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The role of pharmacists in deprescribing benzodiazepines: A scoping review

Fatemah Zakariya Ashkanani *, Adam Pattison Rathbone, Laura Lindsey

School of Pharmacy, Faculty of Medical Sciences, Newcastle University, King George VI Building, Newcastle upon Tyne, Tyne and Wear NE2 7RU, United Kingdom

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ABSTRACT

Background: Polypharmacy can increase the risk of adverse drug events, hospitalisation, and unnecessary healthcare costs. Evidence indicates that discontinuing certain medications, such as benzodiazepines, can improve health outcomes, by resolving adverse drug effects. This scoping review aims to explore the pharmacists' role in deprescribing benzodiazepines.

Method: A scoping review has been conducted to distinguish and map the literature, discover research gaps, and focus on targeted areas for future studies and research. A systematic search strategy was conducted to identify relevant studies from PubMed, Medline, and EMBASE databases. The eligibility criteria involved studies that focused on the role of pharmacists in benzodiazepine deprescribing, quantitative and qualitative studies conducted in humans, full-text articles published in English.

Results: Twenty studies were identified, revealing three themes: 1) pharmacists' involvement in benzodiazepine deprescribing, 2) the impact of their involvement, and 3) obstacles impeding the process. Pharmacists involved in deprescribing procedures, mainly through completing medication reviews, collaborative work with other healthcare providers, and education. Pharmacists' involvement in benzodiazepine deprescribing intervention led to better health and economic outcomes. Withdrawal symptoms after medication discontinuation, dependence on medication, and lack of time and guidelines were identified in the literature as barriers to deprescribing.

Conclusion: Pharmacists' involvement in deprescribing benzodiazepines is crucial for optimizing medication therapy. This scoping review examines the pharmacists' role in benzodiazepine deprescribing. The findings contribute to enhancing healthcare outcomes and guiding future research in this area.

1. Introduction

Deprescribing can be defined as balancing the potential for benefit and risk by systematically withdrawing inappropriate medications to manage polypharmacy and improve health outcomes.[1] Polypharmacy and the use of potentially inappropriate medications (PIMs) can increase the risk of adverse drug reactions (ADR), hospitalisation, and geriatric syndromes. It has also been linked to unnecessary healthcare costs.[2–4] Deprescribing interventions include identifying inappropriate drugs to be stopped, replaced, or decreased, developing a procedure in collaboration with the patient, supporting the patient, and regularly reviewing their medications.[5] Therefore, deprescribing includes a multifaceted approach to promote more appropriate medication use.

Evidence shows that the cessation of certain medications improves patient health outcomes by resolving ADR.[6] Deprescribing also enhances adherence to other medications and decreases financial costs.[6] However, some harmful effects have been linked to deprescribing, such as withdrawal symptoms and a rebound of the underlying disease.[6] Consequently, patients might resume taking the medication shortly after it has been deprescribed.[7] This suggests that deprescribing presents both facilitators and barriers.

Effective planning for deprescribing, which includes careful tapering, monitoring, and following up with patients after the intervention, can mitigate potential harmful effects of deprescribing.[6] Although deprescribing is an essential component of medication management, healthcare professionals (HCP) often concentrate on developing guidelines for initiating medications; this emphasis results in a notable absence of guidance on discontinuing medications.[8–10] This indicates the need for further research to explore how HCP make decisions about deprescribing and what factors influence their approach to this process.

Benzodiazepines (BZDs) are widely prescribed medications globally, especially in elderly. They are often prescribed for anxiety and sleep disorders. However, their use has been linked to various ADR, including

* Corresponding author: King George VI Building, Newcastle upon Tyne, Tyne and Wear NE2 7RU, United Kingdom.
E-mail addresses: F.Z.A.M.A.Ashkanani2@newcastle.ac.uk (F.Z. Ashkanani), Adam.Rathbone@newcastle.ac.uk (A.P. Rathbone), Laura.lindsey@newcastle.ac.uk (L. Lindsey).

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dependency and addiction, as abrupt cessation can lead to withdrawal symptoms.[11] Furthermore, long-term use of BZDs increases anxiety, worsens insomnia,[12] impairs cognitive function,[13] leads to Alzheimer's disease,[14] asthenia, and falls,[15] which can result in increased healthcare costs.[16] Therefore, careful consideration is required when prescribing BZDs.

