THERAPEUTIC ADVANCES in
Psychopharmacology

Review

Optimizing treatment for older adults with depression

Ther Adv Psychopharmacol

2023, Vol. 13: 1–14

DOI: 10.1177/20451253231212327

Maytinee Srifuengfung, Bethany R. Tellor Pennington and Eric J. Lenze

***Abstract*:** This review presents a comprehensive guide for optimizing medication management in older adults with depression within an outpatient setting. Medication optimization involves tailoring the antidepressant strategy to the individual, ensuring the administration of appropriate medications at optimal dosages. In the case of older adults, this process necessitates not only adjusting or changing antidepressants but also addressing the concurrent use of inappropriate medications, many of which have cognitive side effects. This review outlines various strategies for medication optimization in late-life depression: (1) Utilizing the full dose range of a medication to maximize therapeutic benefits and strive for remission. (2) Transitioning to alternative classes (such as a serotonin and norepinephrine reuptake inhibitor [SNRI], bupropion, or mirtazapine) when first-line treatment with selective serotonin reuptake inhibitors [SSRIs] proves inadequate. (3) Exploring augmentation strategies like aripiprazole for treatment-resistant depression. (4) Implementing measurement-based care to help adjust treatment. (5) Sustaining an effective antidepressant strategy for at least 1 year following depression remission, with longer durations for recurrent episodes or severe presentations. (6) Safely discontinuing anticholinergic medications and benzodiazepines by employing a tapering method when necessary, coupled with counseling about the benefits of stopping them. Additionally, this article explores favorable medications for depression, as well as alternatives for managing anxiety, insomnia, allergy, overactive bladder, psychosis, and muscle spasm in order to avoid potent anticholinergics and benzodiazepines.

Keywords: anticholinergic, benzodiazepine, central nervous system, elderly, depression, drug tapering, guideline, insomnia, sedatives and hypnotics

Received: 31 May 2023; revised manuscript accepted: 18 October 2023.

Correspondence to:
Maytinee Srifuengfung
Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Avenue, PO Box 8134, St. Louis, MO 63110, USA

Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
maytinee.sff@gmail.com

Bethany R. Tellor Pennington
Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA

Eric J. Lenze
Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Introduction

Aging and mental illness present a challenge for patients and practitioners. Late-life depression often arises in the context of medical comorbidities, cognitive impairment, socioeconomic decline, and bereavement. Because depression is common, the utilization of antidepressants is widespread in individuals aged 60 and above, with approximately 19% reporting usage.[1] However, a considerable proportion of this population receives suboptimal doses or durations of antidepressant treatment. For instance, in a German study examining older adults with major depression, subtherapeutic dosages were observed in 26% and 41% of individuals receiving selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), respectively.[2] Similarly, in the United States, 35% of older adults diagnosed with depression were prescribed antidepressants at low-intensity regimens, with 8% receiving inadequate dosages, 19% receiving insufficient treatment durations, and 15% experiencing inadequate follow-up.[3] These suboptimal dosages and regimens are noteworthy, particularly considering that SSRIs and SNRIs are considered straightforward to use. Additionally, prescription of potentially inappropriate medications, such as benzodiazepines and anticholinergics, is particularly common among older adults using antidepressants, seen in approximately 56% of this

population.[4] Consequently, deprescribing has become an integral component of medication optimization. Extensive recommendations emphasize the avoidance of anticholinergics and benzodiazepines in older adults due to the associated risks of falls and cognitive impairment,[5–7] and pragmatic solutions for overcoming barriers in deprescribing and selecting safer alternative options are needed.

Depression in older adults is associated with a more chronic course and is less responsive to antidepressants compared to their younger counterparts. Medical illnesses and cognitive dysfunction appear to reduce antidepressant efficacy in older adults.[8,9] Considering these challenges, this review focuses on optimizing medication management for late-life depression, encompassing not only antidepressant optimization but also deprescribing practices including alternatives for potent centrally acting anticholinergics and strategies to surmount obstacles in deprescribing benzodiazepines. The literature included in this narrative review is based on a PubMed and Google Scholar search using relevant keywords for each topic, primarily *antidepressant*, *anticholinergic*, and *benzodiazepine*, with a focus on older adults. Standard textbooks and relevant references from the searched articles were reviewed. We prioritized guidelines from authoritative associations, systematic reviews, and meta-analyses that were published within the past 10 years. The final literature selection was justified by the authors.

Common causes of inadequate care of older adults with late-life depression and how to correct them

Table 1 summarizes the common causes of inadequate medication optimization for late-life depression and solutions for these; below we discuss these in detail.

1. Suboptimal dose

The geriatric principle of 'start low, go slow' requires a modification: 'but go!' Response to antidepressants can generally be seen within 4–6 weeks. Therefore, it is reasonable to schedule a clinical follow-up at approximately 4–6 weeks after initiating antidepressants. The dose increase should be made as needed and tolerated, utilizing

Table 1. Challenges in medication optimization for late-life depression and solutions.

Challenges	Solutions
1. Suboptimal dose	Increase the dose every 4–6 weeks and use the full therapeutic dose range until achieving depression remission.
2. Staying on an ineffective medication	If first-line treatment (SSRI) is ineffective, switch to an SNRI, mirtazapine, bupropion, vortioxetine, or vilazodone.
3. Treatment-resistant depression	After two antidepressant classes have failed to achieve remission, move to augmentation, with aripiprazole preferably.
4. Provider is unaware that treatment intensification is needed	Perform measurement-based care: use a scale such as PHQ-9 at each appointment to help adjust treatment. Psychotherapy and/or case manager can help with psychosocial aspect of depression.
5. Suboptimal duration of antidepressant treatment	Maintaining antidepressant for at least 1 year after remission, but longer for recurrent episodes or severe presentation.
6. Patient is taking centrally acting anticholinergic or antihistaminergic agents	Stopping or switching to an agent with no/fewer anticholinergic/antihistaminergic properties (Table 2).
7. Patient is taking a benzodiazepine	Tapering the dose to reduce risks of falls and cognitive impairment.

