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REVIEW ARTICLE

Problematic Opioid Use Among Older Adults: Epidemiology, Adverse Outcomes and Treatment Considerations

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Abstract

With the aging population, an increasing number of older adults (> 65 years) will be affected by problematic opioid use and opioid use disorder (OUD), with both illicit and prescription opioids. Problematic opioid use is defined as the use of opioids resulting in social, medical or psychological consequences, whereas OUD is a form of problematic use that meets diagnostic criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Problematic use of opioids by older adults is associated with a number of pertinent adverse effects, including sedation, cognitive impairment, falls, fractures and constipation. Risk factors for problematic opioid use in this population include pain, comorbid medical illnesses, concurrent alcohol use disorder and depression. Treatment of OUD consists of acute detoxification and maintenance therapy. At this time, there have been no randomized controlled trials examining the effectiveness of pharmacological interventions for OUD in this population, with recommendations based on data from younger adults. Despite this, opioid agonist therapy (OAT) is recommended for both stages of treatment in older adults with OUD. Buprenorphine is recommended as a first line agent over methadone in the older adult population, due to a more favourable safety profile and relative accessibility. Use of methadone in this population is complicated by risk of QT interval prolongation and respiratory depression. Available observational data suggests that older adults respond well to OAT and age should not be a barrier to treatment. Further research is required to inform treatment decisions in this population.

Key Points

Rates of problematic opioid use are increasing in the older adult population.

There have been no randomized control trials examining the effectiveness of interventions for the management of problematic opioid use in this age group, with recommendations based on data from younger adults.

Available observational data suggests that older adults respond well to opioid agonist therapy and age should not be a barrier to treatment.

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1 Introduction

Substance use among older adults is a concern that is often underdiagnosed and undertreated [1, 2]. Moreover, there is a dearth of research within this area of medicine [1, 2]. However, substance use in this population is common, with older adults accounting for an increasingly larger proportion of individuals seeking treatment [1, 2]. For example, a cross-sectional analysis of 3.5 million first-time substance use treatment admissions in the United States demonstrated an increase in the proportion of individuals over the age of 55 years presenting for treatment, with this group accounting for 4.42% of first time admissions in 2008, compared with 2.86% in 1998 [3]. This change is purported to be largely driven by the fact that the baby boomer generation (born between 1946 and 1964), which accounts for approximately 22% of the American population, is now entering older adulthood [4]. As such, the aging of this group will significantly affect the size and characteristics of the geriatric population, including patterns of substance use [5]. Therefore, with an estimated 5.7 million older adults in the United States requiring addiction treatment in 2020 [6–8],

the number of older adults with substance use disorders is expected to continue to rise over the next decade.

The concerns described above also include opioid use among older adults. The opioid epidemic, which has been associated with a high burden of morbidity and mortality in the general population, has not left older adults unscathed [9]. Furthermore, the use of opioids by older adults carries specific risks and treatment considerations [5]. The goal of this review is to provide a comprehensive overview of problematic opioid use and use disorder in the older adult population. In terms of specific objectives, this article will provide readers with an up-to-date review of the epidemiology of problematic opioid use among older adults. This will be followed by an approach to screening and diagnosis in this age group, while highlighting risk factors for problematic opioid use among older adults. Subsequently, this review will present the physiological changes of aging that can impact opioid pharmacokinetics and accompanying adverse effects. The article will conclude with an overview of the available pharmacological treatments for problematic opioid use in older adults, informed by recommendations from recent American, British and Canadian guidelines. This broad and thorough overview is meant to increase awareness of this topic, while also providing the basis for diagnosis and treatment. To accomplish the above objectives, we completed a narrative review of the literature. In our search strategy, there were no limits in terms of date of publication, geographical location or study type. Despite this wide search strategy, identified papers were generally limited to observational studies published after the year 2000 and from Western European and North-American countries. Moreover, there was significant heterogeneity in regard to available research and at what age someone is considered an older adult, ranging from 37 to 65 years in published studies [10, 11]. For the purpose of this review, the term older adults will refer to individuals 65 years of age and older, unless otherwise specified. Due to this paucity of research related to older adults, certain recommendations and discussion points must be gleaned from younger individuals. Lastly, a number of terms are used to describe opioid use in the literature and will be used throughout this review. This includes appropriate medicinal use of opioids, as well as the diagnosis of opioid use disorder (OUD) as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [12]. In between appropriate medical use of opioids and OUD is the concept of problematic opioid use, which can encompass a number of behaviours (e.g. using higher then intended doses, stockpiling medication and combining opioids with other psychoactive medications) and medical or psychosocial consequences [13]. It should be noted that an individual engaging in problematic opioid use may or may not meet criteria for OUD. However, an older adult with OUD would by DSM-5 definition be engaging in problematic opioid use, as the basis of this diagnosis includes the use of opioids resulting in significant medical or psychosocial impairment [1, 13]. As such, for the purpose of this paper, OUD can be seen as a severe form of problematic opioid use.

