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Interactions between Reproductive Transitions during Aging and Addiction: Promoting Translational Crosstalk between Different Fields of Research

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Abstract

Discovery of neural mechanisms underlying neuropsychiatric disorders within the aging and addiction fields has been a main focus of the National Institutes of Health. However, there is a dearth of knowledge regarding the biological interactions of aging and addiction, which may have important influences on progression of disease and treatment outcomes in aging individuals with a history of chronic drug use. Thus, there is a large gap in these fields of research which has slowed progress in understanding and treating substance use disorders (SUDs) as well as age-related diseases, specifically in women who experience precipitous reproductive cycle transitions during aging. The goal of this review is to highlight overlap of SUDs and age-related processes with a specific focus on menopause and smoking, and identify critical gaps. We have narrowed its focus of the review to smoking, as the majority of findings on hormonal and aging influences on drug use have come from this area of research. Further, we highlight female-specific issues such as transitional menopause and exogenous estrogen use. These issues may impact drug use cessation as well as outcomes with aging and age-related neurodegenerative diseases in women. We first review clinical studies for smoking, normal aging, and pathological aging, and discuss the few aging-related studies taking smoking history into account. Conversely, we highlight the dearth of clinical smoking studies taking age as a biological variable into account. Preclinical and clinical literature show that aging, age-related pathological brain disease, and addiction engage overlapping neural mechanisms. We hypothesize that these putative drivers interact in meaningful ways that may exacerbate disease and hinder successful treatment outcomes in such comorbid populations. We highlight areas where preclinical studies are needed to uncover neural mechanisms in aging and addiction processes. Collectively, this review highlights the need for crosstalk between different fields of research to address medical complexities of older adults, and specifically women, who smoke.

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Introduction

Recently, there have been significant efforts to discover neurobiological mechanisms driving neuropsychiatric disorders within the aging and addiction fields. The goal of these efforts is the discovery of novel efficacious treatments. Alzheimer's Disease (AD) and opioid use disorder have received significant increases in funding from the National Institutes of Health. Since 2014, the National Institute on Aging in the United States has devoted $1.7 billion to Alzheimer's Research, constituting a significant percentage of the funding portfolio of the institute (National Institute on Aging, 2018). Between 2016 and 2018, the National Institute on Drug Abuse received a doubled budget to combat the opioid epidemic ($600 million to $1.1 billion; National Insitutes of Health, 2018). Although these individual institutes have received increased funding to combat these disorders, there is a dearth of knowledge regarding how aging and addiction interact biologically, which may have an important influence on clinical trial outcomes in aging individuals with a history of chronic drug use. It is also notable that preclinical studies in the aging and addiction areas of research do not typically examine overlapping neurobehavioral mechanisms that may exacerbate these diseases. For example, within the preclinical addiction literature, studies rarely examine aging as a biological variable, and typically focus on young adult or adolescent animals.

As mentioned above, no preclinical studies to date have examined neurobehavioral mechanisms of addiction while considering aging as a biological variable. This represents a large information gap in these fields which may impede progress in understanding and treating substance use disorders (SUDs), as well as pathological (e.g., AD) and normal aging processes. Clinical studies on aging or SUD do not typically include, respectively, substance use or aging as variables. Within the literature on SUDs, the most information regarding the interaction of substance use and aging-related biological processes is in the smoking/tobacco use disorder literature, although some work has been done in the alcohol field—showing, for example, that the increase in alcohol use among women may be attributed to hormonal changes across the lifespan (Emmanuel, et al., 2003; Peltier et al., 2020). Given that the majority of knowledge regarding aging, hormones, and SUD comes from the smoking literature, the rest of this review will narrow its focus on the smoking/tobacco field of research.