PHQ-9, 9-item Patient Health Questionnaire; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

the medication's full therapeutic dose range to achieve remission of depression.[10,11] More frequent follow-ups (every 1–2 weeks) may be necessary for patients with severe depression and/or suicidal ideation. Antidepressant prescription information approved by the United States Food and Drug Administration (FDA) indicate that the efficacious dose range for older adults is generally similar to that of younger adults. However, certain older adults may have increased drug concentrations due to factors such as drug–drug interactions (resulting from being prescribed more medications than younger patients), hepatic impairment, or renal impairment, which can affect the required dosage. These aging-related factors are in addition to genetic variability in drug-metabolizing enzymes. SSRIs are commonly regarded as the first-line antidepressants for older adults due to their user-friendly dosing (typically once daily with rapid attainment of therapeutic levels) and favorable safety profiles.[11–14] Sertraline and escitalopram are preferred choices within this class due to their minimal potential for drug interactions.[10] It is noteworthy that escitalopram is subject to Health Canada advisory regarding QTc prolongation, and there has been a suggestion to limit the dose in older adults to 10 mg/day. This differs from the US FDA which does not advice against escitalopram at doses up to 20 mg/day. The fastest-growing age group consists of individuals aged 85 and above (referred to as the 'oldest old'), and unfortunately there is limited knowledge regarding the appropriate dose range for this specific population. In spite of these concerns, increasing the dose of an apparently ineffective medication is often the most appropriate step.

2. Staying on an ineffective medication

Regardless of the selected treatment approach (SSRIs, SNRIs, mirtazapine, or bupropion), roughly half of older adults will not achieve remission.[15–20] If a patient fails to achieve remission after receiving the highest recommended/tolerated dose for a minimum of 8 weeks, alternative treatment options should be considered.[10,11,21]

In general, switching to an SNRI is a good choice due to its favorable safety profile[22] and high likelihood of achieving remission (approximately 47% remission rate following an adequate non-SNRI trial).[16] When SSRIs/SNRIs are poorly tolerated, bupropion or mirtazapine may serve as viable alternatives.[23] Furthermore, vortioxetine (an SSRI, $5HT_{1A}$ agonist, and $5HT_3$ antagonist) and vilazodone (an SSRI and $5HT_{1A}$ partial agonist) offer alternative options characterized by excellent safety and tolerability profiles.[24] Vortioxetine, in particular, holds promise in geriatric depression due to its well-established pro-cognitive benefits beyond its antidepressant effects.[25,26] Moclobemide, a reversible inhibitor of monoamine oxidase (RIMA) used in Canada, the United Kingdom, and other countries, is also recommended as an alternative antidepressant for older adults.[11,14]

We argue that an antidepressant's ease of use, safety, and cost should be of primary consideration when selecting a treatment particularly for a first or second trial. Further, to individualize the selection of an antidepressant for a specific patient, several additional factors should be considered. These factors include (1) concurrent symptoms (e.g. mirtazapine may be particularly beneficial for addressing weight loss and insomnia); (2) comorbidities (e.g. duloxetine is approved for pain and fibromyalgia, while bupropion is approved for smoking cessation); (3) potential adverse effects (e.g. SSRIs and SNRIs may contribute to hyponatremia and sexual dysfunction); and (4) family history of response to a particular antidepressant, as genetic factors significantly influence treatment responsiveness and tolerability.[27]

3. Treatment-resistant depression

When two antidepressants from different classes, such as an SSRI followed by an SNRI, fail to achieve remission, this is called 'treatment-resistant depression'. It is frequently observed in older adults. How to overcome treatment-resistant depression is a great challenge. A large randomized controlled trial (RCT) investigating pharmacologic strategies for treatment-resistant depression in older adults ($n = 742$) can inform treatment decisions. The trial compared popular augmentation and switch strategies and made several observations.[28] First, augmentation with aripiprazole or bupropion demonstrated superior effectiveness compared to switching to bupropion alone (remission rates: aripiprazole augmentation = 29%; bupropion augmentation = 28%; bupropion switch = 19%). Second, bupropion augmentation was associated with a higher incidence of falls than aripiprazole augmentation (fall rates: 0.55 and 0.33 during approximately 10 weeks of acute treatment, respectively). Overall, there were no

significant differences in adverse events between the augmentation and switch strategies. Consequently, these findings suggest that augmentation with aripiprazole is a reasonable option for treatment-resistant depression in older adults. The trial contained a second step for individuals with more highly treatment-resistant depression who failed one of the abovementioned approaches, testing augmentation with lithium or switching to nortriptyline. These options demonstrated comparable effectiveness and safety. However, the low rates of remission (19–22%) observed with these strategies indicate that alternative options such as electroconvulsive therapy, transcranial magnetic stimulation, or ketamine[29] may be preferable once a patient's depression has failed to remit with 'first-line' augmentation such as aripiprazole or bupropion.

4. Provider is unaware that treatment intensification is needed

Treatment modifications require an understanding on behalf of the provider that the adjustment is needed – that is, that the patient is not doing well and therefore treatment intensification is needed. This might be missed in a time-limited clinical setting unless a patient actively advocates for a change. However, the implementation of measurement-based care can address this issue effectively. Measurement-based care involves regularly using validated rating scales, such as the Patient Health Questionnaire (PHQ-9), to guide treatment decisions and monitor depression.[30] This straightforward approach can increase awareness for both the patient and the provider regarding the necessity for treatment intensification, as indicated by elevated scores on the depression scale. A meta-analysis revealed that routine implementation of measurement-based care resulted in greater rates of depression remission [odds ratio (OR) = 1.83; 95% CI 1.12–2.97], improved medication adherence (OR = 1.68; 95% CI 1.22–2.30), and reduced depression severity (OR = 0.53; 95% CI 0.06–0.99) than standard care.[30] Furthermore, depression is a bio-psychosocial phenomenon. Besides medications, psychotherapy plays a crucial role in addressing the psychological aspect of treatment, especially in cognitively intact older adults. Case manager can assist in addressing social challenges such as unstable housing, food insecurity, medication adherence, and transportation to appointments, especially for older adults with cognitive impairment and frailty.