2 Epidemiology of Opioid Use among Older Adults

It is first important to discuss the epidemiology of opioid use among older adults as well as recent trends, as this will help to describe a growing concern in this cohort. Currently, the rate of OUD among older adults is estimated to be small, with an American survey reporting a 12-month prevalence of 0.13% among adults over the age of 50 years [14]. However, the prevalence of OUD disorder among older adults was noted to triple from 2013 to 2018 as determined by cross-sectional analysis of American Medicare data [15]. Rates of problematic opioid use have also been observed to be increasing as noted by a national survey completed in the United States, with 2.0% of adults over the age of 50 years identified as having engaged in past year problematic opioid use in 2014, as compared with 1.1% in 2002 [16]. Moreover, this increase in problematic opioid use appears to be occurring alongside an increase in the proportion of adults over the age of 55 years presenting for treatment of OUD, with this age group accounting for 14.1% of admissions related to heroin use in the United States in 2005 as compared with 5.9% in 1991 [17, 18].

While rates of diagnosed OUD are relatively small in this population, exposure to opioids is not uncommon, with approximately 15% of community-dwelling individuals over the age of 50 years being provided a prescription for opioids at some point within the past year, as reported by a cross-sectional analysis of American Medicare data [19]. Further, the prevalence of problematic use has been noted to be higher in certain groups of older adults. For example, a cross-sectional study from New York identified that in individuals over the age of 50 years prescribed opioids for chronic pain, up to 35% reported misusing their prescription [20]. Rates of OUD are common in the clinical setting. For example, a cross-sectional analysis of American addictions treatment data identified that among adults over the age of 55 years, opioids were the primary substance of use in approximately 20% of treatment admissions [17]. Problematic opioid use is also associated with emergency department (ED) presentation and admission [21]. A cross-sectional study examining American ED visits related to problematic opioid use in older adults identified an approximate 220% increase in ED presentations from 2006 to 2014 [21]. From this same study, older adults presenting with problematic opioid use were more likely to be

hospitalized or suffer injury than older adults with no problematic use identified [21]. In a 10-year, cross-sectional analysis of Canadian hospital admissions, older adults had the highest rate of hospitalizations for opioid poisonings [22]. Further, based on cross-sectional analysis of American Poison Center data from 2011 to 2012, individuals over the age of 60 years had the highest rates of mortality due to accidental and intentional opioid overdoses. Data from this study also identified an increase in the rate of overdoses associated with suicidal intent in this population [23]. Lastly, data from the Veteran's Health Administration National Patient Care Database in the United States identified that individuals over the age of 50 years diagnosed with OUD had an increased all-cause mortality rate as compared with younger adults with OUD [24]. In addition, individuals over the age of 50 years with OUD had an increased relative risk of death related to human immunodeficiency virus (HIV), liver disease and opioid overdose as compared with age-matched healthy controls [24].

A number of studies have provided information regarding the physical and mental health of older adults with OUD and problematic opioid use. OUD in individuals over the age of 50 years has been shown to be frequently comorbid with a number of psychiatric illnesses as noted in a systematic review, including major depressive disorder, anxiety disorders, post-traumatic stress disorder (PTSD) and other substance use disorders [25]. Additionally, cross-sectional analysis of national survey data from the United States documented an increased prevalence of suicidal ideation among individuals over the age of 50 years who engage in problematic prescription opioid use [26]. Furthermore, observational studies from the United States and Canada have noted that older methadone maintenance patients are frequently afflicted by numerous physical comorbidities such as arthritis, hepatitis C, hypertension, cardiac illness, respiratory disease (e.g. chronic obstructive pulmonary disease [COPD]), cirrhosis and diabetes mellitus [27, 28]. A major limitation of the above research is that the type and route of problematic opioid use, as well as the duration of illness, is not clearly stated. This is notable as the clinical picture of older adults who have engaged in long-term intravenous heroin use may differ significantly compared with older adults who developed problematic use of prescription opioids later in life. The former group would likely be more at risk of bloodborne infections and associated complications. This has been documented in a 33-year cohort study of aging heroin users, which noted that 94.2% tested positive for hepatitis C, 85.6% for hepatitis B and 1.8% for HIV [29]. Despite this limitation, the preceding research suggests that problematic opioid use is a growing concern in this population, associated with significant morbidity and mortality.

