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Special Article

The Safety and Efficacy of Psychedelic-Assisted Therapies for Older Adults: Knowns and Unknowns

C. Bree Johnston, MD, MPH, Maria Mangini, FNP, PhD, Charles Grob, MD, Brian Anderson, MD, MSc

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ABSTRACT

Psychedelics and related compounds have shown efficacy for the treatment of a variety of conditions that are prevalent among older adults, including mood disorders, the psychological distress associated with a serious medical illness, post-traumatic stress disorder (PTSD), and prolonged grief disorder. Psychedelics also have properties that could help provide therapeutic benefits for patients with dementing disorders, as well as promoting personal growth among healthy older adults. This article focuses on psilocybin, a classic psychedelic, and MDMA, a substituted amphetamine with properties similar to classic psychedelics. Both act on the $5HT_{2A}$ receptor. Psychedelics can be safely administered to healthy adults in controlled conditions. However, both psilocybin and MDMA can increase blood pressure and heart rate, which could be a concern if used in older adults with cardiovascular disease. Very few older adults or patients with serious comorbidities have been included in clinical trials of psychedelics to date, raising the question of how generalizable study results are for the patients that most geropsychiatrists will be treating. Research on the neurophysiologic and mechanistic effects of psychedelics in older adults could also provide insights into the aging brain that could have clinical applications in the future.

From the Skagit Regional Health System (CBJ), University of Arizona College of Medicine, 2800 Church Street, Bellingham, WA 98225; Holy Names University (MM), School of Nursing, UC Berkeley Center for the Science of Psychedelics; David Geffen School of Medicine at UCLA, Harbor-UCLA Medical Center (CG), Lundquist Research Institute Affiliation; and the Department of Psychiatry & Behavioral Sciences (BA), UCSF, Zuckerberg San Francisco General Hospital, UC Berkeley Center for the Science of Psychedelics. Send correspondence and reprint requests to C. Bree Johnston MD MPH, Skagit Regional Health System, University of Arizona College of Medicine e-mail: cbreejohnston@gmail.com

Article SummaryA groundswell of interest in the potential therapeutic benefits of psychedelics has emerged over the past few years. This article reviews the most important research studies on psychedelic-assisted therapies published over the past two decades that are likely to be relevant for geriatric psychiatrists and other professionals caring for older adults. The paper also discusses potential safety concerns of using psychedelics in older adults, particularly those with multi-morbidity, and makes suggestions for further research.

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Given the potential of psychedelic compounds to benefit older adults, more research is needed to establish safety and efficacy among older adults, particularly those with multi-morbidity. (Am J Geriatr Psychiatry 2023; 31:44–53)

Highlights

- **What is the primary question addressed by this study?**
  What is the potential benefit of psychedelic medications in older adults?
- **What is the main finding of the study?**
  Psychedelics and related compounds have shown promise in the treatment of a variety of conditions that are prevalent in older adults, including mood disorders, the distress associated with a serious illness, PTSD, substance use disorders, and dementia. Although published research on psychedelic medications has suggested that they are relatively safe when given in controlled conditions, few older people with multimorbidity have been included in clinical trials to date, making the generalizability to older adults with multimorbidity uncertain.
- **What is the meaning of the finding?**
  Given the potential of psychedelic compounds to be beneficial to older adults with a variety of conditions, more research is needed to establish the safety and efficacy of psychedelics in older adults, particularly those with multi-morbidity.

PSYCHEDELIC-ASSISTED THERAPIES FOR OLDER ADULTS

The past decade has seen a groundswell of interest in the use of psychedelic medicines for conditions such as post-traumatic stress disorder (PTSD) and the distress associated with a serious medical illness.[1] The enthusiasm for these compounds is understandable, given the dramatic accounts of improvement reported in both peer-reviewed journals and the popular press.[2] A number of localities have decriminalized psilocybin-containing mushrooms and other psychedelics, and Oregon's measure 109 has established a path for legal "psilocybin services" to be offered in the state starting in 2023. Research is ongoing that may result in reclassification for specific indications of 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin from Schedule 1 of the Controlled Substances Act, paving the way for improved treatment access and expanded research opportunities.

