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Geriatric Disorders (D Steffens and K Zdanys, Section Editors)

Pharmacology of Geriatric Substance Use Disorders: Considerations and Future Directions

Corey Hassell, B.A. M.D.[1]
Kirsten Wilkins, M.D.[2]
Louis A. Trevisan, M.D.[2,*]

Address
[1]Frank H. Netter, M.D. School of Medicine, Quinnipiac University, Hamden, CT, USA
[*,2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
Email: Louis.trevisan@yale.edu

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Opinion statement

The aging of the baby boomer generation, with its relatively high rates of substance use disorders, will necessitate a broader understanding of the treatment of geriatric addiction and will require greater availability of evidenced-based pharmacological treatment options. The appropriateness of various treatments depends on the unique needs of this population. Limitations of treatment of substance use disorders in older adults are often attributable to dysfunctions in metabolism, as well as increased risk of adverse effects of certain drugs in the geriatric population. There has been some established success in treating substance use disorders in geriatric populations using currently available pharmacological treatments, however. Considering the available evidence-based treatments for substance use disorders in younger adults and adhering to the classic geriatric dictum of "start low, go slow, and monitor carefully" may serve as useful starting points in treating older adults in the absence of an abundance of high-quality clinical trials to guide evidence-based treatments in this population.

Introduction

As the current generation of "baby boomers" moves into late adulthood, the need for reliable evidence-based pharmacological treatments for substance use disorders (SUDs) will become increasingly urgent. By 2050, the

older adult population is expected to reach 80 million people, up from 33 million in 1994 [1]. This growing new population of older adults is expected to have a significant burden of substance use disorders. It is estimated that up to 17% of adults aged 60 and older may be affected by substance abuse [1]. Coming of age during the counterculture movements of the 1960s, this generation experimented with marijuana and other drugs more openly and commonly than ever before, and use of substances in this group continues in older age at higher rates than observed in previous generations. It is predicted that the number of older adults that will need treatment for SUDs could increase to 4.4 million people in 2020, nearly double the 1.7 million that were receiving treatment in 2000 [2]. Additionally, the recent prescription opioid epidemic will only amplify the problem of SUDs in this population. Further complicating matters, this population will grow in size and age during a time when evidence for treating geriatric SUDs is scarce. This chapter will summarize the primary treatments used for some of the most commonly abused substances in the general population, the evidence base for such treatments in older adults, and the safety considerations in this population.

Alcohol

Overview of treatments

The three most commonly used pharmacological interventions for the treatment of alcohol use disorder (AUD) in the general population are opioid antagonists, acamprosate, and disulfiram. Decades ago, disulfiram was considered the drug of choice used to treat AUD after detoxification, but recent evidence of the efficacy of the opioid antagonists resulted in increasing use as a first-line treatment [3]. There is also emerging evidence for the use of the anticonvulsant gabapentin for treatment of AUD, when used at high dosages [4].

Naltrexone

The opioid antagonist naltrexone is understood to function through inhibition of the opioid receptors responsible for the rewarding effects of alcohol as well as craving. It can be administered on a daily basis orally, or on a monthly basis using an intramuscular formulation [5].

It is ideally used in patients who have already abstained from drinking for a few days, as use of naltrexone while drinking has not been shown to be effective [6]. Interest in naltrexone as a treatment for AUD has existed since the early 1990s, and evidence for the efficacy of naltrexone in treating various aspects of AUD is increasing. Research suggests that opioid antagonists are efficacious in preventing relapses to alcohol use. A 2005 systematic review of 29 randomized controlled trials concluded that naltrexone paired with psychosocial treatment enhanced short-term outcomes in patients, including decreased relapse rates, fewer returns to drinking, fewer alcohol cravings, and fewer days of drinking [7]. Some studies suggest that naltrexone may be more effective to moderate drinking habits rather than to sustain complete abstinence [8]. A systematic review in 2003 analyzed the usage of naltrexone and acamprosate for AUD in adults and concluded that while both drugs are useful treatments, naltrexone appeared to be more effective in reducing short-term relapse rates, whereas acamprosate was more effective in achieving abstinence [8]. Similarly, a 41-study meta-analysis concluded that naltrexone demonstrated efficacy in reducing short-term relapses and decreased frequency of drinking, but lacked a substantial effect on abstinence [9].