3 Risk Factors for Problematic Opioid Use among Older Adults

Along with understanding the general trends of opioid use in the older adult population, it is also important to develop an appreciation for biological and psychosocial risk factors at an individual patient level, as this will aid with screening and diagnosis of problematic opioid use (see Sect. 4). From a biological perspective, the presence of chronic pain as well as its severity and functional impact have been identified as risk factors for problematic opioid use in older adults [13, 20, 30]. This is notable as an American cross-sectional survey identified that approximately 40% of community dwelling older adults suffer from chronic pain [2, 30, 31]. In addition, individuals over the age of 50 years are more likely to have both cancer and non-cancer pain (e.g. neuropathies, arthritides) compared with the general population [32]. Further, chronic pain increases the likelihood of exposure to prescription opioids, which in turn is a significant risk factor for the development of OUD [13]. In addition to pain, a cross-sectional analysis of American ED visit data reported that the presence of chronic medical conditions was associated with a greater risk of problematic opioid use among older adults, with increased number of comorbid conditions conferring greater risk [21].This same study also identified alcohol use disorder (AUD) as a possible risk factor for problematic opioid use [21]. Additionally, a number of other biological risk factors have been identified among older adults with AUD. These factors should not be taken as specific for OUD, though they may be generalizable. These risk factors include physical disability, poor health status, non-opioid substance use disorders and polypharmacy [1]. From a psychological perspective, a cross-sectional study from the United States identified that depressive symptoms are associated with increased risk of problematic opioid use in older adults [30]. There are also a number of social factors that have been identified in other older substance use populations that should be considered when discussing risk of OUD. Specifically, older individuals are frequently beset with challenges such as bereavement, retirement, social isolation, functional decline and institutionalization [1]. These challenges may increase the risk of problematic substance use. Other social risk factors that have been suggested include low education, low-income status, never married and lack of employment [14]. Lastly, older women appear to be at greater risk of problematic prescription opioid use, whereas older men are generally at greater risk of other forms of problematic substance use [1, 13].

4 Screening for and Diagnosis of Problematic Opioid Use among Older Adults

Given the concerns related to problematic opioid use in this population, it is important to have an approach to screening and diagnosis. As per Canadian and British guidelines, all older adults presenting to clinical services should be screened for substance use and substance use disorders [33, 34]. Unfortunately, there are no validated screening tools for OUD in this population [33]. However, there are a number of warning signs that suggest that a patient is using prescription opioid medications in a problematic manner, prompting further screening. Such signs include over-reporting of symptoms, unauthorized dose escalations, reporting lost prescriptions, use of other illicit drugs and cognitive impairment [35]. British guidelines recommend that screening be carried out in an empathetic and open manner, seeking information regarding quantity and frequency of substance use [33]. As in younger individuals, diagnosis of OUD in older adults is through the application of the DSM-5 criteria. However, as noted in a prior review by Kuerbis et al., these criteria may not be fully applicable in older adults. For example, several of the DSM-5 criteria are related to social impairment (e.g. failure to fulfil role obligations, interpersonal problems and reduction in social activities). These criteria may be less applicable among older adults as they generally have fewer role obligations and engage in fewer social activities [1]. Further, two of the DSM-5 criteria relate to tolerance and withdrawal. These features may be more difficult to detect in this population as older adults can present with more subtle withdrawal symptoms. Individuals also generally become more sensitive to substances over time, resulting in an apparent decrease in tolerance [1]. Given the concerns regarding the application of the DSM-5 criteria in this population, alternative terms such as 'problem use' have been suggested for older adults. In regard to opioids, problem use would be defined as the use of opioids resulting in social, medical or psychological consequences. Quantity and frequency are not considered when diagnosing problem use [1]. Regardless of diagnostic criteria used, a thorough assessment should be completed, the components of which include substance use history, past medical history, past psychiatric history, pain assessment and social history. A physical examination should also be completed, examining for signs of intoxication, withdrawal and physical sequelae (e.g. injuries related to falls) [1, 34]. Laboratory investigations should be guided by history and physical examination [34].