Professionals who work with older adults are often appropriately skeptical about whether the benefits to younger adults shown in clinical trials can be generalized to older, frailer patients, most of whom are excluded from clinical trials.[3] That same skepticism should extend to psychedelics. The conditions for which psychedelics appear to be helpful are prevalent among older adults, so it is important that researchers learn more about the safety and efficacy of these compounds in older patients who may be more vulnerable to adverse effects such as cardiovascular events, dysrhythmias, falls, or delirium.

This paper will review the basic pharmacology of psychedelics, the primary findings of the most important trials that are relevant to older adults, the prevalence of conditions in older adults that might benefit from psychedelic therapies, and what is known about the safety of these substances in older adults, and some thoughts on next steps for studying these medicines in older adults. The term "psychedelic-assisted therapy," refers to the combination of at least one structured and closely monitored psychedelic dosing session with several hours-worth of psychosocial support provided both before and after the dosing session. Because the most robust recent research that is potentially relevant to older adults has been conducted with MDMA and psilocybin, this paper will focus on those two medications.

BACKGROUND

Indigenous peoples have used natural substances containing psychedelic compounds for thousands of years to induce expanded states of consciousness for rites of passage, healing, and to foster spiritual growth and community interconnectedness.[4] Western researchers began studying these compounds after the isolation of mescaline in 1897, the chance discovery of LSD's psychoactive properties by Albert Hoffman in 1943, and Hoffman's later synthesis of psilocybin in 1959.[5] Hundreds of research studies involving thousands of doses of psychedelics were conducted in the 1950s and 1960s for alcoholism, depression, war trauma, and the anxiety associated with a terminal diagnosis.[6] The drugs were also studied for their potential to induce mystical-type states, spur creativity, improve problem-solving, and enhance well-being. Although the results of many of these studies were promising, many lacked the type of study design that would be expected of an experimental protocol today.[7] In 1970 LSD and other psychedelics were placed into the most restrictive category of drugs in the USA, Schedule 1, effectively halting human research for more than two decades.[8]

There has been a so-called renaissance of psychedelic research in the last two decades that has made tremendous strides in furthering understanding of the potential usefulness of these compounds using rigorous scientific protocols. Correctly, it has been pointed out that much of the research has not been inclusive enough of people of color and other marginalized groups.[9] We would add older adults to the list of inadequately represented study participants.

Pharmacology of the Psychedelics

The so-called classic psychedelics include psilocybin, derived from certain mushroom species, mescaline, derived from peyote and San Pedro cacti, and LSD, a synthetic compound derived from the ergot fungus, among others. Extensive research has demonstrated that the classic psychedelics are agonists or partial agonists of serotonin (5-HT) receptors, among which the most important for their psychedelics effects appears to be the 5-HT_{2A} receptor, found in brain, particularly the frontal cortex, the claustrum, parts of the limbic system, and the basal ganglia. In the periphery, the $5HT_{2A}$ receptor is found in vascular smooth muscle, including the gastrointestinal tract.[10]

MDMA is a novel substituted amphetamine that has some similarity in its effects to classic psychedelics, but primarily produces an enhanced sense of empathy, elevation of mood, and less sensory disruption than classic psychedelics. MDMA stimulates release and inhibits reuptake of serotonin, dopamine, and norepinephrine.[11] Similar to classic psychedelics, it has affinity for 5-HT_{2A} receptors.[12]

Psychedelics may act to suppress typical brain communication functions (e.g., the Default Mode Network DMN). This alteration in brain function is associated with the subjective experiences of timelessness, somatic boundlessness, ego dissolution, and perceptual alterations. The clinical response to psychedelic therapies may be mediated, in part, by the induction of a "mystical-type," or transcendent, experience in participants.[13-15] Classic psychedelics may also have anti-inflammatory, analgesic, and other properties that could contribute to their therapeutic effects.[16,17]