5. Suboptimal duration of antidepressant treatment

Randomized controlled trials conducted in older adults have demonstrated that maintaining an effective antidepressant at the same dose that led to remission significantly reduces the risk of depression recurrence.[31,32] Guidelines provided by the Japanese Society of Mood Disorders, Indian Psychiatric Society, and Canadian Coalition for Seniors' Mental Health recommend maintaining the antidepressant at the same dosage for at least 1 year after remission. Subsequently, a gradual tapering process over several months is advised to minimize the potential risks associated with antidepressant discontinuation syndrome and to monitor for signs of recurrent depression. In the case of a second episode of major depression, maintenance of the antidepressant should continue for 1–2 years. However, for individuals experiencing three or more episodes (or those with severe symptoms, such as requirement of electroconvulsive therapy), maintenance treatment should be extended for a minimum of 3 years or possibly even lifelong.[10–12]

6. Patient is taking centrally acting anticholinergic or antihistaminergic agents

The utilization of anticholinergic drugs has been linked to various adverse effects, including confusion, brain atrophy, and an increased risk of cognitive impairment in a dose-dependent manner. Furthermore, the risk of developing dementia is elevated by approximately 20% with anticholinergic drug use.[7,33,34] Therefore, strong centrally acting anticholinergic medications should be avoided in older adults.[7] It is crucial to explore the individual patient's preference for pharmacological and non-pharmacological options for a shared decision-making approach to treatment. In cases where pharmacological treatment is necessary, medications with minimal or no anticholinergic burden are preferable. However, if potent anticholinergic medications are used (for instance, when there are limited alternatives or the patient does not respond to safer options), clinicians should periodically weigh the benefits against the risk of anticholinergic consequences, such as dry mouth, constipation, confusion, and drug tolerance,[7] which may warrant dose reduction. The timing to stop medications with anticholinergic effects should be guided by underlying disease. For example, antipsychotics may be necessary acutely or even chronically to mitigate aggression or psychosis. Most centrally acting anticholinergics and antihistamines, including

over-the-counter medications such as diphenhydramine, do not necessitate a tapering process and can be safely discontinued immediately.[35] Table 2 provides an overview of potent anticholinergic medications identified in the 2019 Beers criteria, along with alternative medications that have little to no central anticholinergic effects that can be employed if necessary.

Alternatives for depression/anxiety/insomnia. Various alternatives are available for managing depression, anxiety, and insomnia with minimal anticholinergic effects. SSRIs (except paroxetine), SNRIs (e.g. venlafaxine, desvenlafaxine, duloxetine, levomilnacipran), bupropion, and mirtazapine have minimal anticholinergic effects.[36,37] Moclobemide exhibits a safety profile, including a lack of anticholinergic and sedative effects, as well as being unlikely to cause a hypertensive crisis when combined with tyramine diets, making it advantageous for older patients.[8] Buspirone, a partial $5HT_{1A}$ agonist, is approved for anxiety disorders and short-term anxiety relief.[38] Pregabalin is approved for generalized anxiety disorder

Table 2. Commonly used strong anticholinergic medications from the 2019 Beers criteria and medications with no/fewer anticholinergic effects.

Strong anticholinergics medications	Alternative medications with fewer/no anticholinergic effects
Antidepressants TCAs: Amitriptyline Clomipramine Desipramine Doxepin (>6 mg) Imipramine Nortriptyline SSRI: Paroxetine	For depression and/or anxiety: SSRIs (escitalopram, sertraline) SNRIs (venlafaxine, desvenlafaxine, duloxetine, levomilnacipran) Bupropion Buspirone (for anxiety) Mirtazapine (also sedating) Moclobemide Pregabalin (for anxiety) For insomnia: Agomelatine (also helps depression) Doxepin (1–6 mg) Prazosin (for PTSD-associated nightmares) Quetiapine (25–50 mg) for augmenting in cases of anxiety/depression with comorbid insomnia Ramelteon (for initial insomnia) Trazodone (25–150 mg)
First generation antihistamines Brompheniramine Chlorpheniramine Cyproheptadine Dicyclomine Dimenhydrinate Diphenhydramine Doxylamine Hydroxyzine Hyoscyamine Meclizine Promethazine	For allergic rhinitis: Topical antihistamines/anticholinergics/steroids For allergic skin reactions: Moisturizers Topical antihistamines/steroids For allergic reactions: 2nd and 3rd generation antihistamine: Bilastine Cetirizine Fexofenadine Levocetirizine
Antimuscarinics Darifenacin Fesoterodine Oxybutynin Solifenacin Tolterodine Trospium*	For overactive bladder: Beta-3 adrenoceptor agonists: Mirabegron Vibegron
Antiparkinsonian agents Benztropine Trihexyphenidyl	For Parkinsonism, anticholinergics should be avoided.

(Continued)

Table 2. (Continued)

Strong anticholinergics medications	Alternative medications with fewer/no anticholinergic effects
Antipsychotics Chlorpromazine Clozapine Olanzapine Quetiapine (high dose)	For psychosis: Aripiprazole Paliperidone Risperidone Newer atypical antipsychotics (lurasidone, cariprazine, brexpiprazole) can be tried but there is less evidence in older adults.
Skeletal muscle relaxants Cyclobenzaprine Orphenadrine	For muscle spasms: Baclofen (limit use to short duration) Tizanidine (limit use to short duration)

*If antimuscarinic is to be used, trospium is least likely to affect the brain.
NSAID, non-steroidal anti-inflammatory drug; PTSD, post-traumatic stress disorder; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

(GAD) in Europe and the United Kingdom, and is recommended as one of the first-line agents for GAD in Canada[39] and the United Kingdom.[40] An RCT showed that a mean dose of 270 mg/day (range 150–600 mg/day) in older adults with GAD is well-tolerated, with dizziness and somnolence being common adverse events.[41] Pregabalin may be less used in the US because of a lack of FDA indication for GAD, as well as a growing concern regarding its potential misuse, especially among patients with a history of substance abuse.[42]