Disulfiram

Disulfiram was one of the original drugs used to treat AUD dating back to the 1950s [3]. Its understood mechanism of action is inhibition of acetaldehyde dehydrogenase, resulting in the accumulation of acetaldehyde, which leads to a number of unpleasant effects, including flushing, nausea, dizziness, and changes in heart rate and blood pressure [3]. It can be taken daily orally, or in the form of a one-time implant [3]. Ideally, it is used once an individual has already gone through withdrawal detoxification and is committed to taking the medication once daily under the supervision of family or a treatment program [4]. Evidence for the efficacy of disulfiram in treating AUD is sparse and inconclusive. A review of five RCTs found that disulfiram is modestly effective for decreasing drinking frequencies without significantly enhancing abstinence rates [9]. The reliance on the patient to take the drug on a daily basis has proven to be problematic in achieving the adherence needed for quality studies [10]. Another challenge has been the varied response in patients to the standard 250-mg dose, which in some patients may not be sufficient to produce an alcohol-induced reaction [10]. A meta-analysis of 11 clinical trials reported some support for the ability of disulfiram to reduce drinking frequency, but minimal evidence supporting disulfiram's ability to help a patient achieve abstinence [9]. A trial that studied supervised administration of disulfiram had significantly reduced drinking frequencies and amounts, although the trial was not double blinded [9]. The implanted form of the drug may mitigate the issue of adherence, but its bioavailability post-implantation has not yet been demonstrated in trials [9]. Despite some of these concerns, disulfiram is still believed to be a viable treatment for select patients, including highly motivated patients, older patients with few medical problems, patients with social support, and patients that tend to be impulsive [10].

Acamprosate

Acamprosate is similar to homotaurine, a structural analogue of GABA. It is believed to operate by reducing the post-synaptic efficacy of excitatory neurons, thus attenuating the glutamatergic upregulation experienced by chronic alcohol abusers and facilitating abstinence in patients after alcohol withdrawal [11]. Like naltrexone and disulfiram, it is ideally used once a patient has gone through withdrawal and is committed to abstinence [12]. It is taken orally, three times per day via extended-release tablets [12]. Acamprosate has been shown to be effective in reducing the frequency and amount of alcohol consumption. Evidence for its efficacy in maintaining abstinence has been mixed, however. A European review of 33 RCTs comparing naltrexone to acamprosate revealed that acamprosate was "especially useful in a therapeutic approach achieving abstinence," versus naltrexone's relative efficacy in "controlled consumption" [8]. Another meta-analysis of 41 studies found that acamprosate was effective at reducing drinking frequency, but showed no clear evidence of its benefit for abstinence [9].

Given its different mechanism of action and lack of any known interactions with other drugs, early evidence suggests that acamprosate is most effective when co-administered with another drug, such as naltrexone or disulfiram, especially in patients that have previously failed these drugs as monotherapies [12]. It has been shown that for the outcome of abstinence, combined

naltrexone-acamprosate therapy was more effective than either of the two drugs given as monotherapies [13]. Similar results have been demonstrated when it has been combined with disulfiram: the combination disulfiram-acamprosate was more beneficial than either drug as monotherapy [14]. Despite differing evidence, acamprosate is indicated in patients for whom abstinence, rather than a reduction in drinking, is a goal [6].

Gabapentin

Gabapentin is an anticonvulsant commonly used for the treatment of epilepsy that operates by binding to the alpha-2 delta subunit of voltage-sensitive calcium channels, decreasing excessive neuronal firing and neurotransmitter release [15]. Studies have shown gabapentin to be effective for the treatment of both alcohol withdrawal and AUD by reducing alcohol cravings and alcohol consumption and improving sleep in subjects [16].