The generation for which smoking prevalence was high and age of smoking initiation fell below 18 years of age (specifically, between the years of 1930-1960; Thun et al., 2013) is now maturing into ages with markedly elevated risk of conditions such as neurodegenerative disease. Of note, much less is known regarding the neurobiology of SUDs in women than men; historically, the majority of addiction research has been conducted in males. Fortunately, however, the smoking clinical field now is becoming highly focused on interactions between ovarian hormones, aging, and smoking in women. Such research in

females has increased of late in large part due to the National Institutes of Health implementing a mandatory consideration of sex as a biological variable in grants within the United States (Lee, 2019; Miller et al., 2017). Underscoring the importance of this mandate, the landmark United States Surgeon General's report describing smoking as causally related to lung cancer published in 1964 (United States Surgeon General's Advisory Committee on Smoking and Health, 1964) did not include women in this report, titled, "Cigarette smoking is causally related to lung cancer in men." Given that individuals of both sexes, especially within this generation, may have histories of chronic smoking, studies specific to solely males likely has a significant impact on clinical outcomes for treatment of aging-related diseases.

It is thought that drugs of abuse can contribute to accelerated age-related illness (Bachi et al., 2017). Aging is a progressive biological process which leads to altered neuroendocrine trajectories and profiles, and this differs as a function of sex. Importantly, genetic risk for dementia and AD is greater in females than males, as evidenced by a recent twin study (Beam et al., 2020), and the burden of pathology progresses differently in men and women (Leisinger et al., 2018). Women comprise almost two thirds of AD cases in the United States (Alzheimer's Disease Facts and Figures, 2020). In women, transitional menopause occurs when follicles progressively deplete across time (transitional menopause can last up to ten years), estrogen levels fluctuate, and to follow is a precipitous loss of estrogens and progesterone to often undetectable levels (Burger, 2008; Koebele and Bimonte-Nelson, 2017). Underscoring the importance of estrogens, and their depletion, on aging-related functional outcomes, loss of estrogens with menopause can impair cognition, and estrogens given exogenously can benefit cognition and related brain variables in both women and rodent models that have undergone estrogen depletion (Koebele and Bimonte-Nelson, 2015). Men undergo a different process during natural aging, where gradual, progressive reductions in testosterone and growth hormone occur across decades (termed "andropause"; Basaria, 2013). Women are typically more vulnerable to SUDs, and in relation to smoking, clinical trials have shown that long-term smoking cessation is more difficult to achieve in women than men (Anker and Carroll, 2010; Perkins et al., 1999; Perkins and Scott, 2008; Piper et al., 2007; Piper et al., 2017). Further, clinical research studies suggest that the menstrual cycle in women can affect cigarette craving and smoking relapse vulnerability during abstinence (Allen et al., 2008; Carpenter et al., 2006; Franklin et al., 2008). Collectively, these studies illustrate that smoking and reproductive profiles in women have important relationships (although they are not yet well understood), and highlight the need to better understand how hormones interact with neural mechanisms of drug use across the lifespan. Thus, preclinical animal studies on neurobehavioral mechanisms underlying nicotine addiction are needed in which aging as a biological variable is considered.

This review includes a position statement on the dearth of research bridging fields of aging and addiction at the clinical and preclinical levels of analysis. Our goal is to highlight where research gaps exist, rather than synthesizing disparate fields of research. Here, we raise the issues in the two fields and call for more cross-talk and collaborative research in these areas, which could enhance treatment outcomes in normal aging, treatment-resistant aging populations with comorbid neurodegenerative disorders, and SUDs. Here, as stated above, we are specifically focused on smoking in women as a function of reproductive aging.

Below we (1) describe the rates of enrollment of women in clinical trials for smoking, as well as consideration of age as a biological variable in these studies, (2) reflect on smoking status in clinical trials for neurodegenerative diseases and with use of hormone therapy (HT) in women, and (3) highlight two potentially overlapping neural mechanisms in aging and addiction from the clinical and preclinical literature, which may be synergistic or additive, thereby exacerbating disease and potentially increasing morbidity and mortality. We specifically focus on two exemplar mechanisms that have been derived from either the aging field (specifically, cholinergic signaling) or the substance use field (specifically, neuroimmune signaling). Further, we focus on sex differences in these mechanisms, and how this may contribute to exacerbation of disease in aging populations. Through this focus, we provide evidence that aging and addiction interact, underscore the large gap in related information in these fields of research, and identify hormones as a putative modulator of relationships between aging and addiction. In concluding statements, we broaden perspectives and applications to SUDs more generally, providing an expansive scope to the context of smoking.