According to British Medical Association and Royal Pharmaceutical Society, BZDs should be prescribed for short-term use (2–4 weeks)[17]; however, evidence suggests that BZDs are typically used for longer periods.[18,19] Despite the well-documented ADR of long-term use of BZDs, BZDs usage in European countries persists at 2–3% of the general public.[20] Moreover, the number of BZD prescriptions in the United States of America (USA) has surged, associated with a four-fold rise in BZD-related overdose deaths.[21] Several studies identified potentially inappropriate use of BZDs among patients following a medication review.[22–25] Given these findings, there is an urgent need to explore the deprescribing of BZDs.

Pharmacy services improved patient outcomes and reduced healthcare costs, particularly among the elderly and those taking PIMs.[26–28] Deprescribing is a crucial intervention that pharmacists can deliver across different medical settings. Numerous studies illustrated that pharmacists involved in deprescribing for range of medications, including antidiabetics,[29] non-steroidal anti-inflammatory drugs (NSAIDs),[30] anticholinergics,[31,32] proton pump inhibitors,[33] and non-statin lipid-lowering medication,[34] resulting in positive health and economic outcomes.[26,30] Thus, pharmacists can play a vital role in deprescribing, contributing to enhanced patient outcomes and more efficient utilization of healthcare resources.

This review aims to explore the pharmacists' role in deprescribing BZDs by identifying how pharmacists are involved in deprescribing interventions in different health settings, the impact of their involvement in the deprescribing process, and the barriers they face in the deprescribing process.

2. Method

A scoping review was undertaken to map the existing literature, identify research gaps, and focus on targeted areas for future studies and research.[35] The review underwent following stages: formulating the research question, identifying relevant articles through specific databases, extracting data, selecting themes, and constructing findings. This methodical approach allowed for a comprehensive analysis of the available literature, providing insights into the current state of knowledge in the field and informing future research directions.

2.1. Search strategy

Rigorous searches were completed on PubMed, Medline, and EMBASE to identify relevant studies. The search strategy was constructed individually in each database to use the appropriate terms.

2.2. Searches

Twenty studies were identified through the screening. The screening process that performed in November 2022 is presented in Fig. 1. A list of keywords was identified to cover all the available previous studies on pharmacists' roles in deprescribing BZDs. These keywords are “pharmacist”, “pharmacy”, “pharmacies”, “deprescribing”, “deprescription”, “benzodiazepine”, “hypnotic”, and “sedative”. The keywords within a concept were combined using OR and concepts with AND (see Table.1).