A RCT found that high-dose gabapentin (1800 mg) was more effective than lower doses in improving these symptoms in abstinent adults [17].

It has also been found to be beneficial by providing additive effects when combined with naltrexone therapy versus naltrexone plus placebo. A trial of the combination AUD found that, in the early weeks of treatment, it was more effective for decreasing the amount of heavy drinking days, increasing time to return to drinking, and decreasing drinks per day compared with naltrexone alone [18].

Alcohol detoxification

The goal of detoxification is prevention and management of potentially dangerous withdrawal symptoms including autonomic hyperactivity, delirium, seizures, and hallucinations. Pharmacological treatment options consist of benzodiazepines, anticonvulsants, baclofen, gamma-hydroxybutyrate (GHB), and psychotropic analgesic nitrous oxide (PAN). An overview of reviews of studies comparing these five agents found that benzodiazepines were the most efficacious of the group compared to placebo (using seizure prevention as an indicator for efficacy) [19]. Benzodiazepines are the most well-studied and widely used pharmacological treatment for alcohol withdrawal. By acting on the GABAa receptor, they are useful as anxiolytics and for decreasing the occurrence of seizures and delirium tremens. They are generally well tolerated and include specific agents which are not dependent on hepatic elimination [20].

Geriatric considerations in the treatment of AUDs

Naltrexone has been shown to be a tolerable treatment option for adults 50 years and older, with minimal side effects, despite past reports of possible hepatotoxicity with naltrexone use in older adults [21]. A prominent concern of naltrexone is its hepatic metabolism. It has been shown that plasma levels of naltrexone may become significantly elevated in patients with cirrhosis. Thus, in older adults with possible hepatic dysfunction, caution is warranted when administering this treatment [22]. Another possible area of concern is the cross-reactivity of naltrexone with opioid medications, which are increasingly prescribed for pain control among older adults. In opioid-dependent patients, the antagonistic action of naltrexone could precipitate opioid withdrawal

symptoms unexpectedly [22]. Naltrexone does not appear to be metabolized by the CYP enzyme system and is not known to adversely interact with many non-opioid drugs, improving safety of use in an older adult population [22]. The most commonly reported side effects of naltrexone are dizziness, nausea, vomiting, abdominal pain, reduced appetite, and increased daytime sleepiness, all of which could be significant in particular geriatric patients [22]. FDA standard daily dosing of naltrexone consists of 50 mg/day [23], and it has been shown that this dosage to be well-tolerated and effective for decreasing relapse rates in a cohort of adults greater than age 50, with sleep disturbances and anxiety being the most commonly reported side effects [24].

Generally, disulfiram is not recommended for geriatric populations due to its side effect profile [25]. The side effects and/or effects of disulfiram in response to an alcohol challenge may be extremely unpleasant and potentially unsafe in an older adult, including hypotension, tachycardia, hyperthermia, headache, chest pain, respiratory depression, and hyperventilation [22]. Given the potentially intense nature of these effects, it would be crucial to monitor older adult patients treated with disulfiram carefully, especially since the nature of a disulfiram response in an individual is difficult to predict [22]. Disulfiram is hepatically metabolized, so appropriate precautions should be taken in patients with suspected hepatic dysfunction. It is also known to interact with warfarin and phenytoin metabolism [22]. Disulfiram is currently dosed with an initial administration at 250 mg/day, followed by daily subsequent dosing of 125–500 mg/day. The average daily dose currently is 250 mg/day. Proper dosing for elderly patients has not been established, but generally should be approached with lower than the standard doses if indicated [26]. At least one trial has shown disulfiram to be effective at preventing relapse to drinking in an elderly population relative to naltrexone. This study reported administering dosages of 250 mg/day that were well tolerated [27].

Acamprosate appears to have a mild side effect profile most notable for diarrhea, which can be mitigated with decreasing dosage [22]. However, acamprosate's safety profile and efficacy for geriatric populations has not been studied [28].

