item (e.g. BCT, intervention functions), the APEASE criteria are a useful guide.

Table 26: APEASE criteria for the evaluation of selected items, based on Mitchie et al. 2014, own illustration

A	Affordability	Interventions often have an implicit or explicit budget. It does not matter how effective, or even cost-effective it may be if it cannot be afforded. An intervention is affordable if within an acceptable budget it can be delivered to, or accessed by, all those for whom it would be relevant or of benefit.
P	Practicability	An intervention is practicable to the extent that it can be delivered as designed through the means intended to the target population. For example, an intervention may be effective when delivered by highly selected and trained staff and extensive resources but in routine clinical practice this may not be achievable.
E	Effectiveness / Cost-effectiveness	Effectiveness refers to the effect size of the intervention in relation to the desired objectives in a real world context. It is distinct from efficacy which refers to the effect size of the intervention when delivered under optimal conditions in comparative evaluations.

A	Acceptability	Acceptability refers to the extent to which an intervention is judged to be appropriate by relevant stakeholders (public, professional and political). Acceptability may differ for different stakeholders. For example, the general public may favour an intervention that restricts marketing of alcohol or tobacco but politicians considering legislation on this may take a different view. Interventions that appear to limit agency on the part of the target group are often only considered acceptable for more serious problems
S	Side-effects/ safety	An intervention may be effective and practicable, but have unwanted side-effects or unintended consequences. These need to be considered when deciding whether or not to proceed.
E	Equity	An important consideration is the extent to which an intervention may reduce or increase the disparities in standard of living, wellbeing or health between different sectors of society.

After applying the APEASE criteria, we then selected the two most promising IFs for each subtheme by discussion between members of the study team until consent was reached. Having two IFs per subtheme gave us the opportunity to eventually chose one item from a broad range of BCTs to be included in the intervention.

Table 27: Selection of most appropriate intervention functions

	Selected subtheme	**Intervention function (candidate)**	**Does the intervention function candidate meet the APEASE criteria (affordability, practicability, effectiveness/cost-effectiveness, acceptability, side-effects/safety, equity) in the context of decision-making towards deprescribing antidepressants?**
1	Lack of time	*Training* *Restriction* *Environmental restructuring* *Enablement*	No No as counterproductive Yes No
2	Lack of established routine	*Training* *Environmental restructuring* *Enablement*	Yes Yes Yes
3	Lack of practical tools	*Training* *Restriction* *Environmental restructuring* *Enablement*	No No Yes Yes
4	Lack of engagement by general practitioners from	*Modelling* *Restriction*	No No

	other disciplines (outpatient care setting)	*Environmental restructuring* *Enablement*	No as too complex for the intervention No
5	Lack or inadequacy of guidelines	*Training* *Restriction* *Environmental restructuring* *Enablement*	No No No as too complex for the intervention No
6	Uncertainties regarding the decision to deprescribe	*Education* *Persuasion* *Modelling* *Enablement*	Yes Yes Yes Yes
7	Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary	*Training* *Incentivisation* *Coercion* *Environmental restructuring*	Yes Yes No Yes
8	Financial and economic deficiencies/disadvantages	*Training* *Restriction* *Environmental restructuring* *Enablement*	No No No as too complex for the intervention No as too complex for the intervention
9	Lack of collaboration/awareness regarding medication safety by hospital general practitioners	*Modelling* *Restriction* *Environmental restructuring* *Enablement*	No No No as too complex for the intervention No
10	Uncertainties if originally prescribed by general practitioners from other disciplines	*Education* *Persuasion* *Modelling* *Enablement*	Yes Yes Yes Yes

6. *Choose supporting policy categories: Identify the policy categories that will best support the intervention functions. Not applicable*

Stage 3: Identify content and implementation options

7. Identify behaviour change techniques (BCT): which BCT best serves the identified intervention function? Link intervention functions to appropriate BCTs.

When considering BCTs, it is essential to be guided by the definition not by the label (see appendix **Table 30**, page 127). Thus, we first reviewed the definitions of all possible BCTs that are linked to each of the intervention function in the comprehensive list given by the BCW framework. Afterwards, we mapped selected IFs to BCTs and applied the APEASE criteria to select appropriate candidate BCTs. We then discussed for examples of chosen BCTs as stated in **Table 31**. Finally, we chose final BCTs by consensus discussion within the study team (J.V., T.D., V.B.).

Table 28: Selection of BCTs applying APEASE criteria

	Selected subtheme	**Intervention function (candidate)**	**BCT**	**Does the intervention function candidate meet the APEASE criteria (affordability, practicability, effectiveness/cost-effectiveness, acceptability, side-effects/safety, equity) in the context of decision-making towards deprescribing antidepressants?**
1	Lack of time	*Environmental restructuring*	Adding objects to the environment	No
			Prompts/cues	No
			Restructuring the physical environment	No as too complex for the intervention
2	Lack of established routine	*Environmental restructuring*	Adding objects to the environment	Yes
			Prompts/cues	Yes
			Restructuring the physical environment	No as to complex for the intervention
		Enablement	Social support (unspecified)	Yes
			Social support (practical)	Yes
			Goal setting (behaviour)	Yes
			Goal setting (outcome)	Yes
			Adding objects to the environment	Yes
			Problem solving	Yes
			Action planning	Yes
			Self-monitoring of behaviour	Yes
			Restructuring the physical environment	No as to complex for the intervention
			Review behaviour goal(s)	Yes
			Review outcome goal(s)	Yes
			Identity associated with changed behaviour	Yes
3	Lack of practical tools	*Environmental restructuring*	Adding objects to the environment	Yes
			Prompts/cues	No
			Restructuring the physical environment	No as to complex for the intervention
		Enablement	Social support (unspecified)	No

			Social support (practical)	No
			Goal setting (behaviour)	No
			Goal setting (outcome)	No
			Adding objects to the environment	Yes
			Problem solving	No
			Action planning	No
			Self-monitoring of behaviour	No
			Restructuring the physical environment	No
			Review behaviour goal(s)	No
			Review outcome goal(s)	No
4	Lack of engagement by general practitioners from other disciplines (outpatient care setting)	*Not applicable*		
5	Lack or inadequacy of guidelines	*Not applicable*		
6	Uncertainties regarding the decision to deprescribe	*Education*	Information about social and environmental consequences	Yes.
			Information about health consequences	Yes
			Feedback on behaviour	Yes
			Feedback on outcome(s) of the behaviour	Yes.
			Prompts/cues	No
		Enablement	Self-monitoring of behaviour	Yes
			Social support (unspecified)	Yes
			Social support (practical)	Yes
			Goal setting (behaviour)	Yes
			Goal setting (outcome)	Yes
			Adding objects to the environment	Yes
			Problem solving	No
			Action planning	Yes
			Self-monitoring of behaviour	Yes
			Restructuring the physical environment	No
			Review behaviour goal(s)	Yes
			Review outcome goal(s)	Yes
7	Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary	*Training*	Demonstration of the behaviour	Yes
			Instruction on how to perform a behaviour	Yes
			Feedback on the behaviour	Yes
			Feedback on outcome(s) of behaviour	Yes
			Self-monitoring of behaviour	Yes
			Behavioural practice/rehearsal	Yes
		Environmental restructuring	Adding objects to the environment	Yes
			Prompts/cues	Yes
			Restructuring the physical environment	No

8	Financial and economic deficiencies/disadvantages	*Not applicable*		
9	Lack of collaboration/ awareness regarding medication safety by hospital general practitioners	*Not applicable*		
10	Uncertainties if originally prescribed by general practitioners from other disciplines	*Education* *Enablement*	Information about social and environmental consequences Information about health consequences Feedback on behaviour Feedback on outcome(s) of the behaviour Prompts/cues Self-monitoring of behaviour Social support (unspecified) Social support (practical) Goal setting (behaviour) Goal setting (outcome) Adding objects to the environment Problem solving Action planning Self-monitoring of behaviour Restructuring the physical environment Review behaviour goal(s) Review outcome goal(s)	Yes . Yes Yes Yes . Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes No Yes Yes

8. Select the mode of delivery: Integrate the selected intervention functions and policy categories by developing practical methods and channels for implementation (mode of delivery).

As we identified BCTs, we already got an idea about possible modes of delivery. As done in previous steps, APEASE criteria needed to be applied to modes of delivery in order to get the most promising mode of delivery. Modes are categorized as being ‘face-to-face’ or ‘distance’.

As done in previous steps, APEASE criteria needed to be applied to modes of delivery in order to get the most promising one. Modes are categorized as being ‘face-to-face’ or ‘distance’. Distance as category seemed not relevant to us as we aimed to promote structured medication review via a checklist on a personal GPs level, with the possibility of deprescribing where appropriate. However, we applied the APEASE criteria to evaluate each mode of delivery. We selected ‘individual’ (face-to-face) as the most proper mode of delivery.