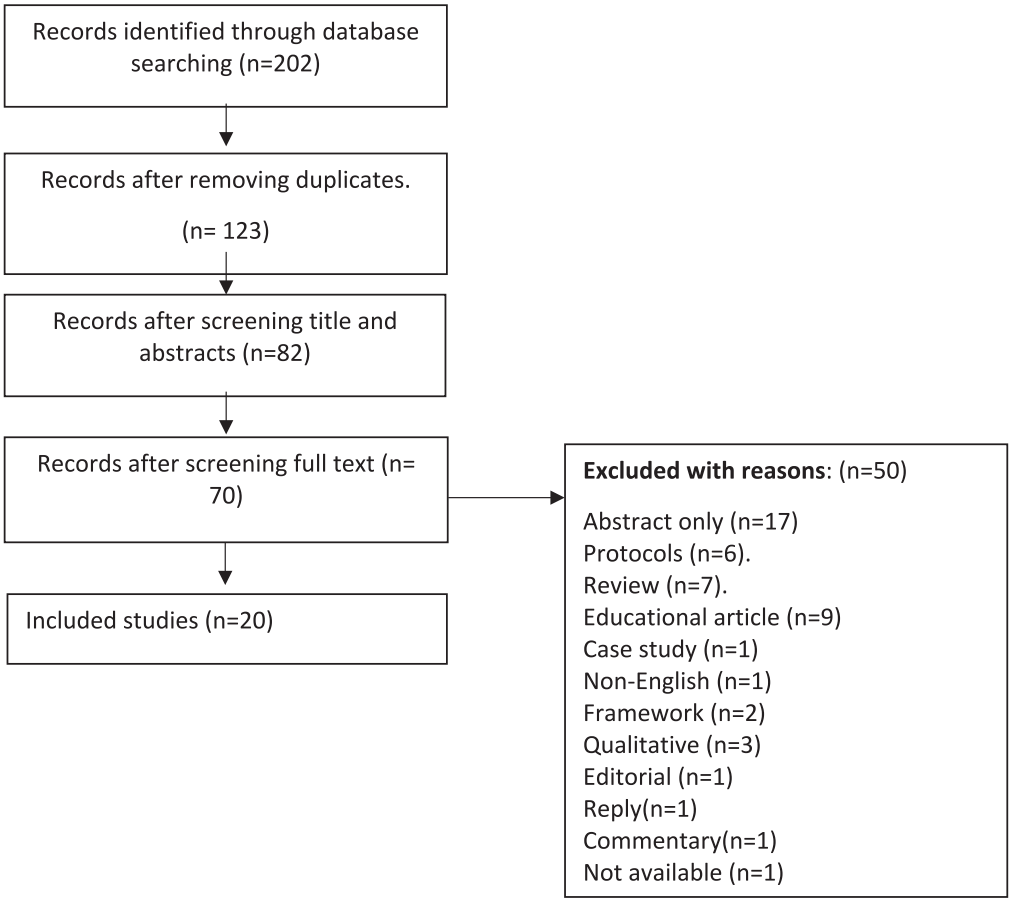

Fig. 1. PRISMA diagram.

Table 1
Table of Search Terms.

Database	Keywords
PubMed	("pharmacist*"[Title/Abstract] OR "pharmacy"[Title/Abstract] OR "pharmacies"[Title/Abstract] AND ("deprescribing"[Title/Abstract] OR "deprescription*"[Title/Abstract] AND ("benzodiazepine*"[Title/Abstract] OR "hypnotic*"[Title/Abstract] OR "sedative*"[Title/Abstract])
Medline	Pharmacist OR pharmacists OR pharmacy OR pharmacies AND deprescribing OR deprescription AND benzodiazepine OR benzodiazepines OR hypnotic OR hypnotics OR sedative OR sedatives.
EMBASE	Pharmacist OR pharmacists OR pharmacy OR pharmacies AND deprescribing OR deprescription AND benzodiazepine OR benzodiazepines OR hypnotic OR hypnotics OR sedative OR sedatives.

2.3. Study selection

Titles and abstracts were screened for relevance, and full texts were selected using eligibility criteria. Eligible studies i) related to pharmacists' role in BZD's deprescribing, ii) quantitative research in humans, iii) were published and available as full-text articles, and iv) were in English. The only exclusion criteria were that articles did not meet the eligibility criteria; this included studies that i) focused on other healthcare professionals, ii) were only available as an abstract, iii) were not written in English, iv) did not report empirical research (adverts, editorials, protocols, practice papers), v) was not in humans (lab research, animal research, and simulations).

2.4. Data syntheses

Data were extracted from all relevant articles in a summary table, including authors' names, year of the study, country, method used, participants, and outcomes. The literature has been categorised according to methodological trends, research areas, and key findings from deductive analysis focusing on three questions. The review's objectives were the guiding questions through data extraction and analysis, and each question has been recognised as the main theme.[36] These questions are how pharmacists are involved in deprescribing interventions; what the impact of their involvement in the deprescribing process is; and what are the potential barriers that could impede the success of deprescribing interventions. The gaps and themes have been identified through the data extraction and analysis process from the existing literature.[36]

3. Results

The twenty studies included in the review were conducted in different health settings: hospitals ($n = 8$),[37–44] community pharmacies ($n = 4$),[25,45–47] and primary care centres ($n = 2$).[24,48] Other settings include intermediary care, such as subacute medical outpatient clinics,[22] residential care settings,[23,49] long-term care,[50] nursing facilities,[51] and geriatric oncology clinics at cancer centres.[52] Most of the studies were conducted in high-income countries, including Canada ($n = 7$),[38,43,45–48,50] United States of America ($n = 4$) (USA),[24,37,39,52] Australia ($n = 3$),[41,44,49] Denmark ($n = 2$),[22,40] and Netherlands (n = 2).[25,51] Only one study was done in a middle-income country, India.[42] While the database search was not restricted by date, the majority of the studies were conducted in recent years, with four in 2021,[22,24,47,48] one in 2020,[40] six in 2018,[23,25,37–39,42] six in 2019,[43,45,49–52] and one in each of the following years: 2016,[41] 2015,[44] and 2014.[46] Most of the study's population was elderly.[23,25,38–41,43,45–47,49,51,52]