Most adverse effects of psilocybin and MDMA have been reported to be mild-to-moderate in severity when administered to healthy volunteers and clinical populations in an optimal therapeutic environment in conjunction with psychosocial support and careful screening.[18,19] From the perspective of physiologic toxicity, psilocybin and MDMA are safe drugs when used at standard doses in healthy adults.[18-20] In a review of adult healthy volunteers and patients (N=257) administered psilocybin across 11 clinical trials the most common physical side effects of psilocybin include hypertension, tachycardia, nausea, and headache; most participants were <65 years old, but at least a few were >70 years old.[18] In phase I and II studies of MDMA-assisted psychotherapy for PTSD (N=107, mean age 41), the most commonly reported physical reactions on the day of the medication session were anxiety, bruxism, lack of appetite, headache, and fatigue.[18-21] The only drug-related serious adverse event in these trials was a transient increase in pre-existing ventricular ectopy that required overnight monitoring. In a pooled analysis of MDMA trials in healthy adults (N=166, mean age 25), MDMA increased systolic blood pressure to >160 mmHg, heart rate >100 beats/-min, and body temperature >38°C in 33%, 29% and 19% of the subjects, respectively.[19] In a phase III trial of MDMA for PTSD (N=90, mean age 41)

no treatment-emergent serious adverse events were seen in the MDMA group.[22]

Potential adverse psychological reactions to psychedelics include precipitating protracted psychotic and manic states.[23] and although the precise risk of inducing such states with psychedelics is unknown, most trials have excluded patients at risk for these reactions. In addition, patients under the influence of psychedelic compounds can be extremely vulnerable, so conducting therapeutic sessions with clear physical and professional boundaries and careful screening of potential clients is critical to safe and therapeutic use.[24]

Acute adverse psychological reactions remain the biggest concern in classic psychedelic administration, and may include fear, panic, paranoia and aggression. Such experiences have been reported most often in the context of nonmedical use.[25] In a phase III trial of MDMA for PTSD (N=90), suicidal ideation occurred in 3 of 46 patients in the MDMA arm versus 5 of 44 patients in the placebo arm. One participant withdrew from the trial after experiencing negative emotions related to clinical assessment questions and an MDMA session.[22]

Researchers have learned that "set" (the mental state with which the participant enters the experience), "setting" (the physical environment, support staff, and other features such as music that surround the experience), and the correct dose of the psychedelic are critical elements than can promote a therapeutic experience and reduce the risk of harm from an acute, challenging psychological reaction. Furthermore, the counseling portion of psychedelic therapy is essential. Frequently patients relate that difficult psychological material encountered during a session while distressing at the moment, can nevertheless be therapeutic when managed by a skilled therapist.[26]

While the controlled use of psilocybin and MDMA have been associated with few severe adverse reactions, and almost no serious adverse reactions, in the modern phase I, II, and III trials conducted over the last thirty years, most study participants administered psychedelics have been relatively healthy and very few were over the age of 60.

Mood Disorders

Life changes, loss, and declining health can contribute to depression among older adults. Two to 5% of community-dwelling adults aged 65 years and older meet diagnostic criteria for major depression.[27] The prevalence of major depressive disorder and overall depressive disorders increases with advancing age and worsening health status.[27-29] Depression and depressive symptoms are associated with poor health outcomes and worse qualify of life in older adults.[27] Yet, one-half to two-thirds of depressed older adults fail to remit with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI).[30-31] In addition, SSRIs and taking daily medications are associated with falls and other adverse effects in older adults.[32-33] For all of these reasons, novel approaches for addressing treatment-resistant mood disorders in older adults are clearly needed.

The FDA recently designated psilocybin as a "breakthrough therapy" for both major depression and treatment-resistant depression, giving it priority consideration in the regulatory process.[1] Psilocybin-assisted therapy has the potential to be a valuable treatment modality for older adults with treatment-resistant depression if safety and efficacy can be robustly demonstrated in this population. Psychedelic-assisted therapy occurs in a limited number of sessions with a limited number of medication administrations, and instead of being an adjunctive treatment to conventional pharmacotherapies like SSRIs, would theoretically be used as an alternative to these drugs. Results from one open-label pilot trial in treatment-resistant depression (N=20, mean age 44 years) and one randomized double-blind waitlist-controlled trial in major depression (N=24, mean age 40 years) suggest that psilocybin therapy may produce large pre-post improvements in depressive symptoms (Cohen's d >2) that persist for weeks after a single dose of the medication.[34,35] A phase II double-blind randomized trial of two doses of psilocybin vs daily escitalopram (both with psychosocial support) in major depression (N=59, mean age 41 years) also resulted in clinically meaningful pre-post changes in depression symptoms, but did not ultimately demonstrate superiority on the primary endpoint at six weeks.[36] As with other psychedelic trials, few patients in these early phase trials of psilocybin for depressive disorders were over the age of 60, and no patients were above the age of 70.