It is primarily renally excreted, and thus, plasma levels may be elevated in patients with renal dysfunction. Notably, concurrent naltrexone use has also been shown to increase plasma levels of acamprosate [22]. In the elderly and/or those with renal dysfunction, it is currently recommended that acamprosate be administered as 333 mg three times daily and renal function carefully monitored [22].

Gabapentin has been shown to be most effective at doses in the range of 1200–1800 mg, (above two trials) but some older adults may benefit from lower doses. Renal function is a primary consideration to dosing in elderly patients, as this is its primary known means of metabolism, and dosing may be adjusted according to creatinine clearance. Gabapentin's side effect profile includes numerous CNS effects such as dizziness, fatigue, and ataxia, which are of possible concern for an elderly patient [15].

For alcohol withdrawal in elderly patients, benzodiazepines may be utilized, but their possible adverse effects on this population must be considered. As elderly individuals also tend to experience a stronger sedative effect with benzodiazepines in general, dosing and response must be monitored closely. Various dosing schedules may be followed, but frequent monitoring is critical to individualize the treatment plan [20].

Generally, a fixed schedule is beneficial for preventing delirium tremens and seizures in high-risk patients, utilizing oxazepam PO 30–60 mg q4h or lorazepam 1–2 mg PO/IV/IM q4h on day 1, followed by a 50% decrease on days 2 and 3, with continuing q1–2 h for as-needed doses. This schedule risks the possibility of over-sedation and extended stay, however.

Front loading may be used for rapid control of symptoms, using Lorazepam 1–2 mg PO/IM/IV q1–2 h until the symptoms are under control. It has the disadvantage of lacking self-tapering if short-acting benzos are used.

Symptom-triggered dosing is effective for avoiding over-medication and tailoring the treatment to the individual. It is done with oxazepam 30–60 mg PO or lorazepam 1–2 mg PO/IV/IM, given hourly when symptomatic (CIWA-Ar >8–10, check symptoms q4h and 1 h after each medication dose). However, this approach is not proven in patients with past withdrawal seizures.

Anticonvulsants such as topiramate with known cognitive side effects may be relatively contraindicated in geriatric populations [29].

Opioids

Overview of treatments

Currently, the major pharmacological treatment modalities for opioid use disorder (OUD) include naltrexone, methadone, buprenorphine, clonidine, and buprenorphine/naloxone. Treatment goals center largely on maintaining patients in treatment and attenuating withdrawal symptoms [30].

Currently, the majority of treatments are opioid receptor modulators, but there is a role for alpha-2 agonists as well.

Methadone

Treatment with methadone aims to manage opioid withdrawal symptoms, as well as provide maintenance treatment. In addition to stimulating opioid receptors to prevent withdrawal symptoms, it also blocks euphoric effects of opiate drugs, which allows for participation in rehabilitative activities during treatment [31].

As a long-acting opioid agonist, it can be administered once daily and is used for both heroin addictions as well as prescription opioid addictions [31].

Due to its opioid receptor agonist effects, initial dosing must be carefully considered so as not to precipitate an overdose [32]. A meta-analysis of RCTs for methadone maintenance therapy (MMT) reported that MMT was effective for retaining patients in treatment, with fewer self-reports of drug use compared with placebo conditions (drug-free treatment, detox, placebo medications, etc.), as well as a decrease in mortality (that was, however, not statistically significant) [33]. The use of methadone as a maintenance therapy is controversial. Regardless, evidence favors this harm reduction strategy for retaining patients with OUD in treatment and for reducing long-term drug use when compared with detox therapy alone [33].