Three themes were generated from the review's objectives:

1) How are pharmacists involved in the deprescribing of BZDs?
2) What is the impact of their involvement in BZD deprescribing practices?
3) What are the potential obstacles that could hinder the accomplishment of deprescribing interventions?

4. How are pharmacists involved in the deprescribing of BZD?

4.1. Collaboration: medication review, patient conversations, and follow up

Pharmacists have collaborated with physicians to deliver deprescribing services. In four studies, pharmacists recommended physicians to deprescribe BZDs, following a comprehensive medication review using several tools.[22–25] Pharmacists' recommendations were based on their knowledge, experience, and specific guidelines related to each disease.[24] Pharmacists also had a motivational conversation with the patients about deprescribing[22] and followed up with them after implementing the intervention regularly.[22,23]

One study evaluated the collaborative efforts between pharmacists and geriatricians in deprescribing within an emergency department for elderly patients. In this context, pharmacists conducted a complete medication review using screening tools and checked the appropriateness of the prescribed medications.[40] Recommendations were made to stop PIMs, which were then discussed with the geriatrician, who held the authority to endure or reject these suggestions.[40]

Blenk et al. (2018) described a successful deprescribing intervention at a newly admitted psychogeriatric nursing facility, where pharmacists and physicians collaborated closely.[53] Each conducted a separate medication review, comparing patients' medical conditions with their prescribed medicines and identifying ADR.[53] Based on these findings, a treatment plan was developed and then discussed with the patient's official representative.[53] After implementing the changes, patients were followed up to monitor their progress.[53]

Pharmacists also participated in BZD deprescribing services using a combination of medication review, patient education, and healthcare professional counselling.[38] They collaborated with physicians to reach the optimal outcome. The pharmacist's key role was to obtain a medication history through medication reconciliation and have a direct conversation with the patients about BZDs usage and its side effects to involve them in shared decision-making as well as follow up with them after the intervention.[38]

An Indian study by Shilpa., et al. (2019) reports another instance of collaboration between pharmacists and psychiatrists, where the pharmacists recommended deprescribing BZDs and *Z*-drugs to inappropriate users.[42] The deprescribing intervention encompassed a multifaceted approach, including a thorough medical and medication review, identification of inappropriate use of BZDs and Z-drugs, Involvement of patient and psychiatrist in discussions, implementation of the intervention, and diligent monitoring of patients for rebound symptoms on a bi-monthly basis.[42]

In a study evaluating the effect of collaborative work on deprescribing, a clinical pharmacist who was part of a multidisciplinary team took a medication history, detected potential drug or disease interactions, and identified possible harmful medications.[41] The pharmacists also worked with a physician to discontinue or taper potential drugs; the patient was later involved in the intervention discussion. At follow-up visits, the pharmacist confirmed medication changes, while the physician evaluated their clinical impact, suggesting further adjustments if required.[41]

Pharmacists also assessed the deprescribing intervention's effect in a randomised trial on short-term delirium outcomes for adult patients using BZDs.[37] The intervention group used a computerized alert system for deprescribing. Upon alert, a pharmacist reviewed the medication, identified prescribed BZDs and anticholinergics, and collaborated with the medical team for deprescribing.[37] A key factor within this research was the interprofessional collaboration that supported deprescribing.

This section highlighted the importance of collaboration and effective communication between HCP to improve medication management

and promote patient safety, as well as the importance of a patient-centred approach that considers each patient's unique needs and circumstances.