Complicating the diagnosis of OUD in this population is evidence that older adults are screened, assessed and treated less frequently for substance use concerns compared with younger adults [5]. One potential barrier is the possibility of perceived shame on the part of the patient or health-care worker [2]. Additionally, there is the misconception that substance use is not common in this population [12, 18, 36, 37]. Another limiting factor is the misattribution of symptoms related to substance use (e.g. cognitive impairment, falls, depression) as being secondary to the normal aging process or other illness (e.g. dementia, major depressive disorder) [2]. Further, there is the misperception due to ageism that older adults would likely not benefit from treatment or that substance use is "one last pleasure" [38]. Lastly, there is the possibility of purposeful underreporting or that cognitive impairment may limit a patient's accurate recall of substance use [1].

5 Opioid Pharmacokinetics in Older Adults

As individuals age, there are a number of normal physiological changes that occur, in turn leading to notable alterations in opioid pharmacokinetics [35, 39]. An appreciation of these changes is helpful in understanding why older adults may be more at risk of a number of adverse effects. These physiological alterations occur in a number of organ systems, including the renal, gastrointestinal, hepatic and nervous systems [35, 39]. Regarding kidney function, renal clearance declines by 1% per year after the age of 50 [32]. This decline in renal function reduces the clearance of most opioids and can lead to the build-up of metabolites, which are often active and/or neurotoxic [35]. Regarding the hepatic system, the metabolic activity of the liver is reduced by a decrease in size and reduced blood flow. Moreover, there is an associated decrease in first-past metabolism that can increase the bioavailability of certain orally administered opioids (e.g. morphine) [40]. Further, aging is associated with an increase in the percentage of body fat, delaying the elimination of lipophilic agents (e.g. fentanyl and methadone) that accumulate in this tissue. Conversely, there is a decrease in total body water, reducing the volume of distribution and increasing the concentration of water-soluble metabolites [32]. Lastly a number of changes in various neurotransmitters, such as the dopamine, glutamine and serotonin systems, have been observed with aging [41]. Together, these changes can narrow the therapeutic index and increase the likelihood of adverse effects associated with opioid use in older adults [39].

6 Adverse Effects Related to Opioid Use among Older Adults

Use of opioids by older adults can be associated with a number of significant adverse effects, including sedation, impaired motor coordination, dizziness, risk of falls,

constipation, respiratory depression, anorexia, nausea and impaired cognitive functioning [13, 35]. In addition to increased risk of falls, opioid use in this population is associated with greater fall-related injuries such as non-spinal and hip fractures [42, 43]. The risk of constipation associated with opioid use is increased in older adults as aging is associated with decreased gastric and intestinal motility, as well as reduced absorption [35]. In addition to discomfort, constipation can be associated with significant outcomes such as faecal impaction and bowel perforation [44]. Use of opioids can also affect respiratory function, leading to sleep-disordered breathing or a worsening of underlying obstructive sleep apnoea in older individuals [45, 46]. Risk of respiratory depression can be further compounded in older adults by accumulation of medical comorbidities (e.g. COPD and congestive heart failure) as well as decreased renal clearance of active metabolites [35]. From a cardiac standpoint, a cohort study from the United States identified that opioid use is associated with an elevated relative risk of cardiovascular events (e.g. myocardial infarction, stroke, heart failure) in older adults as compared with other analgesic medications (e.g. nonsteroidal anti-inflammatory drugs) [47]. Regarding neuropsychiatric symptoms, use of opioids has been associated with delirium [48]. Moreover, a systematic review of studies in younger adults demonstrated that opioid use is associated with cognitive impairments in several domains such as learning and memory as well as complex attention [49]. These neurocognitive effects are important to consider in older adults who may already have underlying cognitive impairment. An appreciation of these adverse effects is important both for counselling patients using opiates, and when employing opioid agonist treatment (OAT) as will be discussed in section 7.