Very low-dose doxepin (1–6 mg), which selectively blocks H_1 receptors without significant anticholinergic effects, is helpful for insomnia.[43] However, as a tricyclic antidepressant, doxepin blocks voltage-sensitive sodium channels in the heart and brain in a dose-dependent manner. Consequently, an overdose can lead to seizures and fatal cardiac arrhythmias.[43] Melatonergic receptor (MT_1 and MT_2) agonists appeal due to their favorable safety profiles: ramelteon aids in sleep onset, but its efficacy in maintaining sleep may be limited[43]; agomelatine, which also blocks $5HT_{2c}$ receptors, increases norepinephrine and dopamine levels, thereby assisting with depression.[43] Agomelatine is approved for major depression in Europe but requires monitoring of liver enzymes before treatment initiation and periodically during the first year due to the risk of transaminitis.[44] Trazodone at low doses (25–150 mg) promotes sleep by blocking H_1, α_1 (interfering with monoamine arousal), and $5HT_{2A}$ (enhancing slow-wave sleep). However, caution should be exercised due to potential dizziness and orthostatic hypotension.[38,43] Quetiapine at low doses (25–50 mg) primarily acts by blocking H_1 receptors, providing a sedative effect that may be used to treat comorbid insomnia in mood disorders. However, its use as a monotherapy for insomnia is not recommended due to metabolic risks.[43] In a retrospective study, the α_1-blocker prazosin demonstrated effectiveness for managing PTSD-associated nightmares in older adults with relatively stable blood pressure. The mean dose used was 5 mg (range: 0–17 mg), with 1–2 mg titration at each visit.[45] A systematic review encompassing RCTs and quasi-experimental studies investigating nonbenzodiazepine/Z-drug agents for insomnia in older adults revealed promising findings. Specifically, doxepin (three studies), ramelteon (four studies), and suvorexant (one study) demonstrated improvements in sleep latency and total sleep time without significant adverse effects compared to placebo. Conversely, melatonin, diphenhydramine, paroxetine, tiagabine, and valerian did not demonstrate a clear benefit.[46] Diphenhydramine should be avoided due to its high anticholinergic properties. Furthermore, suvorexant cannot be currently recommended in older adults due to concerns regarding the potential exacerbation of depression, the risk of dependence, and the limited geriatric data available.[38]

Alternatives for treating allergies. When allergies manifest in older individuals, it is helpful to investigate the underlying causes. These may include detergent allergies and medication-induced allergies which can sometimes be due to psychotropic drugs, such as acetylcholinesterase inhibitor-induced rhinorrhea, risperidone-induced rhinitis, and bupropion-induced pruritus. In managing allergies, topical medications are typically recommended as the initial approach to minimize systemic adverse

effects. Second- and third-generation antihistamines, such as cetirizine and fexofenadine, are preferred due to their reduced ability to cross the blood–brain barrier, resulting in minimal sedative effects. These antihistamines exhibit high selectivity as H_1 antagonists and demonstrate no or weak affinity toward cholinergic or α-adrenergic receptors.[47]

Alternatives for overactive bladder. Nonpharmacological interventions for managing urinary incontinence include caffeine avoidance, scheduled voiding, and pelvic floor muscle exercises.[48,49] Beta-3 adrenoceptor agonists, namely, mirabegron and vibegron, offer alternatives that relax the bladder muscle without exerting anticholinergic effects and are less likely to penetrate the blood–brain barrier.[49] Despite being listed in the Beers criteria, trospium possesses distinct molecular properties as a quaternary amine (which increases hydrophilicity) and serves as a substrate for the permeability-glycoprotein system (which facilitates its active transport out of the brain). As a result, it exhibits minimal ability to cross the blood–brain barrier. Multiple studies have corroborated the absence of cognitive adverse effects associated with trospium, and its detection in cerebral spinal fluid among older adults remains negligible despite its presence in plasma.[48] For individuals using acetylcholinesterase inhibitors (typically because of dementia although sometimes seen in late-life depression), it is important to note that urinary incontinence may worsen due to the increased contractile effect of acetylcholine on the bladder muscle.[48] However, this and other peripheral pro-cholinergic side effects can be managed by adding a peripheral-acting anticholinergic (such as trospium) rather than stopping the acetylcholinesterase inhibitor.[50]

Alternatives for Parkinsonism. Managing depression (often complicated by psychosis) in this context usually requires the input of a specialist such as a geriatric psychiatrist. Centrally acting anticholinergic medications are better avoided in these circumstances, including in Parkinson's disease and drug-induced parkinsonism. To address antipsychotic-induced parkinsonism, it may be safer to lower the dose or switch to an antipsychotic with fewer dopamine-blocking effects. When Parkinson's disease is accompanied by psychosis or dementia, the reduction of anticholinergic medications should be prioritized, and a reduction of levodopa to be the last.[51] Should an antipsychotic be necessary for Parkinson's disease psychosis, pimavanserin, a selective $5HT_{2A}$ receptor inverse agonist but presently a costly medication, is currently the only drug approved for this condition by the US FDA.[38] Quetiapine is also recommended for this purpose, albeit without clear efficacy from controlled trials. Clozapine is sometimes favored for this purpose but is challenging to use given its complex pharmacodynamics and need for routine blood draws to evaluate agranulocytosis risk.[51]

Alternatives for psychosis. Among antipsychotic medications, aripiprazole, brexpiprazole, cariprazine (referred to as 'two pips and a rip'), risperidone, paliperidone, ziprasidone, iloperidone, lurasidone, and lumateperone (referred to as 'dones and a rone') do not possess anticholinergic properties. It is important to note that these medications exhibit some potency for H_1 receptors, except lurasidone and lumateperone, which lack antihistamine properties.[43] In older adults, it is challenging using ziprasidone due to its propensity to prolong the QT interval ranking second only to thioridazine. Newer atypical antipsychotics, including iloperidone, lurasidone, lumateperone, brexpiprazole, and cariprazine, are generally believed to offer better tolerability than clozapine and olanzapine.[38] Nonetheless, the latter drugs still hold their place in treating some older adults. At higher doses (i.e. 300–800 md/day), quetiapine exerts moderate anticholinergic effects, although this may be less pronounced than olanzapine, clozapine, and chlorpromazine.[38,43]

Alternatives for muscle spasms. When addressing muscle spasms in older adults, it is crucial to exercise caution as many muscle relaxants are generally poorly tolerated in this population and should be avoided.[7] However, tizanidine and baclofen can be considered for short-term use in managing muscle spasms, but the potential risks of dizziness, drowsiness, and falls should be acknowledged.[52] Additionally, nonpharmacological alternatives such as trigger point injection, nerve block, radiofrequency ablation, transcranial magnetic stimulation, and acupuncture can serve as viable options for addressing this condition.[52]

7. Patient is taking benzodiazepines

When considering the deprescribing of benzodiazepines, numerous challenges arise for patients and healthcare providers.[53] The following section discusses potential solutions to these challenges (summarized in Table 3).