Clinical Trial Enrollment: Aging-Related Disease and Smoking in Women

Within the addiction literature, most work associated with aging has been done in relation to smoking. Natural reproductive aging in women, or transitional menopause, represents an important biological process that is not often considered in clinical or preclinical studies of addiction. During menopause, a precipitous loss of E2 levels, amongst other steroid hormones, occurs due to loss of ovarian follicles (Chakraborty and Gore, 2004). As a result, wide-ranging neurobiological consequences occur, with the hypothalamus and pituitary most focused upon and characterized scientifically (Gill et al., 2002; Hall et al., 2000; Reame et al., 1996; Yin et al., 2015). Importantly, smoking is related to an earlier onset of menopause by more than one year, compared to never-smoking women (48.9 versus 47.8 years of age; Oboni et al., 2016). As well, younger age at menopause is associated with mortality at an earlier age, which is more strongly related in current smokers (Bellavia et al., 2016). Compared to current smokers, the risk of early menopause is reduced in women who quit smoking (Hayatbakhsh et al., 2012), suggesting that smoking cessation interventions are impactful, and critical, in promoting reproductive health in aging women. The presence of menopausal symptoms is associated with lower rates of smoking abstinence (Copeland et al., 2017), and one recent study found that in postmenopausal women, menopausal symptom severity was related to increased motivation and readiness to quit smoking (Peltier et al., 2018). Smoking during transitional menopause necessitates higher oral HT levels for therapeutic efficacy, which can yield toxic or mutagenic effects (Tansavatdi et al., 2004, Mueck and Seeger, 2005). Nicotine has been shown to have anti-estrogenic effects, with it resulting in lower levels of endogenous biologically active estrogens (Mueck and Seeger, 2005). This is also reflected in altered functional outcomes for clinically-important menopausal symptoms in women, with smoking attenuating oral estrogen-induced benefits on hot flashes, urogenital symptoms, lipid metabolism, and osteoporosis (Mueck and Seeger, 2005). The specific mechanisms for diminished oral estrogen-related efficacy and lower circulating estrogens have been attributed in part to increased hepatic metabolism, whereby smokers exhibited reduced urinary excretion of estriol relative to estrone. These results

indicate that smoking increases estradiol 2-hydroxylation and this reduces competing metabolic pathways (Michnovicz et al., 1986). Ethinyl estradiol (EE), which is the most common estrogen in the oral contraceptive pill and is also present in some HTs, is a synthetic form of endogenously circulating E2 (Mennenga et al., 2015; Shively, 1998). EE-containing medications are prescribed to women from puberty to post-menopause for other non-contraceptive related indications including acne, pelvic inflammatory disease, endometriosis (Dayal and Barnhart, 2001), and menopause-related symptoms for menopausal women (Collins, Fantasia, and Sutherland, 2014). Given these women-specific issues, it is of note that when investigational pharmacotherapies are being evaluated in clinical trials for SUDs, enrollment of women is low compared to men (~15-25% women are represented in several clinical trials for various SUDs (Dunn et al., 2017; Kampman et al., 2015; Larowe et al., 2013)) and age as a biological variable is rarely considered.

Smoking has been identified as a potential risk factor for onset and progression of AD (Hersi et al., 2017). Prevalence of AD is significantly higher in women than men, with women comprising two-thirds of the population of patients diagnosed with AD (Alzheimer's Disease Facts and Figures, 2020; Plassman et al., 2007). Given the disparate incidence of this age-related disease in women compared to men, there is a need to focus on women-specific processes and issues when evaluating investigational pharmacotherapies. Importantly, some studies suggest that current and/or ever smoking is associated with greater risk for AD (Beydoun et al., 2014; Zhong et al., 2015; Zhou et al., 2011), although these studies were not specific to women. The possible links between smoking, early onset of menopause, and onset and/or progression of neurodegenerative disorders specifically in women have not been thoroughly examined.