Table 29: Selection of mode of delivery

Mode of delivery				**Does the mode of delivery meet the APEASE criteria (affordability, practicability, effectiveness/ cost-effectiveness, acceptability, side- effects/safety, equity)?**
Face-to-face	Individual			Yes
	Group			No
Distance	Population-level	Broadcast media	TV	No
			Radio	No
		Outdoor media	Billboard	No
			Poster	No
		Print media	Newspaper	No
			Leaflet	Yes
		Digital media	Internet	No
			Mobile phone app	No
	Individual-level	Phone	Phone helpline	No
			Mobile phone text	No
		Individually accessed computer programme		No

Table 30: Grouped BCTs according to BCTTv1 (73)

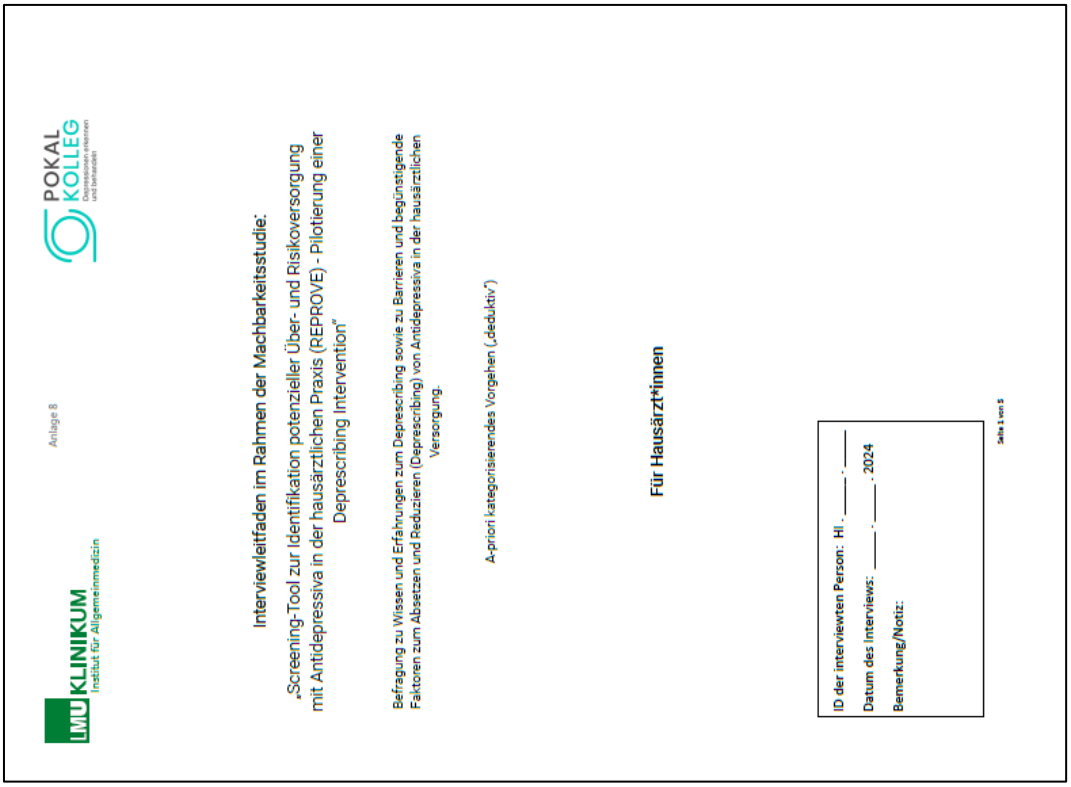
Grouping and BCTs	Grouping and BCTs	Grouping and BCTs
1. Goals and planning 1.1. Goal setting (behaviour) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behaviour goal(s) 1.6. Discrepancy between current behaviour and goal 1.7. Review outcome goal(s) 1.8. Behavioural contract 1.9. Commitment **2. Feedback and monitoring** 2.1. Monitoring of behaviour by others without feed- back 2.2. Feedback on behaviour 2.3. Self-monitoring of behaiour 2.4. Self-monitoring of outcome(s) of behaviour 2.5. Monitoring of outcome(s) of behaviour without feedback 2.6. Biofeedback 2.7. Feedback on outcome(s) of behaviour **3. Social support** 3.1. Social support (unspecified) 3.2. Social support (practical) 3.3. Social support (emotional) **4. Shaping knowledge** 4.1. Instruction on how to pe form the behaviour 4.2. Information about Antecedents 4.3. Re-attribution 4.4. Behavioural experiments **5. Natural consequences** 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.5. Anticipated regret 5.6. Information about emotional consequences	**6. Comparison of behaviour** 6.1. Demonstration of the behaviour 6.2. Social comparison 6.3. Information about others' approval **7. Associations** 7.1. Prompts/cues 7.2. Cue signalling reward 7.3. Reduce prompts/cues 7.4. Remove access to the reward 7.5. Remove aversive stimulus 7.6. Satiation 7.7. Exposure 7.8. Associative learning **8. Repetition and substitution** 8.1. Behavioural practice/ rehearsal 8.2. Behaviour substitution 8.3. Habit formation 8.4. Habit reversal 8.5. Overcorrection 8.6. Generalisation of target behaviour 8.7. Graded tasks **9. Comparison of outcomes** 9.1. Credible source 9.2. Pros and cons 9.3. Comparative imagining of future outcomes **10. Reward and threat** 10.1. Material incentive (behaviour) 10.2. Material reward (behaviour) 10.3. Non-specific reward 10.4. Social reward 10.5. Social incentive 10.6. Non-specific incentive 10.7. Self-incentive 10.8. Incentive (outcome) 10.9. Self-reward 10.10. Reward (outcome) 10.11. Future punishment **11. Regulation** 11.1. Pharmacological support 11.2. Reduce negative emotions 11.3. Conserving mental resources 11.4. Paradoxical instructions	**12. Antecedents** 12.1. Restructuring the physical environment 12.2. Restructuring the social environment 12.3. Avoidance/reducing exposure to cues for the behaviour 12.4. Distraction 12.5. Adding objects to the environment 12.6. Body changes **13. Identity** 13.1. Identification of self as role model 13.2. Framing/reframing 13.3. Incompatible beliefs 13.4. Valued self-identify 13.5 Identity associated with changed behaviour **14. Scheduled consequences** 14.1. Behaviour cost 14.2. Punishment 14.3. Remove reward 14.4. Reward approximation 14.5. Rewarding completion 14.6. Situation-specific reward 14.7. Reward incompatible behaviour 14.8. Reward alternative behaviour 14.9. Reduce reward frequency 14.10. Remove punishment **15. Self-belief** 15.1. Verbal persuasion about capability 15.2. Mental rehearsal of successful performance 15.3. Focus on past success 15.4. Self-talk **16. Covert learning** 16.1. Imaginary punishment 16.2. Imaginary reward 16.3. Vicarious consequences

Table 31: BCTs and examples

Selected subtheme	BCT	Example of BCT
Lack of established routine *Environmental restructuring* *Enablement*	12.5 Adding objects to the environment	Provide visible Leaflet about medication review in patients waiting area
	1.4 Action planning	Install a plan to ensure medication review and increase team's mindset towards medication safety (include meetings, external workshops, memos for general practitioner/front desk, etc.)
	2.3 Self-monitoring of behaviour	Install memory/remembering items, i.e. pop-up in computer calendar or in management software
	3.2 Social support (practical)	Involve practice staff and establish routine and culture of medication reviews
	7.1 Prompts/cues	Put note / memo in patients digital file, instal deprescribing/medication review sheet for every patient appointment
	13.5 Identity associated with changed behaviour	Install culture of medication reviewsor medication safety in practice by regular meetings/talks with the team.
Lack of practical tools *Environmental restructuring* *Enablement*	12.5 Adding objects to the environment	Provide a practical decision-aid (checklist, digital tool)
Uncertainties regarding the decision to deprescribe *Education* *Enablement*	5.3 Information about social and environmental consequences	Leaflet with information on advantages and patient's outcome of medication reviews
	2.4 Self-monitoring of outcomes of behaviour	Diary with notes of successful deprescribing to motivate for reaching certainty
	12.5 Adding objects to the environment	Provide a practical decision-aid (checklist, digital tool) to reach certainty
	3.2 Social support (practical)	Involve practice staff and establish routine and culture of medication reviews
Guidelines, tools, and aids are too complex, time-consuming, not read, and not necessary *Training* *Environmental restructuring*	6.1 Demonstration of the behaviour	Show how to use guidelines/tools/aids (in workshop, practical training sessions)
	4.1 Instruction on how to perform a behaviour	Provide and ensure workshops on how to effectively include guidelines/tools/aids in daily work routine to help medication reviews and deprescribing where appropriate
	12.5 Adding objects to the environment	Provide a practical decision-aid (checklist, digital tool) to reach certainty
Uncertainties if originally prescribed by general practitioners from other disciplines *Education* *Enablement*	5.3 Information about social and environmental consequences	Leaflet with information on advantages and patient's outcome of medication reviews
		Arrange meeting with other general practitioners to arrange consent paper and SOP how to cooperate/communicate
	2.4 Self-monitoring of outcomes of behaviour	Diary with notes of successful medication reviews/deprescribing to motivate for reaching certainty
	12.5 Adding objects to the environment	Provide a practical decision-aid (checklist, digital tool) to reach certainty
	3.2 Social support (practical)	Involve practice staff and establish routine and culture of medication reviews

Interview topic guide and postscript

Figure 12: Interview topic guide (German)



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Anlage 8

POKAL KOLLEG Depressionen erkennen und behandeln

Ziel:

Wir untersuchen die Verschreibung von Antidepressiva in der hausärztlichen Versorgung. Uns interessiert, inwieweit Sie bereits in Berührung mit der Therapie von Antidepressiva gekommen sind. Außerdem möchten wir Sie zu Ihren Erfahrungen bzgl. einer Verschreibung und eines möglichen Absetzens oder Reduzierens (Deprescribing) von Antidepressiva erfahren. Darüber hinaus möchten wir mehr über Ihre Wahrnehmung von hinderlichen (Barrieren) und von begünstigenden (Facilitators) Faktoren zur Erreichung einer angemessenen Behandlung und dem Deprescribing erfahren.

Vor dem Interview-Beginn (Aufzeichnung):

Vielen Dank, dass Sie sich die Zeit nehmen, mit mir zu sprechen.

- Heute möchte ich, dass Sie einige Ihrer Gedanken und Ideen zur Identifizierung und Bewältigung unangemessener Verschreibungen in Ihrer Praxis erörtern.
- Ich werde das Interview aufzeichnen, um mich auf das zu konzentrieren, was Sie sagen, ohne viele Notizen schreiben zu müssen und Sie abzulenken.
- Ich werde vlt. Zwischenfragen stellen und im Verlauf auf bereits besprochene Aspekte nochmal Bezug nehmen.
- Es ist wichtig zu wissen, dass es keine richtigen oder falschen Antworten gibt. Seien Sie einfach Sie selbst und beantworten Sie die Fragen ehrlich.
- Das Gespräch wird vertraulich behandelt. Ihre Antworten werden in anonymer Form gespeichert, sodass Ihr Name in keinem Bericht erscheinen wird.
- Haben Sie die Ihnen zugesandten Dokumente angeschaut, bereits durchgelesen (Informations-broschüren, REPROVE-Tool) bzw. ausgefüllt (COM-B Qv1)?

Die Entwicklung des Interviewleitfadens basiert auf dem COM-B Modell (Capability, Opportunity, Motivation, Behaviour) und dem TDF (Theoretical Domains Framework) aus dem Werk „Behaviour-Change-Wheel – A guide to designing interventions" nach Michie et al., 2014.