Psychological Distress Associated with Serious Medical Illness

Three-quarters of deaths occur in people aged 65 and older,[37] which means that older adults face terminal illnesses more than any other age group. Patients with cancer and other life-threatening medical illnesses often develop psychological distress with depressed mood, anxiety, demoralization, and reduced quality of life. Demoralization, a form of existential suffering characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life, is highly prevalent among patients with serious medical illness.[38] Over 30% of cancer patients experience mood and other psychiatric disorders,[39] and such disorders are associated with poor clinical outcomes.[40] Standard treatments, including antidepressants, benzodiazepines, and various behavioral therapies, often have limited-to-modest efficacy in these patients.[41,42] In addition, possible drug-drug interactions and the long delay in onset of action of typical antidepressants (e.g., weeks) often make them impractical for patients with medical co-morbidities and short life expectancy.

A pilot trial at UCLA (N=12, age range 36 − 58 years), and two phase II trials at Johns Hopkins University (N=51, mean age 56 years) and NYU (N=29, mean age 56 years) demonstrated that psilocybin therapy can be safe, and can produce sustained improvements in mood, anxiety, and well-being in patients facing a life-threatening cancer diagnosis.[43-46] In both the NYU and the Johns Hopkins studies, a majority of patients receiving high dose psilocybin (0.3 − 0.43 mg/kg po) rated the experience as one of the most personally meaningful of their lives.[14,45] There were no treatment-related serious adverse events in any of these trials, and yet there were few patients over the age of 65 in these studies.

A related, small pilot study (N=18) was conducted at UCSF with demoralized older gay men who were living with long-term HIV/AIDS, all of whom were ≥50 years old (nine were 60-64 years old, one was ≥65 years old), and many of whom had other serious comorbid illnesses. This uncontrolled, open-label pilot study demonstrated the feasibility of administering high-dose psilocybin (0.3−0.36mg/kg po) with adjunctive group therapy to an older and clinically complex patient population, and also resulted in zero treatment-related serious adverse events.[47]

MDMA-assisted psychotherapy has also been assessed in a pilot study for the treatment of anxiety related to a life-threatening illness.[48] This small double-blind randomized placebo-controlled trial (N= 18, mean age 55 years) showed a clinically meaningful pre-post improvement in anxiety following two MDMA-assisted therapy sessions with a mean (SD) improvement in STAI-trait score of -23.5 (13.2), but this was not statistically superior to the control arm. There were no reported treatment-related serious adverse events.[48]

Post-traumatic Stress Disorder (PTSD)

Epidemiologic data on PTSD in older adults is somewhat limited, but studies examining smaller subsets of the population demonstrate a reduction in the prevalence of PTSD with aging. [49] However, older people who do have PTSD tend to have chronic and fluctuating symptoms, and have high rates of comorbid conditions including depression, anxiety, pain, and impairments in quality of life.[50]

Treatments for PTSD have included various types of psychotherapy and medications. Only four drugs —sertraline, paroxetine, fluoxetine, and venlafaxine −are approved by the FDA for PTSD. An estimated 40−60% of patients do not have an adequate clinical response to either drugs, therapy, or both, highlighting the need for novel approaches.[51]

Six phase II randomized trials of MDMA-assisted psychotherapy for treatment of PTSD were conducted from 2004 to 2017 (total N=107 across six studies). Active doses of MDMA (75−125 mg) or control doses of inactive placebo or low-dose MDMA (25−40 mg) were combined with manualized "inner-directed" psychotherapy in which participants were supported by a male and female therapy team.[19,21,52] Patients randomized to the active treatment arm had marked improvements in standard PTSD assessments scales (e.g., CAPS-5) that were both clinically and statistically significant. Due to these promising results, the FDA has also designated MDMA a "breakthrough therapy."[1] This was followed by a multi-center phase III trial (N=90) in patients with severe PTSD that found a large and statistically significant greater improvement in PTSD symptoms in patients administered MDMA vs placebo.[20] Nevertheless, the average ages of study participants in both the phase I/II trials and the phase III trial was 41 years, with very few patients over the age of 50, making the generalizability to an older population unknown.