Table 3. Barriers in deprescribing benzodiazepines and solutions.

Barriers to deprescribing benzodiazepines from healthcare providers and/or patients	Solutions/disputes from current evidence
1. Lack of awareness regarding the harmful effects of benzodiazepines	Benzodiazepines lead to falls, fractures, motor vehicle accidents, and possibly dementia. Drug dependence can develop after using for longer than 2–4 weeks.
2. Perceived benefits of benzodiazepines in treating anxiety and insomnia	SSRIs are equally effective in treating panic disorder as benzodiazepines but have fewer adverse effects. The sedating antidepressant, low-dose doxepin, is similar to Z-drugs and benzodiazepines in extending sleep time.
3. Unaware of alternative strategies for insomnia or anxiety	Sleep hygiene, stimulus control, sleep restriction, and relaxation techniques can be tried for insomnia. Cognitive behavioral therapy is effective for generalized anxiety disorder and panic disorder. See Table 2 for medications for anxiety, depression, and insomnia.
4. Fear of withdrawal symptoms and lack of strategy for tapering	Benzodiazepines can be safely discontinued without significant withdrawal symptoms by tapering 10–25% from the initial dose every 2 weeks.
5. Provider does not want to change drug regimen while patients are stable, and/or fears patient resistance	Most of older adults are willing to stop regular medications if their doctor says it is possible. Communication is the key to success: discuss the risks and benefits of benzodiazepines and make a shared decision.
6. The patient is too old or too close to dying to benefit from quitting benzodiazepine	Benzodiazepine should not be used as a routine medication at end-of-life since it can precipitate delirium and may worsen survival outcomes.

SSRI, selective serotonin reuptake inhibitor.

Barrier 1: Lack of awareness regarding the harmful effects of benzodiazepines. The American Geriatrics Society 2019 Beers Criteria,[7] the STOPP/START criteria,[6] and the PRISCUS List from Germany[5] recommend avoiding benzodiazepines, including nonbenzodiazepine benzodiazepine receptor agonists (Z-drugs), in older adults. This recommendation is based on the increased risk of cognitive impairment, falls, fractures, delirium, and motor vehicle accidents associated with their use. In the majority of patients, the risks associated with benzodiazepine use outweigh the benefits when the duration of use exceeds 2–4 weeks, as there are no indications for long-term use, and dependence may develop.[6,54] In a population-based retrospective cohort study, following older adults newly prescribed a benzodiazepine for 1 year, chronic benzodiazepine users (being prescribed a benzodiazepine for >120 days out of a 180-day exposure period) exhibited a higher risk of falls-related hospitalization or emergency department visits [hazard ratio (HR) = 1.13; 95% CI 1.08–1.19], hip fracture [HR = 1.27 (1.10–1.48)], and mortality [HR = 1.30 (1.19–1.43)] compared to intermittent users.[55] It is important to acknowledge that some patients may require or derive benefits from long-term benzodiazepine use, and this guide should not supersede individualized medical decision-making.

Benzodiazepines and Z-drugs have been associated with an increased risk of falls, fractures, and motor vehicle accidents due to their impact on psychomotor activity.[56] While evidence suggests that benzodiazepines can impair various cognitive domains,[57] the causal relationship between benzodiazepine use and dementia is not fully established, as individuals with prodromal mood and behavior symptoms of dementia may require benzodiazepine treatment (i.e. reverse causality). However, a meta-analysis indicated that benzodiazepine use still predicts the incidence of dementia after controlling for reverse causality bias.[58] Additionally, benzodiazepines have been found to

increase the light sleep stage (N2) while reducing deep sleep (N3 stage) and rapid eye movement (REM stage), which are essential for restorative sleep and memory consolidation.[59,60] Notably, alcohol and cannabis can also impair motor function, attention, and reaction time.[61,62] Therefore, concurrent use of benzodiazepines with alcohol or cannabis can significantly increase the risk of accidents and injuries; this hazardous use should be avoided.

Barrier 2: Perceived benefits of benzodiazepines in treating anxiety and insomnia. Evidence does not support the superiority of benzodiazepines over less harmful medications for anxiety or insomnia. A network meta-analysis of RCTs in patients with panic disorder found benzodiazepines not significantly different from SSRIs regarding remission rates [risk ratio (RR) for remission = 1.07; 95% CI 0.96–1.19] but were slightly more effective than SNRIs (RR for remission = 1.16; 95% CI 1.00–1.34). There was no significant difference in the reduction of anxiety or depression between benzodiazepines and SSRIs (no data available for SNRIs). Adverse effects were higher with benzodiazepines than SSRIs (RR = 1.47; 95% CI 1.18–1.84) and slightly higher than SNRIs (RR = 1.42; 95% CI 1.00–2.02). However, lower dropout rates were observed compared to SSRIs [RR = 0.51 (0.38–0.67)] and SNRIs (RR = 0.57; 95% CI 0.37–0.87), which may be attributed to a delayed onset of the antidepressant effect. The clustered ranking plot indicated that SSRIs were the most effective treatment with the mildest adverse effects, and escitalopram showed the best balance between remission rate and adverse effects among SSRIs.[63]

Another network meta-analysis of RCTs evaluated treatments for insomnia in older adults. Benzodiazepines increased total sleep time by 41 minutes ($n = 3$ studies), while doxepin 2–6 mg increased it by 31 min ($n = 2$ studies), and Z-drugs increased it by 24 min ($n = 4$ studies) compared to placebo. However, no significant differences were observed between these treatments regarding their effects on total sleep time. There were no notable differences in dropouts or adverse effects among the treatment groups due to the limited evidence. However, it is important to note that most trials had a short duration of therapy ($\leqslant 3$ weeks), a small number of participants ($N < 30$/arm), and a high risk of bias, which are significant limitations.[64] Large, well-designed RCTs evaluating commonly used medications in clinical practice, such as mirtazapine, agomelatine, trazodone, and ramelteon, are still lacking.