Die folgenden Fragen sind entstanden aus (a) dem Austausch innerhalb des Forschungsteams und (b) auf Grundlage nachstehender Studien

N. Kennie-Kaulbach, R. Cormier, O. Kits, E. Reeve, A. M. Whelan, R. Martin-Misener, et al., 2020
E. Van Leeuwen, S. Anthierens, M. L. van Driel, A. I. M. De Sutter, E. van den Branden and T. Christiaens, 2022
G. Peat, B. Fylan, I. Marques, D. K. Raynor, L. Breen, J. Olaniyan, et al., 2022
J. Measdl, I. Obara and H. Nazar, 2023
M. S. Keller, J. Carrascoza-Bolanos, K. Breda, L. Y. Kim, K. A. Kennelty, D. W. Leang, et al., 2023
M. Donald, R. Partanen, L. Sharman, J. Lynch, G. A. Dingle, C. Haslam, et al., 2021
C. H. Heinrich, S. McHugh, S. McCarthy and M. D. Donovan, 2022

Antworten in kursiv = Hauptfragen entsprechend der Interview Questions aus dem TDF (BCW Buch, Seite 88 ff)

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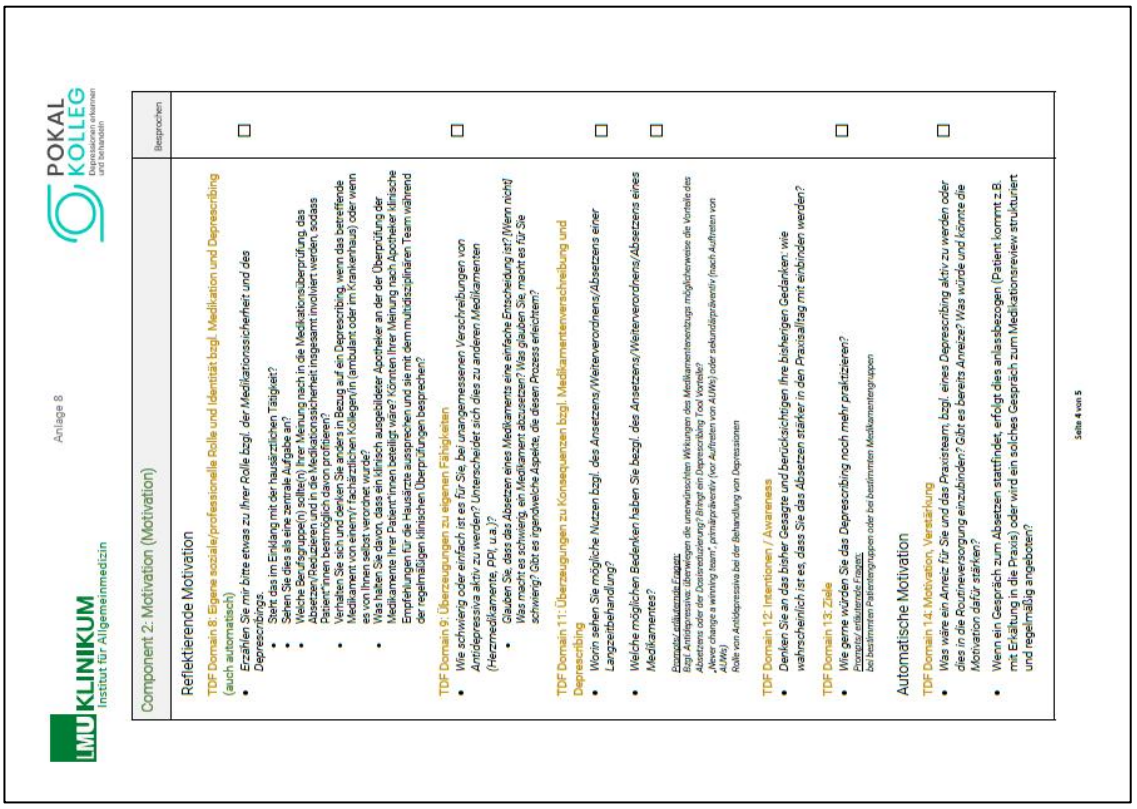
Anlage 8

POKAL KOLLEG Depressionen erkennen und behandeln

Interviewleitfaden

Einleitende Fragen zum Deprescribing	Besprochen
Warum haben Sie sich für eine Studienteilnahme entschieden?	☐
Bitte erzählen Sie mir etwas über Ihre Einstellung gegenüber neuen Interventionen und neuen Versorgungsprogrammen bzgl. Medikationssicherheit u. Deprescribing.	☐

Component 1: Fähigkeit (Capability)	Besprochen
Physische Fähigkeit TDF Domain1: Fertigkeiten/Fähigkeiten • *Bitte erzählen Sie mir etwas über das Erkennen unsachgemäßer Verschreibungen (Erkennen und Stoppen potenziell problematischer Arzneimittel)?* ◦ Welche Verfahren wenden Sie an, um eine Entscheidung über die Verschreibung eines bestimmten Medikaments zu treffen? Wie entscheiden Sie, einem Erwachsenen ein anticholinerges oder sedierendes Medikament zu verschreiben? Was rechtfertigt Ihrer Meinung nach in solchen Fällen die Verschreibung? ◦ Welche Faktoren spielen eine Rolle bei Ihrer Entscheidung, die langfristige Einnahme von Antidepressiva fortzusetzen oder abzubrechen; wie beurteilen Sie dann den weiteren Bedarf? *Prompts/ erläuternde Fragen:* *Erkennen von Risiko- und Überverordnung, Vorgehen beim Absetzen, Tools zum Absetzen, shared decision making, Maßnahmen zur Reduktion des Anticholinergic Burdens, Motivation der Patient*innen, Beteiligung der Praxisangestellten, etc.*	☐
Psychische Fähigkeit TDF Domain 2: Wissen • *Was wissen Sie über Leitlinien und dem Konzept des Deprescribings? Praktikabel?* ◦ Was wissen Sie zu Verordnungen von Antidepressiva? ◦ Was wissen Sie zum Absetzen von Medikamenten, u.a. von Antidepressiva? *Prompts/ erläuternde Fragen:* *Wissen zu unangemessener Verschreibung; Definition von Deprescribing; Wissen zu Risiken beim/nach dem Absetzen; sind Hilfsmittel zum Medikationsreview und zum Deprescribing bekannt?*	☐
TDF Domain 4: Erinnerung/Erfahrung, Aufmerksamkeit, Entscheidungsprozesse • *Erzählen Sie mir von Ihren Erfahrungen mit dem Absetzen von Antidepressiva bei Patient*innen in Langzeitbehandlung.* *Prompts/ erläuternde Fragen:* *Wird dies regelmäßig angewendet?; Wer spricht dies an: Patient*in/Ärzt*in/Anderer?; Erfolgreich/nicht erfolgreich: warum?; was lief gut/schlecht?; Unterstützung für die Patient*innen; welche Schwierigkeiten u. Herausforderungen gab es?; Rückfall/Abbruch des Deprescribings; Absetzsymptome beobachtet?; Gesprächsdauer, wie oft mit Patient*in getroffen bis AD abgesetzt war? Gibt es Unterschiede innerhalb der Antidepressivaklassen beim Absetzen/der Therapie?*	☐
TDF Domain 5: Verhalten(sregulation) • *Verfügen Sie über Mittel und Wege, um die Medikation Ihrer Patient*innen regelmäßig zu überprüfen? Wie entscheiden Sie, ob ein Medikament abgesetzt werden sollte?* *Prompts/ erläuternde Fragen:* *Tools zur Identifikation von PIMs (START-STOPP, PRISCUS, etc.); eigenes Tool; SOPs; regelmäßiger Austausch mit anderen Personen (Praxisteam, Apotheke, Fachzirkel, etc.)*	☐



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Anlage 8

POKAL KOLLEG Depressionen erkennen und behandeln

Component 2: Motivation (Motivation) — Besprochen ☐

Reflektierende Motivation

TDF Domain 8: Eigene soziale/professionelle Rolle und Identität bzgl. Medikation und Depressionbing (auch automatisch)

- *Erzählen Sie mir bitte etwas zu Ihrer Rolle bzgl. der Medikationssicherheit und des Depressionbings.*
  - Startdas im Einklang mit der hausärztlichen Tätigkeit?
  - Sehen Sie dies als eine zentrale Aufgabe an?
  - Welche Berufsgruppe(n) sollte(n) Ihrer Meinung nach in die Medikationsüberprüfung, das Absetzen/Reduzieren und in die Medikationssicherheit insgesamt involviert werden, sodass Patient*innen bestmöglich davon profitieren?
  - Verhalten Sie sich bezüglich des Absetzens von Medikamenten in Bezug auf ein Depressionbing, wenn das betreffende Medikament von einem/r fachärztlichen Kollegen/in (ambulant oder im Krankenhaus) oder wenn es von Ihnen selbst verordnet wurde?
  - Was halten Sie davon, dass ein klinisch ausgebildeter Apotheker an der der Überprüfung der Medikamente Ihrer Patient*innen beteiligt wäre? Könnten Ihrer Meinung nach Apotheker klinische Empfehlungen für die Hausärzte aussprechen und sie mit dem multidisziplinären Team während der regelmäßigen klinischen Überprüfungen besprechen?