7 Pharmacological Treatment of Opioid Use Disorder among Older Adults

The management of individuals with problematic opioid use meeting the criteria for OUD involves detoxification and/or maintenance treatment, most commonly with methadone or buprenorphine. At this time, there are no randomized control trials that have specifically examined the effectiveness of pharmacological strategies in adults over the age of 65 years [10]. Additionally, older adults have been excluded from many trials conducted in the general population [50]. Lastly, while a number of studies did not exclude older adults, no sub-analysis of this age group was reported [10, 11, 50, 51]. Much of what will be discussed is gleaned from studies examining younger adults with OUD. What is encouraging, and has been documented in multiple studies, is that older adults with a substance use disorder, as compared with the general population, are more adherent with treatment recommendations and have outcomes that are equivalent if not better [52]. Evidence regarding treatment options is also lacking in regards to older adults with problematic opioid use and not meeting criteria for OUD. At this less severe stage, interventions should be focussed on the detection of problematic use and the prevention of OUD. These interventions could include but are not limited to annual urine drug screening in individuals prescribed opioids for chronic pain, restricting prescribed opioid dose with a defined upper limit, and referral for evidence-based treatment if OUD is diagnosed [53, 54]. A full discussion of prevention practices and safe opioid prescribing strategies is outside the scope of this paper and these are detailed in Canadian and American guidelines [53, 54].

The first stage of treatment for OUD is detoxification and management of acute opioid withdrawal. Symptoms of opioid withdrawal include nausea, vomiting, diarrhoea, lacrimation, rhinorrhoea, diaphoresis, piloerection, autonomic arousal (hypertension, mydriasis and tachycardia), yawning, myalgia, irritability, insomnia and anxiety [9, 55]. In addition, withdrawal symptoms in older adults may be further worsened by a higher prevalence of comorbid chronic pain [35]. The course of withdrawal is variable and depends on the half-life of the opioid that the individual was using. For short-acting opioids (e.g. morphine, heroin), withdrawal symptoms can appear within 8–12 h of the last dose, peaking within 24–72 h and diminishing over 3–5 days. The course of withdrawal for opioids with longer half-lives is more protracted [9, 35]. While non-life-threatening, withdrawal symptoms are distressing and associated with significant discomfort. If not treated, withdrawal symptoms can increase the risk of relapse [35]. Pharmacological interventions that can be used in this phase include OAT with buprenorphine or methadone. These medications reduce withdrawal symptoms and opioid cravings due to their pharmacological activity at the μ-opioid receptor [55]. In addition to OAT, there are a number of non-opioid options that can be employed for symptomatic treatment. These medications include α-2 adrenergic agonists (e.g. clonidine, lofexidine), antidiarrhoeal medications (e.g. loperamide), analgesics (e.g. acetaminophen, NSAIDS, gabapentin), anti-nausea medications/antiemetics (e.g. ondansetron) and medications for sleep (e.g. trazodone, doxepin, quetiapine). Guidelines developed specifically for the treatment of OUD in older adults (age ≥ 65 years) recommend OAT as the first-line treatment of withdrawal symptoms in this population [34]. This recommendation is made based on the evidence of superior efficacy for OAT over non-opioid medication treatment of withdrawal symptoms in the general adult population [34, 56]. Regarding OAT for withdrawal symptoms, both buprenorphine and methadone have been shown to be equally effective [56]. However, buprenorphine is recommended over methadone due to a more favourable safety

profile, as methadone carries a greater risk of overdose at the time of induction, as well as other adverse effects that are discussed below [34]. If a patient cannot tolerate or refuses OAT, use of non-opioid medications could be considered in a time-limited fashion [34]. In addition to inferior efficacy, non-opioid medications can be associated with a number of adverse effects. For example, a Cochrane review reported that clonidine is associated with increased risk of postural hypotension as compared with methadone, and may increase the risk of falls [57]. Other non-opioid medications such as quetiapine, trazodone and doxepin are from medication classes that are associated with an increased risk of falls in individuals over the age of 60 years [58]. Benzodiazepines, which are sometimes used in younger individuals, are not recommended for treatment of withdrawal symptoms in this population due to their sedating and cognitive side effects and associated increased risk of falls [58, 59].

Following detoxification and management of withdrawal, it is recommended that patients receive ongoing maintenance treatment with an opioid agonist. Ongoing opioid agonist treatment has been associated with reduced risk of relapse and overdose, as compared with individuals who only undergo detoxification [34]. Recently published guidelines for the treatment of OUD in older adults (aged ≥ 65 years) recommend buprenorphine over methadone for maintenance therapy, due to risk of adverse effects and other safety concerns associated with the latter [34]. In terms of effectiveness, a Cochrane review reported that when used at high fixed doses, buprenorphine is as effective as methadone for maintenance therapy in regards to retention in treatment, suppression of illicit opioid use and reduction of mortality in the general adult population [9, 50]. Unfortunately, no studies have examined the outcomes of buprenorphine treatment in older adults.