Barrier 3: Unaware of alternative strategies for insomnia or anxiety. An important initial step in managing patients with sleep complaints is obtaining a thorough history and identifying and treating any underlying causes. Sleep disturbances can be secondary to psychiatric disorders, medical conditions, and substance/medication use. Nonpharmacological strategies that can enhance sleep quality include practicing good sleep hygiene, such as avoiding daytime napping and establishing a consistent wake-up time in the morning (refer to https://sleepeducation.org/healthy-sleep/healthy-sleep-habits for more information). Another practical approach is 'stimulus control', which aims to break the association between insomnia and bedtime by only going to bed when feeling sleepy and leaving the bed if unable to fall asleep within 20–30 min. 'Sleep restriction' is another technique that involves limiting the time spent in bed to actual sleep time, gradually increasing it as total sleep time improves until the desired sleep duration (not less than 5 h) is achieved. Additionally, relaxation techniques such as muscle relaxation and guided imagery can help reduce rumination and promote better sleep. It is important to note that decreased total sleep time and more frequent nighttime awakenings can be a normal part of aging. Patients can be reassured that in older age, it may not be necessary to achieve 8 h of sleep, as long as their daytime functioning remains unimpaired. For some individuals, a shorter duration of sleep may be sufficient.[54]

Regarding anxiety disorders, antidepressants (SSRIs) are considered the first-line treatment. Nonpharmacological interventions that have shown effectiveness in managing anxiety disorders include cognitive behavioral therapy for generalized anxiety disorder and panic disorder, systematic desensitization for phobias, exposure and response prevention for obsessive-compulsive disorder, and cognitive behavioral therapy and eye movement desensitization and reprocessing for posttraumatic stress disorder. Additionally, relaxation techniques and mindfulness practices are beneficial in alleviating anxiety symptoms in general.[38,65] Benzodiazepines should be reserved for situations where their use is deemed necessary, such as for severe breakthrough panic attacks. Refer to earlier discussions and Table 2 for alternative medications to treat anxiety, depression, and insomnia.

Barrier 4: Fear of withdrawal symptoms and lack of strategy for tapering. To discontinue benzodiazepines safely, tapering is recommended to minimize the risk of withdrawal symptoms. One approach is to reduce the benzodiazepine dose by 10–25% of the initial dose every 2 weeks, with an even slower tapering rate (e.g. 10%) advised when reaching the final dose before complete discontinuation. Patients experiencing withdrawal symptoms may require an extended tapering period with smaller dose reductions.[54] Another tapering strategy involves halving the dose within 6 weeks, reducing it to a quarter within 12 weeks, and stopping the benzodiazepine entirely within 22 weeks. Gradually increasing the number of days with a reduced dose is part of this approach. For instance, during weeks 1–2, patients may be prescribed a half dose for 1 day per week (with a full dose on the remaining days), followed by 3 days per week during weeks 3–4, and finally, daily during weeks 5–6.[66] Throughout the benzodiazepine tapering process, it is important to monitor for possible rebound or withdrawal symptoms, which can manifest as psychological (anxiety, insomnia), physical (agitation, flu-like symptoms), and sensory symptoms (hyperacusis, photophobia).[67] Adjustments to the tapering plan should be made if these symptoms occur. The onset and duration of withdrawal symptoms depend on the type of benzodiazepine. Short-acting benzodiazepines such as alprazolam typically elicit withdrawal symptoms within 2–3 days, which subside within 4–5 days, while long-acting benzodiazepines such as diazepam may lead to withdrawal symptoms within 5–10 days, resolving within 2–4 weeks.[54,67]

Barrier 5: Provider does not want to change drug regimen while patients are stable, and/or fears patient resistance. It is important to discuss with patients the risks and benefits of continuing or discontinuing benzodiazepines, ultimately reaching a shared decision. Nonpharmacological and pharmacological alternatives should be presented as options. To avoid misuse, reasons should be documented when initiating, adjusting the dose, or discontinuing benzodiazepines, especially if their use extends beyond 4 weeks. Interestingly, studies have shown that 80–90% of older adults are willing to discontinue one or more of their regular medications if advised by their healthcare provider.[68,69] A systematic review focusing on interventions for discontinuation in older adults who were long-term users of benzodiazepines and Z-drugs demonstrated success rates ranging from 27% to 80%. Educational interventions that included tapering recommendations resulted in successful discontinuation in 35–38% of patients.[70]

Barrier 6: The patient is too old or too close to dying to benefit from quitting benzodiazepine. In cases of end-of-life care, palliative sedation may be considered to alleviate suffering. This option should be reserved for patients with a life expectancy of <2 weeks and only when standard treatments, such as pain control, have been ineffective in managing refractory and intolerable symptoms. Midazolam is commonly used for palliative sedation, but it is important to note that tolerance may develop, and in rare cases (occurring in 2% of patients), paradoxical excitation may occur. Engaging in discussions with the patient or their family members is crucial, especially in situations where the patient is incapacitated.[71]

When dealing with severe delirium-related agitation requiring pharmacological intervention, it may be best to limit the use of benzodiazepines to cases where antipsychotics have been unsuccessful to avoid worsening confusion and administered for the shortest duration possible. It is also important to recognize that both antipsychotics and benzodiazepines may have the potential to worsen, precipitate, or mask delirium while also presenting adverse events that can distress patients and negatively impact survival outcomes.[72]

Conclusion

Medication optimization in older adults with depression is a complex yet crucial aspect of their care. It involves two primary goals: optimizing the use of antidepressants, and deprescribing inappropriate medications to enhance mental and cognitive functioning. Several strategies can be employed to achieve these goals:

- Maximize the dosage within the recommended range for antidepressants to achieve remission.
- Switch to alternative classes such as SNRIs or bupropion if the initial SSRI treatment proves inadequate.
- Explore augmentation strategies like aripiprazole for treatment-resistant depression.
- Use a measurement-based care approach to help adjust treatment.
- Maintain antidepressant therapy for a minimum of 1 year following depression remission.

- Deprescribe medications with anticholinergic properties and benzodiazepine or transitioning to safer alternatives.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Maytinee Srifuengfung: Conceptualization; Project administration; Writing – original draft; Writing – review & editing.

Bethany R. Tellor Pennington: Conceptualization; Writing – review & editing.

Eric J. Lenze: Conceptualization; Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
EJL: Fast Grants, the Patient-Centered Outcomes Research Institute, Janssen, MagStim (support in kind). Consulting fees: Merck, IngenioRx, Boeringer-Ingelheim, Prodeo, Pritikin ICR. Patent: Has applied for a patent for the use of fluvoxamine in the treatment of COVID-19.