4.2. Education

Consultant pharmacists and community pharmacies were involved in the Reducing Use of Sedatives (RedUSe) intervention, including BZDs, in residential aged care facilities in Australia.[49] The community pharmacies provided the prescribing data, and the consultant pharmacists were responsible for educating the staff about psychotropic medications and non-pharmacological treatments for managing behavioural and psychological symptoms of dementia, anxiety, and insomnia.[49] The pharmacists were trained on implementing RedUSe, and the interdisciplinary review was encouraged to occur every three months, including recommendations from pharmacists and nurses.[49]

Another randomised trial compared the success of pharmacist-led educational interventions versus usual care on deprescribing PIMs, including BZDs.[45] The pharmacists in the intervention group distributed educational material to patients and prescribers. The educational material for patients contained PIMs, reasons, solutions, and tapering schedules for sedative-hypnotics, while the physicians' educational material contained evidence-based pharmacists' perspectives and recommendations on deprescribing.[45]

In keeping with the previous study's findings, a randomised control trial was conducted to assess the impact of a pharmacist's direct-to-patient education compared to receiving usual care on BZDs cessation in older adults.[46] In the intervention group, the pharmacist explained the BZDs usage risks and described the stepwise tapering process to patients.[46]

Another study by Whitman., et al. (2018) showed that pharmacists conducted medication assessment and deprescribing for elderly patients with cancer and polypharmacy through multiple screening tools to identify PIMs. Instructions, reasons for deprescribing, and tapering processes were given to patients and their caregivers. Patients were then followed up regarding medication changes.[52] The critical role across these studies was pharmacists being the educators as effective deprescribing interventions require a strong foundation of knowledge and skills.

4.3. Cognitive behavioural therapy for insomnia

Evidence showed pharmacists managed sedative-hypnotic deprescribing for patients referred by physicians in team-based primary care practice. As an alternative, cognitive behavioural therapy for insomnia (CBT—I) was delivered to some participants (who had sleep disorders when they were referred) by a pharmacist or a social worker.[48] Pharmacists collaborated with patients and worked on deprescribing by following EMPOWER trials and clinical guidelines. The patients had been followed up regularly in person or by phone by the pharmacist.[48]

4.4. Guidelines

Two studies showed that pharmacists implemented deprescribing guidelines to deliver deprescribing interventions and evaluate their feasibility and impact.[25,50] Additionally, in a study done by Lindsay., et al. (2015), pharmacists were involved in developing and assessing deprescribing guidelines in palliative care.[44] This is consistent with the study undertaken by Feldman. et al. (2019) showed that pharmacists had the authority to apply the deprescribing guideline developed by the hospital to identify and deprescribe high-risk medications, including BZDs.[39] This implies that deprescribing guidelines can help provide guidance and structure for pharmacists and other healthcare professionals in the deprescribing process.

5. What is the impact of pharmacist involvement in BZD deprescribing practices?

This theme focuses on the quantity of deprescribing reported in the literature and the reported cost reduction.

Pharmacist-doctor collaboration effectively enhanced the deprescribing process.[22,23,25,40,53] In one study, 69% (32 out of 52) of medications identified by pharmacists for deprescribing were stopped by the physician, and BZDs were one of the most frequently deprescribed medications in this study.[22] Another recent study found that general practitioners (GPs) followed 72% (33 out of 45) of the deprescribing recommendations made by pharmacists for sedatives following peer-reviewed deprescribing guidelines.[23] As a result, the number of prescribed medicines decreased substantially, and the health outcomes, such as mood, falls, and frailty, and decreasing ADR, improved significantly.[23]

Physicians in another collaborative study agreed with the pharmacists' recommendations on 108 patients out of 212; and with suggestions to change medications in 97 patients.[25] Temazepam was one of the most proposed inappropriate medications that required cessation.[25] Moreover, the geriatrician in the emergency department implemented 95 (out of 106) of the clinical pharmacist recommendations on medicine changes and 79 of these changes was continued 30 days after discharge.[40] In detail, 66 medications were deprescribed in 33 patients, and BZDs were one of the drug classes where the intervention revealed the most considerable development in the medication appropriateness index between admission and 30 days after discharge.[40] Additionally, physicians and nurses in home-based primary care accepted 53 out of 175 pharmacists' recommendations. Twenty-seven medications were stopped out of 81 recommended to be deprescribed; BZDs were on the list of (PIMs).[24]