Buprenorphine is a partial μ-opioid receptor agonist and κ- and δ-opioid receptor antagonist. Buprenorphine has high affinity for and low intrinsic activity at the μ-opioid receptor and will displace full opioid agonists [60]. In addition to reducing opioid cravings, buprenorphine's pharmacological profile will reduce the effects of illicit opioids (e.g. euphoria, respiratory depression) [55]. For the most part, buprenorphine is not metabolized and is excreted unchanged through the biliary system [61]. A portion of the parent drug is metabolized by the liver into multiple metabolites, which are excreted by the biliary system or by the kidneys [39]. Buprenorphine can be prescribed safely in individuals with renal impairment, as there is no significant accumulation of active metabolites, and no adjustments are required [60]. As buprenorphine is metabolized by the hepatic system, dose reductions could be considered in the context of hepatic disease, though its pharmacokinetic profile has been shown to be relatively unchanged in mild–moderate hepatic impairment [39, 60]. Combination formulations that also include naloxone should be used cautiously in moderate hepatic impairment and avoided in severe hepatic disease. This caution is due to reduced clearance of naloxone and the possibility of precipitated withdrawal [55]. Metabolism relies in part on the activity of the cytochrome P450 (CYP) 3A4 enzyme, though this accounts for only 30% of buprenorphine's metabolism and the risk of clinically relevant drug–drug interactions is felt to be low [39].

Buprenorphine is currently available in multiple formulations including a sublingual tablet/film, a transdermal patch, monthly subcutaneous injections and an implantable form. There are also sublingual tablets/films that contain both buprenorphine and naloxone. Guidelines for the treatment of OUD in older adults (age ≥ 65 years) recommend that the sublingual formulation of buprenorphine be used for initiation [34]. Formulations that contain both buprenorphine and naloxone should be used to limit possible diversion and intravenous use [34]. There is a lack of research regarding initiation doses, titration schedules and other dosing parameters for buprenorphine in this age group. The aforementioned guidelines recommend reducing the initial dose by 25–50% and lengthening the interval between dose escalation by 25–50% in older adults [34]. Further dose adjustments should be considered in the context of each individual, taking into account co-prescribed medications as well as psychiatric/medical comorbidities. For treatment of withdrawal in general adults, the American Society of Addiction Medicine (ASAM) recommends starting buprenorphine at a dose of 2–4 mg with titration as needed until withdrawal symptoms are supressed (target range of 4–24 mg per day) [9]. As it is only a partial agonist, buprenorphine can precipitate withdrawal symptoms by displacing full opioid agonists at the μ-opioid receptor. Therefore, standard doses of buprenorphine should only be administered once patients are experiencing moderate withdrawal symptoms [62]. The risk of precipitated withdrawal can be limited through use of the transdermal formulation or micro-dosing protocols [63, 64]. Buprenorphine is well tolerated in adults over the age of 50 years with common adverse effects including sedation, constipation, nausea/vomiting, headache, dry mouth, peripheral oedema and dizziness [60, 65].

If treatment with buprenorphine is ineffective or intolerable, methadone maintenance therapy should be considered. Methadone is a full μ-opioid receptor agonist and *N*-methyl-D-aspartic acid (NMDA) receptor antagonist [66]. Use of methadone is made challenging by complex pharmacokinetics with variability in absorption, bioavailability, distribution and elimination [62]. Methadone is metabolized by the liver to a number of inactive metabolites that are mostly excreted in the urine, or to a lesser degree through the faecal route

[40]. In the context of severe renal impairment, the half-life of methadone increases and dose reductions should be considered in individuals with a creatinine clearance of < 10 [40, 67]. Methadone should also be used with caution in individuals with hepatic disease [9]. In terms of drug–drug interactions, methadone is metabolized in part by CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. There is a significant risk of drug–drug interactions with medications that induce or inhibit these enzymes, as this may lead to increased methadone serum levels and the possibility of adverse effects (e.g. respiratory depression, QT interval prolongation) [39]. Methadone itself is a weak inhibitor of CYP3A4 and may impact the levels of medications metabolized by this enzyme [55].