Naltrexone

Naltrexone is an opioid antagonist and competitively binds to the same receptors as the opioid drug of dependence, thereby reducing feelings of euphoria associated with its use. As naltrexone can precipitate withdrawal symptoms, it is administered 5–7 or 7–10 days after the last opioid or

methadone dose has been taken, respectively [34]. Naltrexone maintenance therapy (NMT) has been shown to be beneficial for retention in therapy, lower opioids in urine screenings, fewer cravings, and less opioids abused during the follow-up period according to a meta-analysis of 15 studies on NMT [35]. It is also suggested that naltrexone may be an effective treatment for preventing relapse to opioid use in dependent drug users, although the poor quality and scarcity of studies in this review called the statistical significance of the studies into question [36]. Still another meta-analysis found naltrexone more effective than placebo for limiting heroin use during therapy, but yielded no statistical significance to the difference when including only studies considering naltrexone versus placebo [37]. While some evidence supports the use of naltrexone for OUD, a common limitation of these studies is heterogeneity of the trials in both intervention and study populations, as well as the difficulty in encouraging populations to participate in longer term studies and follow-up [37].

Buprenorphine

Buprenorphine is a partial opioid agonist. Buprenorphine acts as an agonist at the opioid receptor at low- and mid-range doses and as an antagonist at higher doses giving its pharmacological profile a "ceiling effect" [38]. At higher doses, the pharmacological effects of buprenorphine will begin to plateau, and the OUD patient may experience withdrawal symptoms rather than the expected effect of the buprenorphine. There is thus an upper limit on dosing of buprenorphine due to its partial agonist nature [38].

Buprenorphine has been found to be effective in retaining patients in treatment and for suppressing heroin use at high doses in a meta-analysis comparing it to placebo [39]. It was not found to be effective for low- and medium-dose heroin use suppression.[39] The same analysis found low-dose buprenorphine to be not as effective as low-dose methadone for treatment retention. While flexible-dose methadone is more effective in treatment retention, buprenorphine may still have a role as a substitute for methadone when higher dosages of methadone are required but not feasible [39]. Despite methadone's greater ability to maintain retention, buprenorphine is still used as a first-line treatment as well, as both treatments have been shown to be effective at decreasing overall opioid use [39].

Buprenorphine/naloxone

Buprenorphine/naloxone (b/n) is a first-line treatment for OUD. In addition to the partial agonist opioid agonist action of buprenorphine, naloxone exerts its effects through full antagonism of opioid receptors. The overall result is opioid stimulation at low doses, with antagonistic effects at higher doses [40]. The naloxone component is included in the formulation to prevent diversion and illicit use of buprenorphine parenterally and may precipitate an immediate withdrawal syndrome [40]. It is recommended to induce therapy with buprenorphine alone when there may be other concerns such as pregnancy or the need to determine the etiology of lingering withdrawal symptoms, and switching to the combination b/n once the patient is stable [32]. Similarly to MMT, b/n may possibly impair cognitive functioning in patients and must be administered cautiously [41].

Alpha-2 agonists

Alpha-2 agonists such as clonidine and lofexidine are used to manage withdrawal from opiates. Stimulation of alpha-2 receptors results in an inhibitory effect on the locus coeruleus hyperactivity that occurs during withdrawal [32]. While it is able to produce a quick and long-lasting attenuation of withdrawal symptoms, another agent is usually required for treatment of remaining symptoms [32]. Clonidine is associated with numerous side effects, namely hypotension, but its analogue lofexidine has a milder side effect profile [32]. A review of RCTs evaluating the efficacy of lofexidine for detoxification reveals promising evidence in its role for inducing detoxification, in some cases, in as short a time frame as 5 days [42].

Alpha-2 agonists are also being explored as therapies for ultrarapid detoxification done after precipitation of withdrawal with opioid antagonists while under mechanical ventilation [43]. The alpha-2 agonists are then used to effectively attenuate the withdrawal symptoms. The benefits of ultrafast detoxification on long-term abstinence and treatment retention are still unclear, however [43].

Geriatric considerations in the treatment of OUD

Potential concerns regarding pharmacologic treatment of OUD in the geriatric population stem from the opioid receptor modulating nature of the various treatments. For instance, methadone, as an opioid agonist, has classic opioid side effects of depressing respiratory drive as well as cardiac effects, such as QTc prolongation [44]. Additionally, the pharmacokinetic profile of methadone can be highly variable and difficult to predict. This is especially relevant in the geriatric population, in whom heart disease, renal impairment, CYP-450-inhibiting medications, and medications that affect the QTc may be commonly present [44]. Dosages for methadone are administered as the minimum dose necessary to suppress withdrawal symptoms, can vary widely, and are titrated to the specific needs of the individual. A study that examined effective doses for MMT found a range of effective doses for suppressing withdrawal symptoms from 1.5 to 191.2 mg [45]. While there is not yet established evidence for diminished methadone metabolism due to age, caution due to possible hepatic or renal dysfunction is warranted in dosing for older patients [46].