Availability of data and materials
Not applicable.

ORCID iDs
Maytinee Srifuengfung https://orcid.org/0000-0002-4383-6540

Bethany R. Tellor Pennington https://orcid.org/0000-0003-1571-6434

References
1. Brody DJ and Gu Q. Antidepressant use among adults: United States, 2015-2018. *NCHS Data Brief* 2020; 1–8.
2. Boehlen FH, Freigofas J, Herzog W, *et al.* Evidence for underuse and overuse of antidepressants in older adults: results of a large population-based study. *Int J Geriatr Psychiatry* 2019; 34: 539–547.
3. Wang PS, Schneeweiss S, Brookhart MA, *et al.* Suboptimal antidepressant use in the elderly. *J Clin Psychopharmacol* 2005; 25: 118–126.
4. Ishtiak-Ahmed K, Köhler-Forsberg O, Mortensen EL, *et al.* Concurrent use of polypharmacy and potentially inappropriate medications with antidepressants in older adults: a nationwide descriptive study in Denmark during 2015–2019. *Gen Hosp Psychiatry* 2023; 82: 66–74.
5. Holt S, Schmiedl S and andThürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int* 2010; 107: 543–551.
6. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; 44: 213–218.
7. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019; 67: 674–694.
8. Cleare A, Pariante CM, Young AH, *et al.* Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2015; 29: 459–525.
9. Haigh EAP, Bogucki OE, Sigmon ST, *et al.* Depression among older adults: a 20-year update on five common myths and misconceptions. *Am J Geriatr Psychiatry* 2018; 26: 107–122.
10. Avasthi A and Grover S. Clinical practice guidelines for management of depression in elderly. *Indian J Psychiatry* 2018; 60: S341–S362.
11. Canadian Coalition for Seniors' Mental Health. *Canadian guidelines on prevention, assessment and treatment of depression among older adults*, https://ccsmh.ca/wp-content/uploads/2021/06/CCSMH_Depression_Guidelines_FINAL_EN.pdf (2021, accessed 1 March 2023).
12. Baba H, Kito S, Nukariya K, *et al.* Guidelines for diagnosis and treatment of depression in older adults: a report from the Japanese Society of Mood Disorders. *Psychiatry Clin Neurosci* 2022; 76: 222–234.
13. Kok RM and Reynolds CF. Management of depression in older adults: a review. *JAMA* 2017; 317: 2114–2122.
14. MacQueen GM, Frey BN, Ismail Z, *et al.* Canadian Network for Mood and Anxiety

Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. Special populations: youth, women, and the elderly. *Can J Psychiatry* 2016; 61: 588–603.

15. Allard P, Gram L, Timdahl K, *et al*. Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. *Int J Geriatr Psychiatry* 2004; 19: 1123–1130.
16. Buchalter ELF, Oughli HA, Lenze EJ, *et al*. Predicting remission in late-life major depression: a clinical algorithm based upon past treatment history. *J Clin Psychiatry* 2019; 80: 18m12483.
17. Hewett K, Chrzanowski W, Jokinen R, *et al*. Double-blind, placebo-controlled evaluation of extended-release bupropion in elderly patients with major depressive disorder. *J Psychopharmacol* 2010; 24: 521–529.
18. Kok RM, Nolen WA and Heeren TJ. Venlafaxine versus nortriptyline in the treatment of elderly depressed inpatients: a randomised, double-blind, controlled trial. *Int J Geriatr Psychiatry* 2007; 22: 1247–1254.
19. Raskin J, Wiltse CG, Siegal A, *et al*. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* 2007; 164: 900–909.
20. Schatzberg AF, Kremer C, Rodrigues HE, *et al*. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; 10: 541–550.
21. Malhi GS, Bell E, Singh AB, *et al*. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Bipolar Disord* 2020; 22: 788–804.
22. Behlke LM, Lenze EJ and Carney RM. The cardiovascular effects of newer antidepressants in older adults and those with or at high risk for cardiovascular diseases. *CNS Drugs* 2020; 34: 1133–1147.
23. Oughli HA, Karp JF and Lenze EJ. Depression in older adults. In: *Depression*. New York, NY: Oxford University Press, 2020, pp. 418–434.
24. Citrome L. Vortioxetine for major depressive disorder: An indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord* 2016; 196: 225–233.
25. Katona C, Hansen T and Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 2012; 27: 215–223.
26. Lenze EJ, Stevens A, Waring JD, *et al*. Augmenting computerized cognitive training with vortioxetine for age-related cognitive decline: a randomized controlled trial. *Am J Psychiatry* 2020; 177: 548–555.
27. Fabbri C, Crisafulli C, Calabrò M, *et al*. Progress and prospects in pharmacogenetics of antidepressant drugs. *Expert Opin Drug Metab Toxicol* 2016; 12: 1157–1168.
28. Lenze EJ, Mulsant BH, Roose SP, *et al*. Antidepressant augmentation versus switch in treatment-resistant geriatric depression. *N Engl J Med* 2023; 388: 1067–1079.
29. Oughli HA, Gebara MA, Ciarleglio A, *et al*. Intravenous ketamine for late-life treatment-resistant depression: a pilot study of tolerability, safety, clinical benefits, and effect on cognition. *Am J Geriatr Psychiatry* 2023; 31: 210–221.
30. Zhu M, Hong RH, Yang T, *et al*. The efficacy of measurement-based care for depressive disorders: systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2021; 82: 21r14034.
31. Reynolds CF, Frank E, Perel JM, *et al*. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA* 1999; 281: 39–45.
32. Reynolds CF, Dew MA, Pollock BG, *et al*. Maintenance treatment of major depression in old age. *N Engl J Med* 2006; 354: 1130–1138.
33. Risacher SL, McDonald BC, Tallman EF, *et al*. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol* 2016; 73: 721–732.
34. Zheng Y-B, Shi L, Zhu X-M, *et al*. Anticholinergic drugs and the risk of dementia: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2021; 127: 296–306.
35. Liacos M, Page AT and Etherton-Beer C. Deprescribing in older people. *Aust Prescr* 2020; 43: 114–120.