Age as a Biological Variable in Clinical Trials for Smoking

Clinical studies on smoking have focused on the impact of hormones, but many do not take age as a biological variable into account. This creates a gap in which women undergoing transitional menopause are not specifically examined in these studies, limiting our knowledge of the impact of smoking in this population. Within clinical trials for smoking, age typically falls within the range of 18-60 years (Carson-Chahhoud et al., 2020; Machado et al., 2020) with a mean age of ~40-48 age, which is within the window of the transition to menopause in women (Bohadana, Freier-Dror, Peles, Babai, & Izbicki, 2020). In clinical trials for AD/dementia, the average age is much older, typically ~70-80 years (Asthana et al., 2001; Asthana et al., 1999; Edwards et al., 2007; Farlow et al., 2015), which is not an age range often reflected in trials for smoking. Further, given the low enrollment of women in trials evaluating smoking and treatments, and the lack of focus on women-related health factors, there has likely been insufficient power to detect effects of aging-related issues such as menopause on clinical outcomes. Systematic evaluations at both the preclinical and clinical levels of analysis comparing across the sexes, as well as female-specific health considerations, will help map the impact and potentially altered trajectories corresponding with use of various drugs of abuse. Characterizing such factors could impact multiple aspects of women's health. For example, the development of at-risk hormone and aging profiles could drive novel intervention directions for addiction, and vice versa, with

addiction history profiles driving novel directions for aging, menopause, and neurodegenerative disease treatments.

Consideration of Smoking History in Clinical Trials for AD

In many clinical trials for treatments of neurodegenerative disorders, history of smoking is not considered as a moderating variable. Within the aging literature, smoking is considered a lifestyle risk factor for AD (Rahman et al., 2020). Although, studies considering smoking as a risk factor have shown mixed results. One recent study, for example, found no significant increased risk for AD in ever versus never smokers, current versus never smokers, current versus former smokers, or former versus never smokers, in a study conducted across 7 countries in dementia-free individuals aged 65 years or older (Otuyama et al., 2019). It should be noted, however, that this was a secondary analysis from a study in which participants were initially interviewed, and follow-up occurred ~4 years later (3.8 +/− 1.3 years; mean +/− standard deviation or SD), without additional follow-up. At the follow-up visit, 9.6% of participants were diagnosed with AD (1,069 individuals). Contrary to this study, others have found an increased risk for AD due to smoking status. For example, The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study was a longitudinal study which followed 1449 participants from their 40s with a follow-up ~21 years later (21 +/− 4.9 years, mean +/− SD); the average age of participants was 65-79 at the time of follow-up (Kivipelto et al., 2005)). This study found that smoking along with drinking, physical inactivity, and high intake of saturated fats all increased risk of dementia at older ages (65 years and older). Of the total participants, 61 were diagnosed with dementia (~4%), and 48 met criteria for AD (~3%) at the ~21-year follow-up visit. In addition to studies for AD, smoking has been considered in studies for vascular dementia due to its strong association with increased risk of ischemic events, accelerated cerebral atrophy, and increased blood brain barrier permeability (Debette et al., 2011; Durazzo et al., 2010; Gons et al., 2011; Mazzone et al., 2010; Meyer et al., 1999).

Consideration of Smoking Status in Clinical Trials for HT in Postmenopausal Women

In postmenopausal women receiving HT, smoking status has long been considered a detrimental factor. In 1985, one study showed that postmenopausal women who smoked had reduced levels of the estrogens estradiol and its weaker metabolite estrone, compared to nonsmokers (Jensen et al., 1985), suggesting increased hepatic metabolism of estrogens in postmenopausal women who smoke. In support of the link between smoking and increased menopausal symptoms, one study showed that increased duration of vasomotor symptoms, such as hot flashes and night sweats, were significantly and positively associated with current smoking (Gold et al., 2006). In the double-blind, placebo-controlled Women's Health Initiative Memory Study, examining conjugated equine estrogens (CEE) with or without the progestin medroxyprogesterone acetate HT, smoking status was assessed as a risk factor for dementia and mild cognitive impairment incidence in women aged 65-79 years (Shumaker et al., 2004). In this trial, CEE-including HT did not decrease risk of probable dementia or mild cognitive impairment, and in fact increased risk of probable