Substance Use Disorders

Nicotine and alcohol abuse are significant but sometimes under-recognized problems among older adults. About 10% of people over the age of 60 are current tobacco users, with the percentage decreasing with increasing age.[53] Approximately 10 − 15% of men and 5 − 7% of women engage in alcohol use that is considered high risk.[54] Pilot studies of psilocybin and MDMA have shown promise in alcohol and nicotine use disorders.[15,55,56] The studies done to date have been small but have included some patients over the age of 60.[15,55-56]

Alzheimer Disease and other Dementias

It is estimated that 11% of people over the age of 65 have dementing illnesses, with Alzheimer disease (AD)as the primary cause. There are theoretical reasons to consider psychedelics as a potential treatment for AD and other dementias.[16,57−60] Psilocybin has the potential to reduce neuronal and synaptic loss, as well as inflammation. In addition, psychedelics induce brain plasticity and modify connectivity between brain regions.[57−60] Classic psychedelics may play a role in learning and memory.[59] There are anecdotal self-reports that micro-dosing of psychedelics is associated with enhanced cognitive function, but there is no high-quality evidence to support this practice for cognitive enhancement.[60]

Neuropsychiatric symptoms, such as aggression, agitation, irritability, and depression, are some of the most disturbing symptoms of dementia, occurring in over 40% of patients with dementia.[61,62] A reduced serotonergic neurotransmission in AD appears to be one of pathophysiologic correlates with such behaviors.[58] Since the classic psychedelics are agonists or partial agonists at the brain serotonin 5-HT2A receptors, they could, theoretically, ameliorate such behaviors. There is currently a pilot study to examine the potential of psilocybin to treat neuropsychiatric symptoms in patients with early-stage dementia or mild cognitive impairment (ClinicalTrials.gov NCT04123314).

Grief

Grief is a normal response to the kinds of loss which are common among older adults, including the deaths of spouses, friends, and the loss of functional abilities. Grief can become pathological when it is prolonged and associated with functional impairment.[63] Among bereaved adults, 7−10% are expected to develop prolonged grief disorder.[63] There are anecdotal data and some observational data suggesting that psychedelic therapies may be beneficial for people with prolonged grief disorder. To date, only one psychedelic trial has reported pre-post improvements in grief symptoms, but this was an uncontrolled, open-label pilot study.[64] Because prolonged grief disorder shares many clinical features with depression (i.e., dysphoria, guilt, anhedonia), it is plausible that patients with grief might benefit from psychedelic therapies.

Psychedelic Use for Personal Growth

Psychedelic therapies might also have benefits for older people who may not meet criteria for a formal psychiatric diagnosis. Normal aging may often be associated with periods of subclinical distress related to loss of function, loss of loved ones, loneliness, coping with a serious illness, or other normal human experiences. Old age in the modern world may be experienced as a time of diminution and loss of status and influence. Older adults' location in multiple overlapping identities may exacerbate the role of inequities based on race, sexuality and ethnicity. If the social disruptions of aging intersect with stressors associated with other stigmatized identities throughout the lifespan, they may compound experiences of disenfranchisement and marginalization.[65] Such stressors may trigger older individuals to re-evaluate their purpose in life and spiritual beliefs, or to seek new avenues for meaning-making, interpersonal connection, and personal growth. There is reason to believe that psychedelic therapies may provide psychological benefits even to healthy people seeking psychological and spiritual growth.[66-67] The states of consciousness and the mystical-type experiences that psychedelic therapies can produce have been linked with improved clinical outcomes, psychological insight, and general psychological and spiritual well- being.[68] However, older adults may historically have categorized psychedelic drug use as dangerous and deviant, and may fear the intersection of legal jeopardy with oppression based on other stigmatized behaviors and identities. More research is needed on whether

psychedelics are beneficial, safe, and acceptable for older adults seeking personal growth.