36. Palmer EC, Binns LN and Carey H. Levomilnacipran: a new serotonin-norepinephrine reuptake inhibitor for the treatment of major depressive disorder. *Ann Pharmacother* 2014; 48: 1030–1039.

37. DiPiro JT, Talbert RL, Yee GC, *et al*. *Pharmacotherapy: a pathophysiologic approach*. 9th ed. New York, NY: McGraw-Hill Medical Publishing, 2014.

38. Steffens DC and Zdanys KF. *The American Psychiatric Association Publishing textbook of geriatric psychiatry*. 6th ed. Washington, DC: American Psychiatric Association Publishing, 2023.

39. Katzman MA, Bleau P, Blier P, *et al*. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry* 2014; 14(Suppl 1): S1.

40. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol* 2014; 28: 403–439.

41. Montgomery S, Chatamra K, Pauer L, *et al*. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. *Br J Psychiatry* 2008; 193: 389–394.

42. Hägg S, Jönsson AK and Ahlner J. Current evidence on abuse and misuse of gabapentinoids. *Drug Saf* 2020; 43: 1235–1254.

43. Stahl SM. *Stahl's essential psychopharmacology*. 5th ed. Cambridge: Cambridge University Press, 2021.

44. Srifuengfung M, Pummangura C and Srifuengfung S. Late onset of serious agomelatine-induced liver injury. *Sleep Med* 2021; 86: 122.

45. Khaw C and Argo T. Prazosin outcomes in older veterans with posttraumatic stress disorder. *Fed Pract* 2020; 37: 72–78.

46. Sys J, Van Cleynenbreugel S, Deschodt M, *et al*. Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review. *Eur J Clin Pharmacol* 2020; 76: 363–381.

47. Bozek A. Pharmacological management of allergic rhinitis in the elderly. *Drugs Aging* 2017; 34: 21–28.

48. Araklitis G, Robinson D and Cardozo L. Cognitive effects of anticholinergic load in women with overactive bladder. *Clin Interv Aging* 2020; 15: 1493–1503.

49. Shaw C and Wagg A. Overactive bladder in frail older adults. *Drugs Aging* 2020; 37: 559–565.

50. Moss DE. Is combining an anticholinergic with a cholinesterase inhibitor a good strategy for high-level CNS cholinesterase inhibition? *J Alzheimers Dis* 2019; 71: 1099–1103.

51. Klietz M, Greten S, Wegner F, *et al*. Safety and tolerability of pharmacotherapies for Parkinson's disease in geriatric patients. *Drugs Aging* 2019; 36: 511–530.

52. Fu JL and Perloff MD. Pharmacotherapy for spine-related pain in older adults. *Drugs Aging* 2022; 39: 523–550.

53. Evrard P, Pétein C, Beuscart J-B, *et al*. Barriers and enablers for deprescribing benzodiazepine receptor agonists in older adults: a systematic review of qualitative and quantitative studies using the theoretical domains framework. *Implement Sci* 2022; 17: 41.

54. Primary Health Tasmania. *A guide to deprescribing benzodiazepine*, https://www.primaryhealthtas.com.au/wp-content/uploads/2023/03/A-guide-to-deprescribing-benzodiazepines.pdf (2022, accessed 31 March 2023).

55. Davies SJ, Rudoler D, de Oliveira C, *et al*. Comparative safety of chronic versus intermittent benzodiazepine prescribing in older adults: a population-based cohort study. *J Psychopharmacol* 2022; 36: 460–469.

56. Brandt J and Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs R D* 2017; 17: 493–507.

57. Crowe SF and Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol* 2018; 33: 901–911.

58. Penninkilampi R and Eslick GD. A systematic review and meta-analysis of the risk of dementia associated with benzodiazepine use, after controlling for protopathic bias. *CNS Drugs* 2018; 32: 485–497.

59. de Mendonça FMR, de Mendonça GPRR, Souza LC, *et al*. Benzodiazepines and sleep architecture: a systematic review. *CNS Neurol Disord Drug Targets* 2023; 22: 172–179.

60. Brodt S, Inostroza M, Niethard N, *et al*. Sleep-A brain-state serving systems memory consolidation. *Neuron* 2023; 111: 1050–1075.

61. Solomon HV, Greenstein AP and DeLisi LE. Cannabis use in older adults: a perspective. *Harv Rev Psychiatry* 2021; 29: 225–233.

62. White AM, Orosz A, Powell PA, *et al*. Alcohol and aging – an area of increasing concern. *Alcohol* 2023; 107: 19–27.

63. Chawla N, Anothaisintawee T, Charoenrungrueangchai K, *et al*. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2022; 376: e066084.

64. Samara MT, Huhn M, Chiocchia V, *et al*. Efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly: a systematic review and network meta-analysis. *Acta Psychiatr Scand* 2020; 142: 6–17.

65. Subramanyam AA, Kedare J, Singh OP, *et al*. Clinical practice guidelines for geriatric anxiety disorders. *Indian J Psychiatry* 2018; 60: S371–S382.

66. Markota M, Rummans TA, Bostwick JM, *et al*. Benzodiazepine use in older adults: dangers, management, and alternative therapies. *Mayo Clinic Proceedings* 2016; 91: 1632–1639.

67. Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med* 2017; 376: 1147–1157.

68. Crutzen S, Abou J, Smits SE, *et al*. Older people's attitudes towards deprescribing cardiometabolic medication. *BMC Geriatr* 2021; 21: 1–12.

69. Rozsnyai Z, Jungo KT, Reeve E, *et al*. What do older adults with multimorbidity and polypharmacy think about deprescribing? The LESS study – a primary care-based survey. *BMC Geriatr* 2020; 20: 435.

70. Reeve E, Ong M, Wu A, *et al*. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. *Eur J Clin Pharmacol* 2017; 73: 927–935.

71. Patel C, Kleinig P, Bakker M, *et al*. Palliative sedation: a safety net for the relief of refractory and intolerable symptoms at the end of life. *Aust J Gen Pract* 2019; 48: 838–845.

72. Gaertner J, Eychmueller S, Leyhe T, *et al*. Benzodiazepines and/or neuroleptics for the treatment of delirium in palliative care? A critical appraisal of recent randomized controlled trials. *Ann Palliat Med* 2019; 8: 504–515.