TDF Domain 9: Überzeugungen zu eigenen Fähigkeiten

- *Wie schwierig oder einfach ist es für Sie, bei unangemessenen Verschreibungen von Antidepressiva aktiv zu werden? Unterscheidet sich dies zu anderen Medikamenten (Herzmedikamente, PPI, u.a.)?*
  - *Glauben Sie, dass das Absetzen eines Medikaments eine einfache Entscheidung ist? Wenn nicht/ Was macht es schwierig, ein Medikament abzusetzen? Was glauben Sie, macht es für Sie schwierig? Gibt es irgendwelche Aspekte, die diesen Prozess erleichtern?*

TDF Domain 11: Überzeugungen zu Konsequenzen bzgl. Medikamentenverschreibung und Depressionbing

- *Worin sehen Sie mögliche Nutzen bzgl. des Ansetzens/Weiterverordnens/Absetzens einer Langzeitbehandlung?* ☐
- *Welche möglichen Bedenken haben Sie bezgl. des Ansetzens/Weiterverordnens/Absetzens eines Medikamentes?* ☐

Beispiel/ zielführende Fragen:
bzgl. Antidepressiva: Überwiegen die unterwünschten Wirkungen des Medikamentenentzugs möglicherweise die Vorteile des Absetzens oder des Dosisreduzierung? Bringt ein Depressionbing Tool Vorteile?
„Never change a winning team", primärpräventiv (vor Auftreten von AUWs) oder sekundärpräventiv (nach Auftreten von AUWs)
Rolle von Antidepressiva bei der Behandlung von Depressionen

TDF Domain 12: Intentionen / Awareness

- *Denken Sie an das bisher Gesagte und berücksichtigen Ihre bisherigen Gedanken: wie wahrscheinlich ist es, dass Sie das Absetzen stärker in den Praxisalltag mit einbinden werden?*

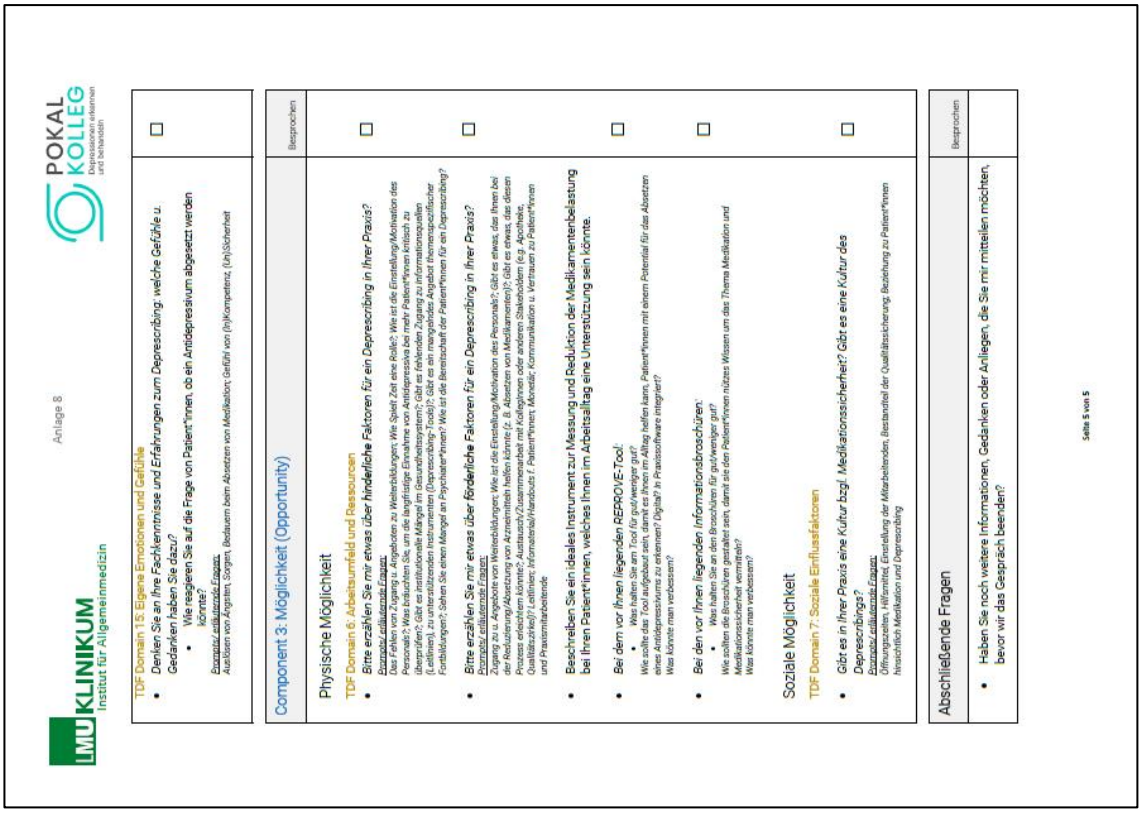
TDF Domain 13: Ziele

- *Wie gerne würden Sie das Depressionbing noch mehr praktizieren?*
  Beispiel/ zielführende Fragen:
  bei bestimmten Patientengruppen oder bei bestimmten Medikamentengruppen

Automatische Motivation

TDF Domain 14: Motivation, Verstärkung

- *Was wäre ein Anreiz für Sie und das Praxisteam, bzgl. eines Depressionbing aktiv zu werden oder dies in die Routineversorgung einzubinden? Gibt es bereits Anreize? Was würde und könnte die Motivation dafür stärken?* ☐
- *Wenn ein Gespräch zum Absetzen stattfindet, erfolgt dies anlassbezogen (Patient kommt z.B. mit Erkältung in die Praxis) oder wird ein solches Gespräch zum Medikationsreview strukturiert und regelmäßig angeboten?*



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TDF Domain 10: Eigene Emotionen und Gefühle

- *Denken Sie an Ihre Fachkenntnisse und Erfahrungen zum Depressionbing: welche Gefühle u. Gedanken haben Sie dazu?* ☐
  - *Wie reagieren Sie auf die Frage von Patient*innen, ob ein Antidepressivum abgesetzt werden könnte?*

Beispiel/ zielführende Fragen:
Ausdrücken von Ärgernis, Sorgen, Bedauern beim Absetzen von Medikationen; Gefühl von (Un)kompetenz, (Un)sicherheit

Component 3: Möglichkeit (Opportunity) — Besprochen

Physische Möglichkeit

TDF Domain 6: Arbeitsumfeld und Ressourcen

- *Bitte erzählen Sie mir etwas über hinderliche Faktoren für ein Depressionbing in Ihrer Praxis?* ☐
  Beispiel/ zielführende Fragen:
  *Das Fehlen von Zugang zu Angeboten zu Weiterbildungen; Wie Spielt Zeit eine Rolle?; Wie ist die Einstellung/Motivation des Personals?; Was behindern Sie, um die langfristige Einnahme von Antidepressiva bei mehr Patient*innen kritisch zu überprüfen?; Gibt es institutionelle Mängel im Gesundheitssystem?; Gibt es fehlenden Zugang zu informationsquellen (Leitlinien), zu unterstützenden Instrumenten (Depressionbing-Tools)?; Gibt es ein mangelndes Angebot themenspezifischer Fortbildungen?; Sehen Sie einen Mangel an Psychiater*innen? Wie ist die Bereitschaft der Patient*innen für ein Depressionbing?*
- *Bitte erzählen Sie mir etwas über förderliche Faktoren für ein Depressionbing in Ihrer Praxis?* ☐
  Beispiel/ zielführende Fragen:
  *Zugang zu u. Angebote von Weiterbildungen; Wie ist die Einstellung/Motivation des Personals?; Gibt es etwas, das Ihnen bei der Reduzierung/Absetzen von Medikamenten helfen könnte (z. B. Absetzen von Medikamenten)?; Gibt es etwas, das den Prozess erleichtern könnte?; Austausch/Zusammenarbeit mit Kolleginnen oder anderen Stakeholdern (e.g. Apotheke, Qualitätszirkel)?; Leitlinien; Informatorial/Handouts f. Patient*innen, Monetär, Kommunikation u. Vertrauen zu Patient*innen und Praxismitarbeitende*
- *Beschreiben Sie ein ideales Instrument zur Messung und Reduktion der Medikamentenbelastung bei Ihren Patient*innen, welches Ihnen im Arbeitsalltag eine Unterstützung sein könnte.*
- *Bei dem vor Ihnen liegenden REPROVE-Tool:* ☐
  - *Was halten Sie am Tool für gut/weniger gut?*

  *Wie sollte das Tool aufgebaut sein, damit es Ihnen im Alltag helfen kann, Patient*innen mit einem Potential für das Absetzen eines Antidepressivums zu erkennen? Digital? In Praxissoftware integriert?*
  Was könnte man verbessern?
- *Bei den vor Ihnen liegenden Informationsbroschüren:* ☐
  - *Was halten Sie an den Broschüren für gut/weniger gut?*

  *Wie sollten die Broschüren gestaltet sein, damit sie den Patient*innen nützen Wissen um das Thema Medikation und Medikationssicherheit vermitteln?*
  Was könnte man verbessern?

Soziale Möglichkeit

TDF Domain 7: Soziale Einflussfaktoren

- *Gibt es in Ihrer Praxis eine Kultur bzgl. Medikationssicherheit? Gibt es eine Kultur des Depressionbings?* ☐
  Beispiel/ zielführende Fragen:
  *Offenheit, Zusammenarbeit, Wertschätzung, Einstellung der Mitarbeitenden, Bestandteil der Qualitätssicherung; Beziehung zu Patient*innen hinsichtlich Medikation und Depressionbing*

Abschließende Fragen — Besprochen

- *Haben Sie noch weitere Informationen, Gedanken oder Anliegen, die Sie mir mitteilen möchten, bevor wir das Gespräch beenden?*

Figure 13: Postscript (German)

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Postscript

ID: HI.____._____ Interview Location: in the practice of the participant

Interview Date: ____.____.2024 Interview Start Time: ____ : ____ Uhr

Duration of Interview (Min:Sec): _____

Interview environment and situation (e.g., practice in rural/urban area, atmosphere, noise level, interview in hallway, etc.)

Occurrences during the interview (noise, phone ringing, door opening/closing, etc.)

Occurrences before the interview (explaining the process, clarifying questions, signing information and consent documents, remarks about the interviewee, etc.)

Occurrences after the interview (atmosphere, questions, etc.)

REPROVE_Interviewstudie

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Interviewer behavior (adhered to guide, feelings, difficulties, etc.)

Information about interviewee (engaged, bored, reflective, etc.)

Other remarks (interpretation ideas of what was said, etc.)?

Helpful questions for the above points.

1. How did I feel?
2. Was anything irritating?
3. What was noticeable?
4. What do I expect from the interviewee?
5. Were expectations/goals for the conversation met?
6. Should questions be asked differently?
7. Should other questions be asked?
8. Werden oft andere Themen genannt, die nicht im Interviewleitfaden enthalten sind?
9. Other thoughts?