Methadone is available in multiple per os (PO) formulations including a liquid concentrate, dissolvable powder and tablets. The Substance Abuse and Mental Health Services Administration (SAMHSA), based in the United States, recommends instating methadone at lower doses in adults aged > 60 years, suggesting an initial range of 10–20 mg [55]. Even lower initial doses (2.5–10 mg) are recommended for individuals with low opioid tolerance [55]. Maintenance doses are generally in the range of 60–120 mg PO daily [9, 55, 68]. Full details regarding the initiation and titration of methadone are outside the scope of this review and are discussed elsewhere [9, 55]. Notable adverse effects associated with methadone include respiratory depression and QT interval prolongation, which in turn is associated with a risk of serious arrhythmia [62]. These concerns are notable for older adults, indicated by a British cohort study that identified an approximate quadrupled risk of methadone-specific death in individuals over the age of 45 years [69]. Initiation of methadone carries a risk of sedation, respiratory depression, respiratory arrest and death. This is due to methadone's full agonist activity at the μ-opioid receptor, imperfect cross-tolerance and variable pharmacokinetics [34, 68]. Due to the risk of respiratory depression, methadone use should be avoided in individuals with significant respiratory insufficiency [9]. Regarding the effects on the QT interval, methadone should be used cautiously in older adults co-prescribed other QT-prolonging medications, use of medications that inhibit CYP3A4, history of structural heart disease, past history of arrhythmia, unexplained syncope, electrolyte abnormalities or other risk factors for QT prolongation [9, 55, 70]. An ECG should be obtained prior to initiating methadone and be repeated within 30 days of starting the medication [62]. If the QTc is between 450 and 500 ms, patients should be informed of the risks/benefits of initiating or continuing methadone treatment. Treatment should not be initiated if the QTc is > 500 ms. Further, if during treatment the interval is found to be > 500 ms, a reduction in dose, addressing other factors associated with QTc prolongation or a switch to buprenorphine should be considered [55].

Comparing the two forms of OAT, buprenorphine is recommended as a first-line option over methadone [34]. This is because of its more favourable safety profile. Unlike methadone, buprenorphine is not associated with QT prolongation, and is considered safer than methadone in older adults with underlying cardiac disease [62, 71]. In addition, buprenorphine is safer in overdose and less likely to cause respiratory depression and respiratory arrest than other opioids, including methadone. This is due to the fact that buprenorphine is a partial agonist and has a ceiling effect in regard to respiratory depression [35, 62]. As such, buprenorphine may also be a safer choice in older individuals with underlying respiratory disease [55]. Both methadone and buprenorphine should not be used concurrently with alcohol or benzodiazepines due to the risk of life-threatening respiratory depression [9]. Methadone may also be associated with a greater risk of constipation as compared with buprenorphine [72]. In terms of impact on cognition, prior evidence suggests a similar pattern of impairment in individuals treated with either buprenorphine or methadone [73]. Buprenorphine may be more accessible to older patients, specifically in regards to take-home dosing or long-acting formulations [34, 74]. Further, buprenorphine can be prescribed in office-based treatment settings, unlike methadone, which is only delivered through opioid treatment programmes (OTPs) [9]. Buprenorphine may be more accessible to home-bound older adults, as it has become increasingly more common to initiate this treatment in the home setting, which is not possible with methadone [9]. Individuals on methadone maintenance treatment may be unable to access services if they become housebound or if they require admission to a long-term care facility [75]. Despite these concerns, methadone is still an effective option that can be implemented safely if a trial of buprenorphine is ineffective or intolerable.

While there are no randomized controlled trials documenting the effectiveness of methadone maintenance treatment (MMT) in this population, information regarding the interplay between MMT and age can be gleaned from a number of observational studies. A 2011 cohort study from Switzerland noted that between 1996 and 2003 there was a ten-fold increase in the number of adults aged > 50 years treated with methadone, and that this age group had a reduced risk of past-month heroin use as compared with younger individuals [76]. Further, older age appears to predict retention in MMT, as documented by cohort studies from the United States, Tanzania, Indonesia and China [77–81]. In terms of the possible benefits of methadone, a 2018 systematic review of observational studies identified that older adults in MMT were often noted to have improved measures related to substance use as compared with younger individuals [10]. In one retrospective chart study from the United States, individuals aged > 40 years who were retained in MMT demonstrated a reduction in substance use as well as improvements in

addiction severity scores related to drug use and psychiatric, medical and legal problems, as compared with individuals who dropped out of treatment [82]. However, this study also noted that older individuals retained in treatment continued to have multiple physical health comorbidities such as diabetes, hepatitis C, liver and gastrointestinal cancer as well as premature mortality. This suggests that treatment of older adults requires a holistic approach, not simply focussing on MMT [82]. While further research is needed, the available data does support the use of methadone in this population [10].