The primary concern with b/n is that of precipitating withdrawal symptoms in dependent individuals in whom treatment has been started too early, due to its partial agonistic properties [44]. It is thus better to initiate treatment when the patient has abstained from use long enough to experience mild withdrawal symptoms [44]. It is not thought to cause QTc prolongation and may be more appropriate in individuals with heart disease [44]. Dosing for b/n can also vary widely. Many patients will stabilize at an effective dose of 8–16 mg/day, so it is generally recommended not to exceed 16 mg/day for several days to allow the drug to reach a steady state [47]. No established criteria have been published regarding geriatric dosing, but cautious prescribing with close monitoring is recommended, due to possible metabolic differences [48].

Similarly, naltrexone may produce withdrawal symptoms through its antagonistic properties, but is generally safe when not given in the presence of exogenous opioids [44]. Its main side effects include vomiting, diarrhea,

headache, dizziness, arthralgia, anxiety, hepatitis, and irritation at the injection site for the long-acting formulation [44]. Naltrexone is typically dosed orally in adults at 50 mg/day, but it may be advisable to start with 25 mg doses to mitigate side effects [49].

Clonidine's side effects of hypotension, bradycardia, fatigue, and drowsiness are possibly concerning for a geriatric population. Its analogue lofexidine may be more appropriate in a geriatric population given its milder side effect profile [44]. Clonidine is typically dosed in adults at 0.2–0.6 mg/day and lofexidine at 0.6–2.0 mg/day [50].

Benzodiazepines

Pharmacological interventions for benzodiazepine use disorder (BUD) are mostly focused on the management of withdrawal symptoms. In addition to traditional benzodiazepine tapers, pharmacologic treatments studied have included anticonvulsants, anti-depressants, and beta-blockers; a meta-analysis found no efficacy for beta-blockers or antidepressants in terms of withdrawal severity, retention in treatment, treatment compliance, or overall benzodiazepine use [51, 52]. A systematic review found that carbamazepine has been shown to be effective in reducing withdrawal symptom severity and also in "improving benzodiazepine free outcomes" [52]. Pregabalin has also been shown to be effective at attenuating withdrawal symptoms [53].

Geriatric considerations in the treatment of benzodiazepine use disorders

As above, the anticonvulsants carbamazepine and pregabalin have been shown to be effective in attenuating benzodiazepine withdrawal symptom severity in general adult populations. While they have not been studied in the elderly for this purpose, both medications carry side effects of potential concern in older adults. Carbamazepine's possible side effects of nausea, vomiting, dizziness, weakness, fatigue, hyponatremia, hematologic effects, and drug-drug interactions would have to be considered very carefully and monitored closely in older adults [15] Pregabalin is renally excreted which requires careful consideration in an older adult with renal impairment [15]. Carbamazepine is typically dosed at 400–1200 mg/day and gabapentin at up to 600 mg/day. For both, it is suggested to begin at lower dosage ranges in geriatric populations [15].

Nicotine

Pharmacological interventions for tobacco use disorder (TUD) consist largely of nicotine replacement therapy (NRT) and nicotine receptor partial agonists (NRPAs). In NRT, the patient is administered increasingly smaller doses of nicotine to attenuate withdrawal symptoms with the ultimate goal of reaching abstinence. It can be administered in various forms, including gum, patch, nasal spray, oral inhaler, tablet, and, recently, via electronic nicotine delivery systems (ENDS) [54]. Current evidence has shown that all forms of nicotine delivery have increased quitting rates of smoking, and the type of treatment modality is

largely tailored to patient preference [54]. Use of NRT has been shown to increase smoking cessation rates by 50–70%, as well as reducing smoking in those who do not wish to abstain completely [55].