REPROVE_Interviewstudie

Coding tree

Table 32: Coding tree in MAXQDA (German)

Liste der Codes	Häufigkeit
Codesystem	1838
Sonstiges (weder Barrier noch Facilitator)	1
Barriers	0
Fähigkeit (Capability): ein Mangel/Fehlen davon	0
Physische Fähigkeit	0
TDF Domain 1: Körperliche Fertigkeiten	0
Psychische (mentale) Fähigkeit	0
TDF Domain 1: Mentale Fertigkeiten	1
Schlechte zwischenmenschliche Kompetenz	2
Kommunikation Arzt-Patient	7
Vertrauen Arzt-Patient	1
TDF Domain 2: Wissen	0
Für die Entscheidung zum Deprescribing (wann ist es sinnvoll?)	0
Situation / Kriterien zum Erkennen von PIM (Wann Deprescribing einleiten?)	4
Interpretation Interviewer: keine "harten" Kriterien (sondern Bauchgefühl) als Barriere für evidenzbasierte Entscheidung	4
Fehlendes Wissen zum Ablauf eines Deprescribing (Tapering)	0
Fehlendes Wisssen zu Leitlinien	12
Fehlendes Wissen über das Konzept des Deprescribings	4
Fehlendes Wissen über Hilfsmittel / Tools für das Erkennen von PIM u. Deprescribing	8
Fehlendes Wissen über Arzneimittelwirkungen u- interaktionen	2
TDF Domain 4: Erinnertes abrufen, Aufmerksamkeit, Entscheidungsprozesse	0
Als Barriere interpretiert: wenn Routinen/ Abläufe, sich der Erkennung von PIMs zu widmen, fehlen	26
Als Barriere geäußert: fehlende Routinen und Abläufe verhindern, sich der Erkennung von PIMs zu widmen	5
TDF Domain 5: Verhaltensregulation	0
Erkennen von PIMs	0
Sekundärpräventiv	17
Viel Zeit dafür aufwenden (müssen)	8
Weiterverordnung, Nicht daran denken abzusetzen / Medikation zu hinterfragen	9
Gelegenheit: ein Mangel/Fehlen davon	0

Physische Gelegenheit	0
TDF Domain 6: Arbeitsumfeld und Ressourcen	0
Fehlende/ inadäquate Leitlinien	22
Strukturelle Mängel in der Hausarztpraxis	1
Softwareprogramme	0
Inadäquate Praxisverwaltungssoftware (PVS)	0
Gewöhnungseffekt / Meldemüdigkeit bei Warnmedlungen der PVS	2
Fehlende oder ungenaue Funktion eines Interaktionschecks/ einer Warnmeldung	9
Kosten	1
Umsetzung einer geeigneten Software schwierig	1
Mangel in der Telematik	0
Elektronische/s Patientenakte / Rezept	3
Personalmangel	3
Interne Meetings /Fortbildungen	1
Mangel oder inadäquate Hilfsmittel/Tools/Listen	0
Zu viele Tools, Insellösungen	4
Keine Hilfsmittel/ Tools/ Listen vorhanden	20
Inadäquate Hilfsmittel/ Tools/ Listen	8
REPROVE-Broschüre	12
REPROVE-Checkliste	29
Inadäquate Veranstaltungen, ein Mangel an Veranstaltungen	0
Fehlende Fortbildungen, Seminare, Workshops	6
Mangel adäquater Qualitätszirkel	3
Finanzielle, wirtschaftliche Mängel/ Nachteile	13
Zeitmangel	0
Für Deprescribing	42
Für Fortbildungen / Literatur/ Leitlinien lesen	7
Soziale Gelegenheit	0
TDF Domain 7: Soziale Einflussfaktoren	1
Gesundheitssystem	5
Mitarbeitende/Angestellte	1
MFAs: mangelnde Kompetenz, nicht dafür verantwortlich	4
Ärztliche KollegInnen: mangelndes Wissen / Fachkompetenz	2
Kultur der Medikationssischerheit, Bewusstsein dafür (vllt. eher: TDF 12 Intention/Awareness?)	3
Multidisziplinäre Arbeit	0
Apotheken	1

Unsensibler Umgang mit und Kommunikation zu PatientInnen (Verunsicherung d. PatientInnen)	11
Mangelnde Zusammenarbeit	5
Fehlender Kontext von Verordnungen	8
Fehlende Neutralität aufgrund monetärer Interessen	4
Mangelndes Angebot ambulanter Behandlungsmöglichkeiten	11
Mangelnde Zusammenarbeit der Krankenversicherungen	2
Mangelnde Zusammenarbeit /fehlendes Bewusstsein f. Medikationsicherheit der Krankenhäuser	21
FachärztInnen	1
Mangelnde Interdisziplinarität	0
Mangelndes Engagement/ Interesse zur Medikationssicherheit	30
Mangelnde Kommunikation mit PatientInnen	5
Mangelnde Zusammenarbeit	11
Mangelnde Kommunikation der ÄrztInnen außerhalb der Praxis	5
Mangelnde Kompetenz bzgl. Medikationssicherheit	6
Mangelnde Verfügbarkeit von Terminen	8
Das Vorhandensein von anderen involvierten ÄrztInnen bei eigenen PatientInnen	19
Altenpflegeheime	0
Barriere zum Deprescribing aufgrund struktureller Zwänge (z.B. Personalmangel, Ruhigstellung)	6
PatientInnen	6
PatientInnen mit anderen psychiatrischen Erkrankungen	3
Hinderliche Gedanken (Ängste, Sorgen, Skepsis, Vorbehalte)	13
Hinderliches Verhalten/ Compliance, keine Weitergabe von Informationen an ÄrztIn	10
Junge PatientInnen	1
Mangelndes Wissen über Medikation und Indikationen	10
PatientIn wünscht ein Antidepressivum / ist gegen ein Deprescribing	13
PatientInnen mit Multimedikation oder Kaskadenverschreibungen	4
PatientInnen mit Langzeittherapie oder schwerer Erkrankung	8
Ältere PatientInnen	4
Politik, Verbände	3
Motivation	0
TDF Domain 10: Optimismus u. Zuversicht	1
Reflektierende Motivation	0
TDF Domain 8: Eigene soziale/berufliche Rolle und Identität	4
Alleingelassen werden	10

Unklarheit über die Rolle des Hausarztes /der Hausärztin zum Erkennen von PIM/ Deprescribing	12
Apotheken haben nicht die Aufgabe für Medikationssicherheit / Deprescribing	8
TDF Domain 9: Überzeugungen zu / Vertrauen in eigenen Fähigkeiten	0
Verhalten bzgl. Deprescribing wenn fremd verordnet	16
Unsicherheiten zur Entscheidung für ein Deprescribing (generell)	14
Unsicherheiten zur Entscheidung für ein Deprescribing (ADs zu anderen Medikamenten))	8
Unsicherheiten im zwischenmenschlichen Bereich	5
TDF Domain 11: Überzeugungen zu Konsequenzen bzgl. Medikamentenverschreibung	0
Meinung, dass Deprescribing kein Benefit hat	6
TDF Domain 13: Ziele	0
Automatische Motivation	0
TDF Domain 14: Motivation und Verstärkung	1
Entmutigende Erfahrung mit Deprescribing	6
Keine Anreize vorhanden	1
Zwänge, ein Medikament zu verschreiben	6
Printmedien (Flyer, Broschüren) in Praxis unterstützen Entscheidung für Deprescribing nicht	3
Tools, Softwareprogramme	0
Leitlinien, Tools, Hilfsmittel sind zu komplex, zeitaufwendig, werden nicht gelesen, nicht notwendig	12
Kosten	3
TDF Domain 15: Eigene Emotionen und Gefühle	0
Sorge der Verschlechterung des Gesundheitszustandes eigener PatientInnen (Rückfall, Wiederauftreten der Symptome)	5
Ängste und Sorgen zum Deprescribing	3
Frust	11
Sonstiges	0
Facilitators	0
Fähigkeit (Capability)	0
Physische Fähigkeit	0
TDF Domain 1: Fähigkeiten	0
Körperliche Fertigkeiten	0
Psychische (mentale) Fähigkeit	0
TDF Domain 1: Mentale Fertigkeiten	0
Entscheidung für ein Deprescribing	0
Gute zwischenmenschliche Kompetenz	0
Shared decision: Kommunikation Arzt-PatientIn, ÄrztIn-Angehörige	39
Vertrauen Arzt-Patient	3

TDF Domain 2: Wissen	0
Entscheidung für ein Deprescribing (wann sinnvoll?)	0
Hier nur, wie es gemacht wird: Situationen / Kriterien zum Erkennen von PIM zum Entscheiden für ein Absetzversuch	58
Shared decision, Patient-Involvement	46
Aussagen, welche Faktoren für ein Deprescribing sinnvoll sind	0
Durchführung eines Deprescribings (Tapering)	0
Prozedere und Ablauf (wenn Entscheidung zum Deprescribing gefallen ist)	40
Shared-decision (Berücksichtigung von PatientInnen-Wünschen)	12
Tools / Hilfsmittel sind bekannt	10
Wissen zu Leitlinien vorhanden	7
Erfahrung /Wissen	8
TDF Domain 4: Erinnerung/Erfahrung, Aufmerksamkeit, Entscheidungsprozesse	0
Etablierte Routinen und Abläufe, sich der Erkennung von PIMs zu widmen (Pläne, Abläufe, Erinnungsmails, etc.)	92
Tatsächlich durch ÄrztInnen geäußerte als förderliche bewertete Abläufe	3
Schwere psychiatrische Fälle	2
TDF Domain 5: Verhaltensregulation	1
Primärpräventiv	26
Weiterverordnungen kontrollieren	11
Kontinuierlich dran bleiben / Thema im Kopf haben und daran denken (besser unter TDF 12 Awareness?)	6
Sonstiges	0
Gelegenheit	0
Physische Gelegenheit (Dinge/Faktoren, die existent sind. Wünsche u. Vorstellungen unter TDF 14 kategorisiert)	0
TDF Domain 6: Arbeitsumfeld und Ressourcen	0
Bundeseinheitlicher Medikationsplan	13
Hilfsmittel/Tools/Listen (integrierte Lösungen fallen unter Softwareprogramme)	0
Digital/Online, (nicht in PVS integrierte)	22
Printform	4
REPROVE-Broschüre	33
REPROVE-Checkliste	33
Strukturelle Potentiale in der Hausarztpraxis	0
Interne Meetings, Fortbildungen, Qualitätszirkel	18
Softwareprogramme	0
PVS	14
Personalisierte PVS-Funktionen	3
Integrierte Tools	10