If the aforementioned strategies are ineffective or intolerable, a number of third-line options could be considered. If a patient has achieved a sustained period of abstinence, treatment with naltrexone could be considered in cases where OAT is not acceptable to the patient, or otherwise contraindicated (e.g. patients requiring opioids for pain control) [34]. Naltrexone is an opioid receptor antagonist that blocks the effects of opioids. Benefits of naltrexone included limited drug–drug interactions, lack of respiratory depression, lack of sedation and lack of abuse/diversion potential [55]. Naltrexone can be associated with an increase in liver enzymes and should be used cautiously in individuals with liver disease, and is contraindicated in the context of acute hepatitis [9]. Naltrexone can be used safely in individuals with renal impairment and no dose adjustments are required. Naltrexone is available as an oral formulation that is taken daily, or an extended-release monthly injection. Multiple trials have shown that extended-release naltrexone is effective in regards to reduction in opioid use, retention in treatment and maintenance of short-term abstinence [83–85], whereas the oral formulation has not been shown to be superior to placebo [34, 86]. To avoid precipitated withdrawal, extended-release naltrexone should only be initiated after a sufficient period of detoxification [9]. Naltrexone is easily accessible and can be prescribed in office-based settings [75]. While not studied specifically in older individuals with OUD, a randomized controlled trial from the United States noted that naltrexone was well tolerated by adults aged > 50 years with AUD [87]. If naltrexone is ineffective or individuals are unable to maintain abstinence, daily witnessed ingestion of a slow-release formulation of morphine could be considered for patients that require ongoing substitution. Associated risks of this intervention include liver toxicity, hyperalgesia and immunosuppression. Slow-release morphine should not be used in older adults with renal impairment [34]. There are no studies examining the effects of slow-release morphine in this population.

8 Conclusion

Opioid use as well as substance use in general is a common occurrence in older adults, though often overlooked and undertreated [1, 2, 88]. Available evidence suggests that the number of older adults with substance use disorders is likely to increase with the aging of the population [6–8]. Previous estimates have predicted a doubling in the number of individuals aged of > 50 years with substance use disorders in the United States, from 2.8 million in 2006 to 5.7 million in 2020 [8]. A proportion of this increase will likely be due to OUD. Further, the availability of age-specific services is limited in many countries such as Canada, the United Kingdom and the United States [33, 34]. Lastly, access to appropriate programmes may be limited by isolation, financial constraint, physical impairments and lack of transportation [1]. As such, policy and treatment must be updated to address this increasing concern.

Available guidelines specific to the older adult population recommend that all individuals be screened for problematic opioid use and OUD [33, 34]. In older adults with OUD, treatment should be initiated in the detoxification stage and include maintenance strategies. Buprenorphine is recommended as first-line treatment, followed by methadone. At this time, there is a lack of high-quality research regarding the effectiveness of treatment in this population. However, the limited data available suggests that older adults treated for OUD respond as well as, if not better than, younger individuals [1, 10, 52]. Similarly, there is a dearth of evidence regarding the treatment options for older adults with problematic opioid use not meeting the criteria for OUD. At this stage, prevention strategies such as the implementation of safe opioid prescribing practices should be considered [53, 54].

These conclusions highlight the limitations of available research as well as areas for future consideration. A major limiting factor in the current research is the lack of consensus regarding the age at which one is considered an older adult, ranging from 37 to 65 years in published studies [10]. This age range represents significant clinical heterogeneity as it is well documented that ageing is associated with increased burden of comorbidities and use of medications, suggesting that an older adult with OUD could have drastically different treatment needs and complications than someone aged < 65 years [89, 90]. As such, future research should endeavour to use a standardized age, which will allow for a better understanding of this unique age group as well as allow for more appropriate comparisons between studies. Moreover, research is needed to fully describe the extent of OUD in the older adult population. Additional information is needed regarding specific risk factors for the development of OUD. This should also be complemented by further characterization of the differences between older adults with OUD due to illicit substance use versus prescription opioid use, as this will allow for a better understanding of each group's specific needs. There is also a need for randomized controlled studies examining the effectiveness of OAT when employed in older adults, as well as other non-opioid-based

treatments and psychosocial treatments. Further evidence is also required to delineate the specific treatment needs of individuals with problematic opioid use without OUD. Older adults with OUD are also noted to have a number of comorbid physical and mental health conditions. Even with appropriate treatment of their substance use disorder, these co-occurring conditions and lifestyle behaviours are associated with premature mortality [80]. As such, due to the complex needs of this population, the development of holistic services will be needed to provide individuals with treatment in the context of their specific medical and psychological needs, while also addressing age-related barriers.

Declarations

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