NRPAs include the drugs varenicline and cytisine. They are partial agonists of nicotinic alpha-4beta-2 acetylcholine receptors that are also the target of nicotine delivered from tobacco use. It is believed that these receptors are responsible for the cognition-enhancing and rewarding effects of nicotine. The NRPAs are believed to attenuate cravings through their partial activity on these receptors, which can mitigate the nicotine withdrawal symptoms of irritability, anxiety, and decreased cognitive performance [56]. It has been shown that varenicline is more effective than NRT or bupropion compared to placebo for achieving in smoking cessation, but combining two types of NRT proved to be as efficacious as varenicline alone for this same parameter [57•]. Evidence for the efficacy of cytisine is limited, but two recent studies support its ability to "increase chances of quitting, although long-term efficacy is not well established" [58].

Bupropion is used as an aminoketone antidepressant and acts by inhibiting reuptake of norepinephrine and dopamine [15] It has also been successfully used as a first-line treatment for TUD. Bupropion is considered effective for smoking cessation during the early phase of nicotine withdrawal, and no evidence currently exists to support its efficacy after 7–9 weeks of treatment [59].

Geriatric considerations in the treatment of tobacco use disorders

Among the available pharmacotherapies for treating TUD in older adults, there is evidence that shows NRT therapy to be an effective and safe treatment modality for the geriatric population for long-term abstinence rates, as was shown in a literature review of 12 studies [59].

Older adults have been studied as smaller subset groups of a handful of studies evaluating bupropion for TUD, but unfortunately, no high-quality studies with large sample sizes exist that evaluate the efficacy of varenicline and bupropion in this population for smoking cessation [59].

Within the general population, bupropion has most often been associated with the side effects of insomnia and dry mouth and has been known in some cases to lower the seizure threshold [15]. It should also be given cautiously when administered to patients with renal and/or hepatic impairment [15].

Varenicline has been studied less than both NRT and bupropion. A systematic review found varenicline to be effective for inducing smoking cessation [57•]. While the efficacy of varenicline for geriatric patients for smoking cessation has not been determined, it has been shown to be safe and tolerated well. The most commonly reported adverse reaction was nausea [60].

Cannabis, cocaine, and stimulants

In addition to the drugs previously mentioned, use of cannabis, cocaine, and stimulants may be an emerging problem as the baby boomer generation approaches old age. Cannabis is the third most prevalently used drug (after alcohol and tobacco) among adults aged 50 and above [61]. Usage rates of

cocaine and stimulants are less clear and are based largely on case reports, but older adults are being admitted at higher rates for cocaine and methamphetamine abuse treatment, [62] and abuse of prescription stimulants occurs in a significant minority of older adults and will likely increase as this population enters old age [63]. A multitude of drugs have been reviewed and studied for the treatment of cannabis use disorder, cocaine use disorder, and stimulant use disorder, but to date, none of them have been proven to be efficacious for improving withdrawal symptoms or abstinence/quit rates [64•, 65–71, 72•].

Conclusion

The need for high-quality evidence-based studies in the field of geriatric substance use disorders is a great one and is growing more urgent every year. The epidemics of prescription opioid and benzodiazepine use disorders will soon be more prevalent in older adults and pharmacological treatments tailored to the medical needs of this patient population will be needed. Despite the current paucity of RCTs investigating pharmacological treatments for geriatric substance use disorders, clinicians may utilize the evidence that currently exists for the general adult population and apply it carefully to the geriatric population. Keeping in mind this population's specific needs and adhering to the geriatric dictum of "start low, go slow, and monitor very closely" will be the starting point in treating geriatric SUDs and establishing evidence-based guidelines in the future.

Compliance with Ethical Standards

Conflict of Interest
Corey Hassell declares that she has no conflict of interest. Kirsten Wilkins declares that she has no conflict of interest. Louis A. Trevisan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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