A study conducted in the Netherlands, where pharmacists and physicians collaborated to deprescribe medications in a nursing facility, was associated with 59.7% (out of 150) of the advised changes made and 55.3% of them concerned ten groups of medications, which include BZDs.[53] In multidisciplinary outpatient clinics for frequently attending patients, collaborative work between pharmacists and HCP in deprescribing interventions led to a substantial decrease in medication count and tablet load, including BZDs.[41]

It has been shown that pharmacists' conversations with patients by informing them about their treatment plans, the reasons for changes, and the aims of deprescribing achieved a high rate of deprescribed medications.[22,38,45] It has also been reported that pharmacists' collaboration with physicians using a combination of medication review, written educational material, and direct patient counselling led to discontinuations of BZDs in six out of 11 hospitalised patients (55%) and >50% of dose reduction of BZDs in the five remaining patients. Significantly, the patients reported that the direct counselling sessions they received from pharmacists and physicians were the most effective intervention in promoting encouragement, education, and shared decision-making.[38] Moreover, following up with patients after deprescribing was reported to be effective in continuing the cessation of the stopped medications.[22,38]

In a study involving pharmacists educating patients, the intervention group comprised 146 individuals identified as sedative-hypnotic users. Of these, 115 patients had discussions with either their physician or pharmacist regarding deprescribing, ultimately leading to 58 patients discontinuing their medication.[45] Moreover, the success of direct-patient education in promoting shared decision-making was also supported by another study that reported a higher rate of BZD discontinuation (27%) in the intervention group compared to the usual care group (5%) after six months.[46]

Sleep quality was gradually improved after deprescribing BZDs and *Z*-drugs in an Indian study.[42] Furthermore, pharmacists involved in deprescribing had a positive economic effect on healthcare costs,[24,42,45,47,52] as a substantial cost reduction has been reported after

BZDs deprescribing.[42]

Approximately 33% of patients who participated in sedative-hypnotic deprescribing programs led by pharmacists achieved a cessation or dose reduction of ≥50%[48]; the percentage of participants who discontinued the medication or reduced the dose was more significant with CBT-I.[48] Pharmacists in the RedUSe intervention significantly decreased the prescription rate of antipsychotics and BZDs, resulting in positive clinical outcomes.[49] However, one study showed no difference in the delirium outcomes after deprescribing intervention delivered by a combination of a computerized alert system with pharmacist support.[37]

6. What are the barriers to the deprescribing process?

The barriers mentioned in the literature that reduced the success of deprescribing interventions have been divided into patient-, practitioner-, and study-related barriers.

6.1. Patient-related barriers

Several patient-related barriers were identified in the literature, including patients or caregivers not being ready to make changes,[24,38,51] patient preference to continue using the medications, and patients' unsuccessful dose reduction.[39] Dependence[45,52] and lack of concern about the harmful effects were other reasons for rejecting the tapering process.[45] Moreover, Carr., et al. (2018) highlighted that deprescribing BZDs could be challenging due to the risk of worsening anxiety symptoms.[54]

Concerns over the potential return of symptoms or exacerbation of their condition are common reasons why patients hesitate to receive deprescribing interventions.[51] Findings from Shilpa., et al. (2019) supported this by reporting that patients were often advised to continue taking BZDs when the drug was deemed necessary for managing conditions that may lead to or worsen insomnia.[42] Other studies confirmed the previous barrier by reporting that deprescribing was not beneficial because of the withdrawal symptoms or exacerbated symptoms after reducing the dose or withdrawing the medication.[38,45,53]

6.2. Practitioners-related barriers

Physicians' or pharmacists' discouragement of initial tapering[38] and physician decision to continue using the treatments based on patient needs or clinical judgment[24] were also reported in the studies as a reason to reject deprescribing recommendations. Furthermore, the HCP mentioned the lack of clear deprescribing guidelines as a barrier to implementing pharmacists' recommendations on deprescribing PIMs.[24] Even though the medical team acknowledged their achievement in deprescribing some PIMs in primary care, they expressed a desire to deprescribe additional medications if they had access to pharmacists who could provide step-by-step recommendations on de-escalating therapy and discuss the plan directly with the patient's family.[24]

6.3. Study-related barrier

Lack of time was mentioned in two studies as a barrier to continuing the deprescribing[24,38] as the tapering process takes time to be completed; however, patients aimed to continue the deprescribing process with their GP after finishing the research.[38]

7. Discussion

The findings in this review indicates that pharmacists' involvement in BZD deprescribing led to better health and economic outcomes. Pharmacists have been involved in deprescribing procedures, mainly by completing medication reviews and collaborating with patients and HCPs. They also engaged in deprescribing interventions through education.