Potential Concerns about Psychedelics in Older Adults

Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22%.[69] Sixty percent of older adults manage two or more chronic conditions.[70] Hypertension is the most common disease of older adults, with an estimated 75% of people over the age of 60 carrying the diagnosis.[71] Older adults are vulnerable to syndromes such as falls, frailty, and delirium. As more older adults enroll in psychedelic therapy trials, attention should be paid to the possibility that these comorbidities or syndromes might be exacerbated by these experimental therapies.

While psychedelics have the potential to aid older adults with depression, demoralization, trauma-related disorders, and other conditions, more needs to be known about the safety and efficacy of these compounds in older adults, particularly those with comorbid conditions. Very few older adults have been included in the clinical trials of psychedelic agents, and those who were included tended to be the "young old" (i.e., less than age 74) and relatively healthy.

Pharmacokinetics and pharmacodynamics are altered in older adults, and the prevalence of polypharmacy among older adults further complicates the issue of drug safety. There are recommendations for many medications, including antidepressants, to be started at a lower dose and titrated up more slowly than in younger adults. Whether the same is true for psychedelics is unknown and warrants further study. A post hoc analyses of pooled data from several previous studies that administered body weight-adjusted doses of psilocybin of 20mg/70kg and 30mg/70 kg -found no significant associations between age, race, sex, or weight of the participant and psilocybin subjective effects. Nevertheless, associations between these variables and adverse reactions were not assessed. The oldest participant included in this analysis was 71; there were few older participants overall, and it was a relatively healthy population.[72]

Cardiovascular safety is a particular concern, given the prevalence of hypertension, stroke, and heart disease among older adults. For instance, one of the few studies to administer a high-dose of a psilocybin to older, more complex patients found higher rates of moderate-to-severe hypertension during the medication session than were reported in other studies using a similar dose of the drug.[47] In an escalating dose pharmacokinetic study, psilocybin was shown to increase the QTc interval in a dose-dependent manner, but likely not to a clinically significant extent when administered in doses ≤30 mg orally.[73]

Recommended Next Steps

The underlying neurophysiologic mechanisms responsible for the clinical effects observed with psychedelic administration are now being investigated in translational and clinical research. How these substances work in older as opposed to younger brains, is an avenue worthy of research. For example, changes seen in the normal aging brain include a loss of connectivity across several brain networks, which psychedelics, as potential promoters of neuroplasticity and synaptogenesis, might impact.[74,75] Further research into the potential of psychedelic medicines to impact learning, memory, mood, inflammation, neuroplasticity as well as the neurophysiologic mechanisms of those actions, could make important contributions to the basic science of the aging brain, and potentially, clinical geropsychiatry.

Future studies should include more older adults, as well as other more marginalized populations, with careful attention to addressing safety as well as efficacy concerns. Given the tendency of psilocybin, MDMA and other psychedelics to increase blood pressure and heart rate, for MDMA to increase temperature, and for psilocybin to prolong the QTc interval, protocols should be developed to ensure that cardiovascular harms are avoided. Assuming that phase III trials of psychedelics continue to confirm the promising results found in earlier trials, it would be reasonable for researchers to develop a psychedelic research agenda specifically tailored to the clinical issues facing older adults.

CONCLUSION

Older age is associated with many health conditions that could potentially benefit from psychedelic-assisted therapy, including the distress associated

with a serious illness, depression, PTSD, prolonged grief disorder, substance use disorders, and dementia. While studies in healthy older adults suggest that psychedelics are safe when used in an optimal, controlled setting, there has not been enough research of older adults with serious comorbidities to establish safety in these populations. More research is needed to guide if and how these substances can be used safely in older adults and older adults with comorbid illness. More research is also needed to understand the mechanistic effects of psychedelics in the aging brain in both health and disease.

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All listed authors contributed to the writing and editing of the manuscript. Drs. Johnston and Anderson, as first and senior authors, made the major contributions, with Drs. Grob and Mangini also making significant contributions. The authors would like to thank Dr. Anthony Back, Dr. Tony Bossis, Dr. Ira Byock, and Dr. Mary Cosimano for their assistance in the preparation of this manuscript.

DISCLOSURES

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DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

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