Telematik	0
Elektronische PatientInnenakte	3
Elektronischer Medikationsplan	7
Abläufe	5
Praxisform und -größe	2
Unterstützung durch Literatur	0
Fachbücher	1
Fachinformation	5
Leitlinien	8
Zeitschriften und Journals	1
Informationen für PatientInnen (Flyer, Fragebögen, Infoblätter, etc.)	2
Veranstaltungen	0
Qualitätszirkel	7
Fortbildungen / Kongresse	11
Soziale Gelegenheit	0
TDF Domain 7: Soziale Einflussfaktoren	0
Verbände, Institutionen	6
Universität / Medizinstudium	2
Multidisziplinäre Arbeit	0
Notfalleinrichtungen	1
Angebote für PatientInnen	0
Broschüren u. Flyer	0
Spezielle Programme u. Interventionen außerhalb der Praxis	2
Föderung der Krankenversicherungen für ein Deprescribing	1
Apotheken	0
Gute Zusammenarbeit und Kollegialität	7
Unterstützung bei Medikationsreviews und Erkennen von PIM	17
Altenpflegeheime	2
Andere FachärztInnen	0
Gute Erreichbarkeit und Kommunikation	16
Hohes Engagement zur Medikationssicherheit	0
Gutes Netzwerk zu anderen ÄrztInnen	2
Direkter Austausch	15
Auf andere Fachärzte verweisen/ Psychiater zurate ziehen ist hilfreich	9
Angehörige	2
Mitarbeitende/Angestellte	0
Ärztliche KollegInnen	2

MFAs	0
Hohe Fachkompetenz /Wissen der MFAs	7
Hohe Motivation u. Engagement der MFAs	6
Gute Sozialkompetenz	0
Kultur der Medikationssischerheit, Bewusstsein dafür (vllt. eher: TDF 12 Intention/Awareness?)	12
PatientInnen	0
Gutes Verhalten/Compliance	10
Gutes Wissen	3
Gute Beziehung zu PatientInnen	11
PatientInnenwunsch abzusetzen	32
Palliativsituation	3
Junge PatientInnen	4
Ältere PatientInnen	3
PatientInnen mit (schweren) Erkrankungen	2
Motivation: Sichtweisen, positive EInstellung zu etwas	0
TDF Domain 10: Optimismus	18
Reflektierende Motivation	0
TDF Domain 8: Eigene soziale/professionelle Rolle und Identität	1
Meinung, dass Erkennen von PIM/ Deprescribing die Aufgabe des Hausarztes/der Hausärztin ist (generell)	32
Meinung, dass Erkennen von PIM/ Deprescribing die Aufgabe des Hausarztes/der Hausärztin ist (wenn fremd verordnet)	1
Meinung, dass Deprescribing auch Aufgabe anderer ÄrztInnen ist	13
Apotheken sollten involviert sein	12
TDF Domain 9: Überzeugungen zu eigenen Fähigkeiten	0
Vertrauen haben und überzeugt sein PIM zu erkennen u. Deprescribing durchzuführen (wenn fremd verordnet)	13
Vertrauen haben und überzeugt sein PIM zu erkennen u. Deprescribing durchzuführen (wenn selbst verordnet)	1
Vertrauen haben u. überzeugt sein, PIM zu erkennen u. Deprescribing durchzuführen zu können (generell)	25
Vertrauen in eigenes Bauchgefühl, subjektives Entscheiden richtig	5
Überzeugung, dass ein Deprescribing von AD einfach ist / einfacher ist als von anderen Medikamenten	13
TDF Domain 11: Überzeugungen zu Konsequenzen Erkennen PIM u. Deprescribing	0
Meinung, dass neue Interventionen sinnvoll sind	22
Meinung, dass Deprescribing sinnvoll ist	31
Absetzen nur mit gutem Konzept sinnvoll (Alternativen, Plan/Betreuung für nach dem Absetzen)	3
TDF Domain 12: Intention / Awareness	0
Die Absicht, Deprescribing zukünftig auszubauen oder dass es ausbaufähig ist	7

Genaueres Hinschauen bei Antidepressiva	0
Multimedikation, Medikationssicherheit neu denken; eine Herausforderung	11
TDF Domain 13: Ziele	0
Änderung von Strukturen, Abläufe, Routinen	5
Den Plan zukünftig Medikationsreviews u. Deprescribing durchzuführen	10
Automatische Motivation	0
TDF Domain 14: Motivation und Verstärkung	0
Verbesserung des PatientInnenwohls	7
Gute Erfahrung mit Depresccribing (ist motivierend)	19
Arbeitsumfeld und Resourcen	0
Finanzielle Aspekte (mehr Geld, bessere Entlohnung, etc.)	14
Infomaterial (Flyer, Broschüren, etc.)	7
Einfach anwendbare Hilfsmittel / Tools/ Fragebögen	12
Strukturierte integrative interdisziplinäre Interventionen	5
Hilfreiche Softwareprogramme	0
PVS: integrierte Softwarelösungen (z.B. KI-gestützt)	47
Hilfsmittel / Tools/ App	23
Unterstützung von Studien / Forschung	18
Mehr Zeit haben	7
Leitlinie zu Deprescribing	7
Qualitästzirkel / Interdisiplinärer Austausch	3
Fortbildungen zu Medikationssicherheit	8
Soziale Einflussfaktoren	0
Mitarbeitende	8
Gesellschaft, Politik, Verbände	7
Bessere Zusammenarbeit mit anderen Berufsgruppen	0
Apotheken	2
TDF Domain 15: Eigene Emotionen und Gefühle	0
Erfüllung im Beruf	0

Appendix: Systematic Review

MiChe: Mini Checklist

Figure 14: Mini-Checklist, Siebenhofer et al. 2016 (107)

Methodological Guideline Quality – Mini-Checklist

1. The guideline has been written in a generally comprehensible manner and its key recommendations are easy to identify.

□ YES □ TO SOME EXTENT □ NO

2. The guideline's target audiences and scope of application were specified.

□ YES □ TO SOME EXTENT □ NO

3. The background, the objectives of the guideline, and the patients for whom the guideline is relevant were clearly described.

□ YES □ TO SOME EXTENT □ NO

4. The persons that developed the guideline are named, and their financial independence and any conflicts of interest are clearly documented.

□ YES □ TO SOME EXTENT □ NO

5. The search for evidence was systematic and the criteria used to select evidence were described.

□ YES □ TO SOME EXTENT □ NO

6. The guideline recommendations are unambiguous and the evidence they are based on is clearly presented.

□ YES □ TO SOME EXTENT □ NO

7. Different treatment options are presented that take account of potential benefits, side effects and risks.

□ YES □ TO SOME EXTENT □ NO

8. Clear information is provided on how up-to-date the guideline is and for how long this is expected to be the case.

□ YES □ TO SOME EXTENT □ NO

Overall assessment of the quality of the guideline based on above results:

Very poor	1	2	3	4	5	6	7	Very good

Would you recommend others use the guideline?

Yes	Yes, with certain reservations	No

Table 33: Detailed quality assessment results (MiChe)

		Items (questions)								Overall	Recommendation for use
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Depression											
Germany	NVL	y	SE	y	SE	y	y	y	y	6	y
UK	NICE	y	y	y	N	y	y	y	y	6	y
	BAP	y	y	y	y	y	y	y	SE	6	y
USA	APA	y	y	y	SE	y	y	y	y	6	y
	ISCI	y	y	y	y	y	SE	y	y	6	y
	VA/DoD	y	y	y	SE	y	y	y	SE	6	y
Canada	CAN-MAT	y	y	y	y	y	y	y	SE	6	y
	CCSMH	y	SE	y	y	y	y	y	SE	6	y
AZ & NZ	RANZCP	y	y	y	y	y	y	y	SE	6	y
Anxiety- and panic disorders											
Germany	AWMF	y	y	y	y	y	y	y	y	7	y
UK	BAP	y	y	y	SE	y	y	y	SE	6	y
	NICE	y	y	y	SE	SE	SE	y	SE	6	y
Canada	CPA	y	y	y	y	y	y	y	SE	6	y
AZ & NZ	RANZCP	y	y	y	y	y	y	y	SE	6	y

Rating items 1 – 8: **Y - Yes; SE - To some extent; N - No**
Overall assessment: Likert scale 1 (very poor) - 7 (very good)
Recommendation: Y - Yes; RES - Yes, with certain reservations; N - No

Indicator set

Table 34: Summary of final indicators of high-risk prescribing, from Brisnik et al. (1)

High-risk prescribing indicators
A. Cardiovascular adverse effects
1. Prescribed SNRI or TCA (in doses ≥50 mg/day) or tranylcypromine - and patient has a history of chronic heart failure.
2. Prescribed TCA (in doses ≥50 mg/day) - and patient has a history of ischemic heart disease.
3. Prescribed >20mg citalopram or >10mg escitalopram daily - and patient is aged ≥65 years (risk of QTc prolongation).
4. Prescribed citalopram, escitalopram - and 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).
5. Prescribed citalopram, escitalopram, TCA (in doses ≥50 mg/day) - and patient is co-prescribed ≥1 further drug with any risk of TdP.
6. Prescribed TCA (in doses ≥50 mg/day) or SNRI or bupropion or tranylcypromine - and patient has developed tachycardia.
7. Prescribed fluoxetine, paroxetine or bupropion - and patient is co-prescribed metoprolol or propranolol (risk of bradycardia).
8. Prescribed SNRI or TCA (in doses ≥50 mg/day) or bupropion or tranylcypromine - and patient has uncontrolled hypertension.
9. Prescribed SNRI or TCA (in doses ≥50 mg/day) or bupropion or tranylcypromine - and achieving hypertension control requires ≥3 antihypertensive drugs.
B. Orthostatic hypotension (OH)/dizziness
10. Prescribed TCA (in doses ≥50 mg/day) or trazodone or tranylcypromine - and patient has developed persistent OH/dizziness under treatment.
11. Prescribed SSRI or SNRI or mirtazapine - and patient is aged ≥65 years and has developed persistent OH/dizziness under treatment.
12. Prescribed TCA (in doses ≥50 mg/day) or trazodone or tranylcypromine - and 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).
13. Prescribed SSRI or SNRI or mirtazapine - and 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).
C. Falls and fall-related injuries
14. Prescribed any antidepressant - and patient is aged ≥65 years and co-prescribed ≥1 further fall-risk-increasing drug.
15. Prescribed any antidepressant - and patient has a history of fall.
16. Prescribed any antidepressant - and patient has cognitive impairment or dementia.
17. Prescribed any antidepressant - and patient has a history of stroke and co-prescribed ≥1 further fall-risk-increasing drug.
D. Cognitive decline & delirium
18. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient has cognitive impairment or dementia.

19. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient has a history of delirium and co-prescribed ≥1 further drug known to induce delirium (e.g., benzodiazepines, opioids, antihistamines, diuretics).
20. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient is aged ≥65 years and co-prescribed ≥2 further drugs known to induce delirium (e.g., benzodiazepines, opioids, antihistamines, diuretics).
E. Serotonin syndrome
21. Prescribed tranylcypromine - and patient is co-prescribed ≥1 further serotonergic drug (e.g., tramadol, fentanyl, triptans, metoclopramide, SSRI, SNRI, TCA).
22. Prescribed SSRI or SNRI or TCA (in doses ≥50 mg/day) - and patient is co-prescribed ≥2 further serotonergic drugs other than tranylcypromine (e.g., tramadol, fentanyl, triptans, metoclopramide, another serotonergic antidepressant).
F. Gastrointestinal bleeding
23. Prescribed SSRI or SNRI - and patient is aged ≥65 years and co-prescribed a single of the following without GI-protection: antiplatelet, anticoagulant, NSAID.
24. Prescribed SSRI or SNRI - and patient is aged ≥65 years and co-prescribed ≥2 of the following: antiplatelet, anticoagulant, NSAID (regardless of GI-protection).
25. Prescribed SSRI or SNRI - and patient has at least one risk factor for GI bleeding (history of peptic ulcer disease, GI-bleeding or haemophilia) and co-prescribed ≥1 of the following: antiplatelet, anticoagulant, NSAID (regardless of GI-protection).
G. Bleeding
26. Prescribed SSRI - and patient has a history of a bleeding event and co-prescribed ≥1 of the following: anticoagulant or antiplatelet.
27. Prescribed SSRI - and 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.
H. Constipation
28. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient has persistent constipation.
29. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient is aged ≥65 years and co-prescribed ≥2 further drugs known to have constipating effects (e.g., calcium antagonists, opioid, antihistamines, antipsychotics).
I. Hyponatraemia
30. Prescribed any antidepressant - and patient has developed hyponatraemia (<130 mmol/l) under treatment without being treated with a diuretic.
31. Prescribed SSRI or SNRI - and patient is aged ≥65 years and co-prescribed ≥2 further drugs known to cause hyponatraemia (e.g., (thiazide) diuretics, antipsychotics, anticonvulsants, proton pump inhibitors).
J. Hepatic injury
32. Prescribed agomelatine - and patient has developed elevated serum transaminase levels (>3 times the upper normal range) under treatment.
33. Prescribed agomelatine - and patient has hepatic impairment (i.e. cirrhosis or active liver disease).
K. Voiding disorders
34. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient has a history of voiding disorders (e.g., urinary retention or benign prostatic hyperplasia) or has developed urinary retention under treatment.
L. Glaucoma

35. Prescribed anticholinergic antidepressant opipramol or other TCA (in doses ≥50 mg/day) or paroxetine - and patient has a history of angle closure glaucoma or has developed angle closure glaucoma under treatment.
M. Sleep disturbances/agitation
36. Prescribed SSRI or SNRI or MAOI or bupropion - and patient has persistent sleeping disturbances (e.g., insomnia, restless leg syndrome) or is experiencing agitation.
N. Sexual dysfunction
37. Prescribed SSRI or SNRI - and patient has developed sexual dysfunction.

Table 35: Summary of final indicators of overprescribing, from Brisnik et al. (1)

Overprescribing indicators

Depression
1. Prescribed an antidepressant - and patient has a first episode of mild depression.
2. Co-prescribed two antidepressants - and patient has a first episode of moderate depression.
3. Prescribed an antidepressant in monotherapy for ≥4 weeks - and patient is aged <65 years with no signs of clinically relevant symptom improvement.
4. Prescribed an antidepressant in monotherapy for ≥6 weeks - and patient is aged ≥65 years with no signs of clinically relevant symptom improvement.
5. Prescribed an antidepressant in monotherapy - and patient has previously used two or more different antidepressants (inadequate response).
6. Prescribed an antidepressant in monotherapy, combination or augmentation >12 months for a first episode of moderate or severe depression - and patient has achieved full remission.
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 patient has achieved full remission.
8. Prescribed SSRI at a dose of >1 DDD - and patient has no clinically relevant symptom improvement under an SSRI dose ≤ 1 DDD (no further dose increase if symptoms remain/worsen).
9. Prescribed two antidepressants - and none of those is mirtazapine or mianserin or trazodone.
Anxiety
10. Prescribed an antidepressant for ≥8 weeks - and patient is aged <65 years with no signs of clinically relevant symptom improvement.
11. Prescribed an antidepressant for ≥12 weeks - and patient is aged ≥65 years with no signs of clinically relevant symptom improvement.
12. Prescribed an antidepressant >12 months for anxiety - and patient has achieved full remission.
13. Prescribed an antidepressant for anxiety - and patient is co-prescribed benzodiazepine >4 weeks.
Insomnia
14. Prescribed TCA ≥50 mg/day for insomnia - and patient has no other indication for an antidepressant.

15. Prescribed trazodone ≥50 mg/day for insomnia - and patient has no other indication for an antidepressant.
16. Prescribed mirtazapine ≥30 mg/day for insomnia - and patient has no other indication for an antidepressant.
17. Prescribed a sedating antidepressant >8 weeks for insomnia - and patient has no other indication for an antidepressant.
Pain
18. Prescribed a TCA ≥75 mg/day for neuropathic pain - and patient has no other indication for an antidepressant.
19. Prescribed venlafaxine ≥150 mg/day for neuropathic pain - and patient has no other indication for an antidepressant.
20. Prescribed SSRI or mirtazapine for neuropathic pain - and patient has no other indication for an antidepressant.
21. Prescribed any antidepressant for non-specific low back pain - and patient has no other indication for an antidepressant.
22. Prescribed TCA or SNRI as analgesic for pain (e.g., pain other than neuropathic pain, tension headache, migraine or fibromyalgia syndrome) - and patient has no other indication for an antidepressant.
Miscellaneous
23. Prescribed any antidepressant - and patient has chronic heart failure and first episode of a mild or moderate depression.
24. Prescribed any antidepressant - and patient has dementia and first episode of a mild or moderate depression.
25. Prescribed agomelatine - and patient is aged ≥75 years.

Appendix: Development of a Study protocol

CONSORT statement 2010: checklist

Table 36: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial

Section/Topic	Item No	Checklist item	Reported on page No …
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	√
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	n/a
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	√
	2b	Specific objectives or research questions for pilot trial	√
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	√
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	√
	4b	Settings and locations where the data were collected	√
	4c	How participants were identified and consented	√
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	√
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	n/a
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	n/a
Sample size	7a	Rationale for numbers in the pilot trial	√

	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	n/a
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	n/a
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	n/a
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	n/a
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	√
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	√
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	n/a
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	n/a
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a

	19a	If relevant, other important unintended consequences	n/a
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	n/a
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	n/a
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	n/a
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	n/a
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	n/a
Protocol	24	Where the pilot trial protocol can be accessed, if available	√
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	√
	26	Ethical approval or approval by research review committee, confirmed with reference number	n/a

Source: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

CRISP: checklist and statements

Table 37: CRISP Checklist - Consensus Reporting Items for Studies in Primary Care (131)

Reporting Item - 1	Included?			Section*	Notes
	Y	N	N/A		
1. Include "primary care" and/or discipline-specific terms in the title, abstract, and/or key words.	√			I	-
Reporting Item - 2	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
2. Describe the study rationale and importance for primary care.					
2a. Explain the rationale for the research question and how it relates to primary care.	√			I	-
2b. Describe the importance or relevance of the topic under study in the primary care setting.	√			I	-
2c. Identify any theory, model, or framework used, and explain why it is appropriate to the research question in primary care.			X	I	-
Reporting Item - 3	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
3. Describe the research team's primary care experience and collaboration.					
3a. Describe the research team's expertise and experience in primary care practice and/or research.	√			M	See appendix to study protocol
3b. Describe whether and how primary care patients, practicing clinicians, community members, or other stakeholders were involved in the research process.	√			M	Study team: see QOREC Development->Interview study: GPs
Reporting Item - 4	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
4. Describe the study participants and populations in the context of primary care.					
4a. Use person-focused language to refer to the research populations and participants, or use terms based on patient preferences	√			R	Participants: general practitioners, patients
4b. If reporting personal characteristics of participants, report the source of the data,	√			R	GP's and patient's characteristics

the rationale for using it, and the rationale for any classifications used.					
4c. Describe the participants and populations in sufficient detail to allow comparison to other primary care patient populations.	√			R	GPs and patients in Southeast Bavaria
4d. Specify whether participants have pre-existing therapeutic relationships with the clinical team or are new patients.	√			M/R	All patients have pre-existing relationship with GPs
Reporting Item - 5	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
5. Describe the conditions under study in the context of primary care.					
5a. Describe whether the condition under study is acute or chronic.	√			M/R	Subacute or chronic depression/anxiety/panic
5b. Report how multimorbidity is considered and how it might affect interpretation of the study findings/ results.	√			M	Patients with multimorbidity and multimedication are Included
Reporting Item - 6	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
6. Describe the clinical encounter under study in the context of primary care.					
6a. Specify whether the study focus is an isolated clinical encounter or a longitudinal course of care. If it is an isolated clinical encounter, specify whether it is the first visit or a follow-up visit for the condition under study	√			M	If decision against deprescribing: one visit If decision for deprescribing: follow-up visits
Reporting Item - 7	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
7. Describe the patient care team.					
7a. If care is delivered by teams, describe the team members and their roles.	√			R	Only GP
7b. For each clinician category, report profession, specialty, and qualifications.	√			R	Incl. criteria
Reporting Item - 8	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
8. Describe the study interventions in the context of primary care.					
8a. Describe interventions and their implementation in sufficient detail to enable the reader to assess applicability in their own setting.	√			M	-

8b. Describe any clustering or grouping of patients, participants, clinicians, teams, or practices, and how it was addressed in the analysis.	√			M/R	Purposive sampling of GPs, only intervention group for patients
8c. Describe the health care system in sufficient detail to allow comparisons to other systems.	√			I/D	-
Reporting Item - 9	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
9. Describe study measures used and their relevance to primary care.					
9a. Report whether study measurement tools have been validated in primary care populations or settings.	√			M	-
9b. Describe how the measurement tools used are meaningful to primary care patients and their care.	√			M	-
9c. Report findings/results to be clinically interpretable by primary care clinicians and patients.			X	R	-
Reporting Item - 10	**Included?**			**Section***	**Notes**
	Y	**N**	**N/A**		
10. Discuss the meaning of study findings/results in the context of primary care.					
10a. Discuss implications of the study findings/results for research, patient care, education, and policy with specific focus on primary care.			X	D	-
10b. Discuss the implications of study recommendations on demands and priorities in primary care practice.			X	D	-
10c. Comment on any research processes that might influence the applicability of the study findings/results in diverse primary care settings.			X	D	-

√ Yes (fulfilled); X No (not fulfilled) / N/A (not applicable);
*Section: I = Introduction, M = Method, R = Results, D = Discussion

Statements on the CRISP-checklist

1. Include “primary care” in wordings

Item 1: Include “primary care” and/or discipline-specific terms in the title, abstract, and/or keywords. *Page x*

Statement: We included general practice in the title, and general practitioners as involved stakeholders throughout the abstract and key words. Page x

2. Describe the study rationale and importance for primary care

Item 2a: Explain the rationale for the research question and how it relates to primary care. *Page x*

Statement: In the introduction section, we described the increasing numbers of prescribed antidepressants worldwide and the need for more medication reviews. As most patients with antidepressants therapy are managed within primary care, it seems relevant to address general practices.