dementia or mild cognitive impairment compared to placebo. There were no significant differences between either HT and placebo in regard to never, previous, and current smoking status. Thus, although smoking has been one important factor considered in some HT clinical trials in older women, the impact of other SUDs on clinical aging-related dementia outcomes has not been thoroughly evaluated in older menopausal women, nor in women at the menopause transition and younger.

Overlapping Neurobiological Mechanisms of Pathological Aging and Smoking

In this section, we highlight two exemplar neurobiological mechanisms that may overlap in pathological aging and smoking, which may exacerbate the progression of disease and be detrimental to treatment efforts. This section is designed to lay the groundwork for future translational studies at both the preclinical and clinical levels of analysis, with directions toward novel pharmacotherapeutic treatment options for comorbid smoking and pathological aging. Importantly, we highlight how these two mechanisms may be impacted by ovarian hormones. This is important given that smoking relapse in women can be hormone-dependent (Carpenter et al., 2006), and risk for AD is higher in women than men (Alzheimer's Disease Facts and Figures, 2020). Although these two mechanisms likely contribute to negative outcomes in clinical studies for both AD and smoking, the narrowed focus on these two mechanisms herein does not preclude other neurobiological mechanisms from being critical in exacerbation of these diseases. Thus, focusing on these two may be important first steps in understanding biological processes that drive these diseases, but may lead to other mechanistic findings that could be critical. The overarching goal of this section is to provide a starting point for preclinical animal studies to uncover neural circuitry and specific biological mechanisms that may lead to more efficacious pharmacotherapeutic drug discovery for both AD and smoking specifically in women.

Within the addiction and aging fields, there is biological plausibility for reciprocal relationships, as overlap exists in the neurobiological mechanisms involved in both addiction and aging. For example, pro-inflammatory and cholinergic signaling are each induced by both addiction (Picciotto et al., 1998; Russo et al., 2009; Witten et al., 2010) and pathological aging (Del Villar and Miller, 2004; Liu et al., 2009; Whitehouse et al., 1988). Thus, in populations for which smoking and aging-related diseases are comorbid, there may be mechanistic overlap leading to synergistic or additive neurobiological consequences which may, in turn, exacerbate disease. Further, given biological conditions specific to women, there may be sex-specific mechanisms which should be taken into consideration that are as of yet unknown. Below, we thus describe these two exemplar neural mechanisms which might interact in addiction and aging-related disease, and then describe mechanisms which may be female-specific.

Neuroimmune Processes.

Chronic nicotine use induces pro-inflammatory cytokine release (Albaugh et al., 2004; Albaugh et al., 2001) and smoking induces compromised cerebral blood flow in humans (Domino et al., 2000; Song et al., 2017). Mechanistically, smoking is associated with

increased oxidative stress and pro-inflammatory cytokine release. In the addiction field, mounting evidence indicates that the nuclear factor-kappa B (NF-κB) pathway is essential to the mechanisms underlying drug-induced neuroinflammation (Crews et al., 2011). The NF-κB pathway is ubiquitously expressed across species and cell types (Gilmore, 2006), and is involved in learning and memory processes (Albensi and Mattson, 2000; Kaltschmidt and Kaltschmidt, 2015), as well as mediating cocaine-induced changes in dendritic spine morphology and behaviors (Russo et al., 2009). In addition, the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) activates NF-κB signaling and through this pathway, has been shown to regulate learning, memory, and synaptic plasticity (Beattie et al., 2002; O'Neill and Kaltschmidt, 1997; Stellwagen et al., 2005; Stellwagen and Malenka, 2006; Meffert et al., 2003). Our recent study showed that motivated nicotine seeking in a rodent model of nicotine relapse is driven by activation of the NF-κB pathway within a key region in the brain reward pathway, the nucleus accumbens core (Namba et al., 2019). Together, these studies suggest that TNFα signaling and the NF-κB pathway play roles in driving drug-induced alterations in synaptic plasticity and drug relapse behavior (Ang et al., 2001; Crews et al., 2011; Cui et al., 2014; Russo et al., 2009).