The review highlights potential facilitators of deprescribing that warrant attention in future research. These include shared decision-making with patients or their caregivers, involving them in treatment plan conversations, and educating them about the appropriate use of BZDs.[23,38,42,45,51] It is noteworthy that in one of the studies, BZD users were not provided with education about appropriate BZD use[38]; this could be a reason for increasing the inappropriate use of BZDs.

Conversations between pharmacists, physicians, and patients' caregivers resulted in patient caregivers' high acceptance of medication change recommendations.[51] Patients also mentioned that person-to-person supportive counselling was most helpful in promoting informed and shared decision-making, more so than the educational flyers, as they liked the social interaction and the fact that they could ask questions and obtain the answers directly from the pharmacists.[38]

Another positive factor that increased the success of deprescribing is a structured medication review which the pharmacists undertook in most studies. Additionally, collaboration between pharmacists and healthcare professionals led to successful deprescribing[34,36,44]; however, this could be improved in some settings, especially in community pharmacies, where pharmacists found it challenging to contact the GP. Following up with patients after providing treatment is also one of the factors that made the deprescribing successful.[22,38]

The previous facilitators should be taken into consideration in future deprescribing interventions. For example, to incorporate structured medication reviews into the deprescribing process, pharmacists can undergo additional training on conducting these reviews and identifying PIMs using validated tools. Furthermore, deprescribing interventions may involve frequent meetings or communication channels between pharmacists and HCPs to build good relationships between them. Electronic health records and telemedicine to facilitate communication and information sharing can be used in settings where communication between HCP is challenging.

To improve the patients' shared decision-making, pharmacists should use clear, simple language, listen actively, and allow them to ask questions and express their concerns. Additionally, patient education, respecting patient autonomy, and sharing responsibility can help patients make informed decisions about their healthcare. It might also be helpful to apply visual aids to help patients understand the options available.

A single study reported the integration of CBT-I to support the BZDs deprescribing process, which significantly improved the deprescribing process.[48] Further studies including CBT-I in their interventions are needed to examine its effectiveness in BZD deprescribing. Another study mentioned using a computer system to alert the use of BZDs in patients with delirium. Still, it did not influence medication use in participants.[48] More studies are needed to explore using this computer system to implement it in practice and think of strategies to overcome the barriers described.

Limited studies have been performed in community pharmacies about deprescribing of BZDs; however, there is a need for specific guidelines and policies to follow, especially in community pharmacies, to guide them in deprescribing BZD and inform them on the best way to collaborate with the doctors. Moreover, the majority of the studies focused on elderly population; therefore, more studies are needed in supporting deprescribing in younger people as BDZ is also taken by them and support is needed around safe tapering.

Other limitations in the review, such as, the limited number of evidence sources used and a restriction to articles published in English may have led to some evidence potentially being missed. However, despite these limitations, the study is the first to explore pharmacists' roles in deprescribing BZDs by synthesising data from the published literature, using a systematic method to identify and standardised method to codifying data to provide a novel perspective of pharmacists' roles in BZDs deprescribng.

8. Conclusion

Pharmacists played a vital role in BZD deprescribing by conducting medication reviews, collaborating with other HCPs, and educating patients. These interventions have been associated with improved health and economic outcomes. However, several obstacles to deprescribing have been identified in the literature, including withdrawal symptoms, dependency, and the lack of time and guidelines to support the deprescribing process. Future interventions could address these barriers and incorporate strategies to support shared decision-making and patient-centred care to improve the deprescribing procedure. By working collaboratively and adapting interventions to patients' preferences, pharmacists and other HCPs can improve the quality of care for patients and reduce the risk of ADR.

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Contribution

The design development was done by Fatemah Ashkanani and Laura Lindsey. Data collection, analysis, and write up were done by Fatemah Ashkanani and has been reviewed and edited by Laura Lindsey and Adam Rathborne. All authors have read and agreed to the published version of the manuscript. All authors have contributed significantly to the publication.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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