Item 2b: Describe the importance or relevance of the topic under study in the primary care setting. *Page x*

Statement: As most patients with depression, anxiety- and panic disorders as well as patients with antidepressants use, are managed in primary care, we identified this as most relevant area to work on. Further explanations are to be found in the introduction section of the study protocol.

Item 2c: Identify any theory, model, or framework used and explain why it is appropriate to the research question in primary care.

Statement: not applicable as no framework will be used

3. Describe the research team’s primary care experience and collaboration

Item 3a: Describe the research team's expertise and experience in primary care practice and/or research.

Statement: Our project team included a general practice residency (JV), a pharmacist and PhD candidate (V.B.), a pharmacist, professor in pharmacy (T.B.) and a biologist, clinical scientist (L.S.). See COREQ-32 checklist in the appendix for more details.

Item 3b: Describe whether and how primary care patients, practicing clinicians, community members, or other stakeholders were involved in the research process. *Page x*

Statement: Patients have not been involved in the development process of the study protocol

4. Describe the study participants and populations in the context of primary care

Item 4a: Use person-focused language to refer to the research populations and participants, or use terms based on patient preferences. *Page x*

Statement: Documents for GPs were written in a more sophisticated way while documents for patients have been written in inclusive language.

Item 4b: If reporting personal characteristics of participants, report the source of the data, the rationale for using it, and the rationale for any classifications used. *Page x*

Statement: Personal characteristics of GPs have been collected by questionnaires and face-to-face interviews while characteristics of the patients have been collected via questionnaires, telephone interviews, and personal interview performed by GPs (if invited by GPs for the interventional deprescribing conversation).

Item 4c: Describe the participants and populations in sufficient detail to allow comparison to other primary care patient populations. *Page x*

Statement: We plan to include (a) actively working general practitioners in the area of Southeast Bavaria (Germany) who would use and test feasibility, usability und effectivity of the intervention, (b) patients of this general practitioners which were identified by the checklist.

Item: 4d: Specify if participants have pre-existing therapeutic relationships with the clinical team or are new patients. *Page x*

Statement: All patients that will be included have existing relationship to and are known by their GPs

5. Describe the conditions under study in the context of primary care

Item 5a: Describe if the condition under study is acute or chronic. *Page x*

Statement: We will include patient which have a subacute or chronic depression (one or several episodes) or anxiety- and panic disorders under active antidepressant therapy. Page x

Item 5b: Report how multimorbidity is considered and how it might affect the interpretation of the study findings/results. *Page x*

Statement: We will include patients diagnosed with only depression/anxiety- and panic disorders or with depression/anxiety- and panic disorders and other diseases. Additionally, persons will be included if taking at least three other medications.

6. Describe the clinical encounter under study in the context of primary care

Item 6a: Specify if the study focus is an isolated clinical encounter or a longitudinal course of care. If it is an isolated clinical encounter, specify if it is the first visit or a follow-up visit for the condition under study. *Page x*

Statement: We include patients that have been identified by the checklist and that will be invited for a conversation on potential deprescribing (if indicated) with the GPs. If decision will be made against discontinuation of an antidepressant, there will be now follow-up visit with the GPs. If decision will be made in favour for discontinuation,

there will be follow-up visits for antidepressant tapering between GPs and the patients. Regarding these follow-ups, data will only be collected via interviews with GPs and patients after tapering.

7. Describe the patient care team

Item 7a: If care is delivered by teams, describe the team members and their roles. *Page x*

Statement: A team is not required to participate in the study. Care will be delivered by the GPs only. Nurses of the general practices will not intentionally be involved, but may support the GPs in scheduling consultations for medication review conversations between GPS and patients, which may include the consideration of deprescribing where clinically appropriate.

Item 7b: For each clinician category, report profession, specialty, and qualifications. *Page x*

Statement: For our study, all GPs are required to have several years of experiences in general practice and need to treat a minimum of patients, including those that are members of the statutory health insurance. Further requirements are stated in the inclusion/exclusion criteria.

8. Describe the study interventions in the context of primary care

Item 8a: Describe interventions and their implementation in sufficient detail to enable the reader to assess applicability in their own setting. *Page x*

Statement: The intervention comprises the checklist which helps identifying patients with deprescribing potential, a patient empowerment brochure to ensure an informed patient, a face-to-face conversation between GPs an patients.

Item 8b: Describe any clustering or grouping of patients, participants, clinicians, teams, or practices and how it was addressed in the analysis. *Page x*

Statement: Purpose sampling of general practitioners through online registries, mouth-to-mouth, institute's research network. Patients will be chosen upon criteria of the checklist and GPs own inclusion criteria (e.g. capability, compliance of the patient). For the pilot study there will only be the intervention group.

Item 8c: Describe the healthcare system in sufficient detail to allow comparisons to other systems. *Page x*

Statement: Germany's healthcare system is structured as a dual system comprising statutory health insurance (GKV) and private health insurance (PKV). The GKV covers about 90% of the population and is primarily funded through income-based contributions, while the PKV serves as an alternative for high-earning employees, self-employed individuals, and civil servants, with premiums based on individual health status and age. Patients are allowed to freely chose medical institutions including general practices. Medical consultations are paid by the health insurance.

Medication GKV: Medications prescribed by a doctor are generally covered by the GKV. The pharmacy bills the insurance directly. Patients usually pay a co-payment

of 10% of the medication cost, with a minimum of €5 and a maximum of €10 per prescription. For some chronic diseases or long-term therapies, there might be exemptions or reduced co-payments.

Medication PKV: Patients initially pay for the medications out of pocket and then submit the receipts to their private insurer for reimbursement. Co-payments and coverage limits vary based on the specific terms of the insurance contract, which can differ significantly from one policy to another.

9. Describe study measures used and their relevance to primary care

Item 9a: Report if study measurement tools have been validated in primary care populations or settings. *Page x*

Statement: Following validated patients questionnaires will be used. Charlson Comorbidity Index, Regensburg Insomnia Scale, PHQ-9, GAD-7, PHQ-15, PTSD5, Patient Assessment of Chronic Care

Item 9b: Describe how the measurement tools used are meaningful to primary care patients and their care. *Page x*

Statement: The questionnaires are mainly used to identify differences between patients who decided for deprescribing and patients who did not want to discontinue their antidepressant. With this we eventually aim to find factors that are associated with positive outcome, i.e. severity of depression, insomnia, comorbidities. This helps to specify for which patients the checklist might be helpful.

Item 9c: Report findings/results in forms that are clinically interpretable by primary care clinicians and patients.

Statement: not applicable

10. Discuss the meaning of study findings/results in the context of primary care

Item 10a: Discuss implications of the study findings/results for research, patient care, education, and policy with specific focus on primary care.

Statement: not applicable

Item 10b: Discuss the implications of study recommendations on demands and priorities in primary care practice.

Statement: not applicable

Item 10c: Comment on any research processes that might influence the applicability of the study findings/results in diverse primary care settings.

Statement: not applicable

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Thank you to everyone who helped make this work possible.

D A N K E

Affidavit

Affidavit

Vukas, Jochen
Surname, first name

I hereby declare, that the submitted thesis entitled:

Development of an Intervention for Antidepressant Deprescribing in Primary Care:

Qualitative Assessment of Implementation Factors
and
Systematic Guideline Review

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.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Munich, 7th January 2026
Place, Date

Jochen Vukas
Signature doctoral candidate

Cofirmation of congruency

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Confirmation of congruency between printed and electronic version of the doctoral thesis

Doctoral candidate: Jochen Vukas

I hereby declare that the electronic version of the submitted thesis, entitled

Development of an Intervention for Antidepressant Deprescribing in Primary Care: Qualitative Assessment of Implementation Factors and Systematic Guideline Review

is congruent with the printed version both in content and format.

Munich, 7th January 2026 — Jochen Vukas

Place, Date — Signature doctoral candidate

Congruency of submitted versions — Date: 7th January 2026

List of Publications

Original papers

Eder J, Pfeiffer L, Wichert SP, Keeser B, Simon MS, Popovic D, Glocker C, Brunoni AR, Schneider A, Gensichen J, Schmitt A, Musil R, Falkai P; POKAL Group (POKAL Group: Tobias Dreischulte, Peter Henningsen, Markus Bühner, Katharina Biersack, Constantin Brand, Vita Brisnik, Christopher Ebert, Feyza Gökce, Carolin Haas, Lukas Kaupe, Jonas Raub, Philipp Reindl-Spanner, Hannah Schillock, Petra Schönweger, Victoria von Schrottenberg, **Jochen Vukas**, Puya Younesi, C Jung-Sievers, Helmut Krcmar, Karoline Lukaschek, Kirsten Lochbühler, Gabriele Pitschel-Walz) Deconstructing depression by machine learning: the POKAL-PSY study Eur Arch Psychiatry Clin Neurosci. 2023 Dec 13. doi: 10.1007/s00406-023-01720-9. Epub ahead of print. PMID: 38091084.

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