Notably, oxidative stress and neuroimmune signaling is associated with increased β-amyloid (Aβ) production as well as production of abnormal tau protein phosphorylation (Cai, Hussain, and Yan, 2014; Spangenberg and Green, 2017; Tönnies and Trushina, 2017). Microglia are resident immune cells in the brain and are activated by Aβ, which leads to a cycle of inflammation in which Aβ accumulates, microglia are activated, and microglial inflammatory mediators increase deposition of Aβ and neuroinflammation. When microglia are in the M1 (pro-inflammatory) state, these cells produce cytokines and chemokines such as IL-1β, IL-6, IL-12, TNFα, and CCL2 (Colton, 2009). As mentioned above, in AD, there is an increasingly studied role of activated microglia in the progression of pathology (Sarlus and Heneka, 2017). AD pathogenesis is marked by accumulation of Aβ in the extracellular space (Hardy and Higgins, 1992) and intracellular deposits of tau (Bakota and Brandt, 2016). Further, several immune genes have emerged as having an association with increased AD risk, such as CD-33, in a recent GWAS study (Lambert et al., 2013). CD-33 inhibits immune cell functions such as monocyte production of IL-1β, TNFα, and IL-8 (Jiang et al., 2014; Lajaunias et al., 2005), and inhibits uptake of Aβ (Griciuc et al., 2013). Interestingly, one study found downregulation of the TNF receptor binding protein DEN/MADD, which is protective against apoptotic cell death, and increased expression of TNFR-associated death domain (TRADD) protein, which induces apoptotic cell death, in the hippocampus of AD-affected tissue compared to normal controls (Del Villar and Miller, 2004). Taken together, these studies indicate an important role of neuroimmune signaling in AD, which, in turn, provide further links to relationships with ovarian hormone milieu.

Ovarian hormones interact with neuroimmune processes, including E2. Is it thus possible that the precipitous loss of E2 during menopause drives pro-inflammatory signaling and exacerbates the onset and/or progression of AD? Notably, E2 interacts with the NF-κB pathway via estrogen receptors (e.g., ER-α and -β), which are transcription factors that mediate biological responses when E2 is bound (Kalaitzidis and Gilmore, 2005). Several studies have shown that in many cell lines, ER-α can inhibit NF-κB activation in an estrogen-dependent manner when estrogen is at nanomolar concentrations (Cerillo et al.,

1998; Hsu et al., 2000; Kalaitzidis et al., 2004; Stein and Yang, 1995). Of note, ERs can directly interact with NF-κB to inhibit its ability to bind to DNA, thus also inhibiting its ability to increase expression of pro-inflammatory genes (Kalaitzidis and Gilmore, 2005; Stein and Yang, 1995). For example, E2 inhibits the ability of NF-κB to increase expression of the gene that encodes for IL-6 by directly inhibiting its binding to the IL6 promoter (Galien and Garcia, 1997). Collectively, these studies demonstrate that E2 could be neuroprotective via inhibition of NF-κB-mediated pro-inflammatory signaling. In this context, it is plausible that the fluctuations in E2 during the menopause transition, and the subsequent precipitous loss of E2 with menopause, increases vulnerability to elevated pro-inflammatory neural signaling, which may be further increased due to factors which have antiestrogenic properties such as smoking (Mueck and Seeger, 2005; Tansavatdi et al., 2004). Moreover, given that studies indicate that higher doses of HT are required to treat some menopausal symptoms in women who smoke, which may also increase the risk for HT-related adverse effects and yield toxic or mutagenic effects, it is possible that smoking attenuates the beneficial effects of HT in several domains including brain- and cognitive-related variables (Mueck and Seeger, 2005). It should also be considered that synthetic EE, which is 10 times more potent than E2 (Fotherby, 1996), is more biologically active than E2, and cannot be converted to weaker estrogens as can E2 (Dickson and Eisenfeld, 1981), might impact the brain and its functioning due to interactions with the NF-κB pathway. That EE is contained in many contraceptives and a few HTs, and is often taken throughout multiple extended timeframes across a woman's lifespan, leads to the tenet that it is critical to determine whether EE exposure modulates outcomes in females, including but not limited to the study of addiction.

Taken together, these results suggest that pro-inflammatory signaling is increased in AD as well as in SUDs, which is a mechanistic link between these two disease states that may therefore interact in individuals with comorbidities. Further, loss of cycling ovarian hormones during menopause may interact with motivated drug use and onset and/or exacerbation of AD through interactions with the NF-κB pathway. Future studies systematically testing factors in these domains are needed to uncover additional insights into these potential mechanistic links. Translationally-focused studies at both the preclinical and clinical levels of analysis are needed to understand the potentially complex relationships between neuroimmune signaling and nicotine use, ovarian hormone changes throughout the life span, as well as normal and pathological aging. Given that clinical trial outcomes for smoking and, separately, AD, have yet to produce pharmacotherapeutic treatment options that are associated with highly efficacious outcomes, more mechanistic animal studies and parallel human clinical studies that are designed based on outcomes from preclinical studies are indeed necessary.

Cholinergic Signaling.

Within the AD preclinical literature, it has been long established that cholinergic neurons are particularly vulnerable to degeneration (Whitehouse et al., 1981). In this section, we describe cholinergic signaling as an important mechanism in pathological aging, noting that this has more recently been studied in the context of addiction at the preclinical level of analysis. Further, nicotine is the primary component in cigarettes that maintains use

(Stolerman & Jarvis, 1995), and preclinical studies have shown that nicotine is an agonist at nicotinic acetylcholine receptors (nAChRs) and this results in activation and desensitization of these receptors (Picciotto, Addy, Mineur, & Brunzell, 2008).

Cholinergic synapses are ubiquitous in the brain, and mediate several biological functions including sleep, learning, and memory, among others (Berger-Sweeney et al., 1994; Croxson et al., 2011). Cholinergic neurons release acetylcholine (ACh), which has activity in the cortex, basal ganglia, hippocampus, and basal forebrain (Mesulam, 2013). As mentioned above, in neurodegenerative diseases such as AD, cholinergic cells within the nucleus basalis (Whitehouse et al., 1981) are vulnerable as early as the asymptomatic/prodromal periods. In the cholinergic hypothesis of AD, neurofibrillary degeneration within the basal forebrain is thought to relate to forebrain cholinergic cell death, which then leads to more widespread cholinergic denervation (Hampel et al., 2018). Further, nAChRs have been studied for their role in dementia (Picciotto and Zoli, 2002). In patients with various types of dementia, there have been reported losses in subunits of nAChRs, as well as binding sites (Nordberg et al., 1992; Nordberg et al., 1997). It has been reported that there is no change in α-bungarotoxin binding sites in the cerebral cortex of patients diagnosed with AD, which suggests that α7-containing nAChRs are preserved in AD (Sugaya et al., 1990). This is notable as α7-containing nAChRs have been implicated in nicotine use disorder (Mansvelder, Keath, & McGehee, 2002).

Nicotine can be neuroprotective (Anan et al., 2017; Guan et al., 2015), and can enhance cognitive ability in multiple species, including rodents and monkeys (French et al., 2006; Katner et al., 2004; Rusted et al., 2000). These findings support the tenet that nicotine exposure could be beneficial to the brain and cognition. In fact, nicotine has been postulated to be a potential therapeutic for the age-related neurodegenerative diseases AD and Parkinson's disease (Quik et al., 2012; Rusted et al., 2000). However, one study found that chronic nicotine exposure through smoking resulted in reduced basal forebrain volume in individuals with mild cognitive impairment, which may be reflective of atrophy of cholinergic input areas of the basal forebrain (Teipel et al., 2016) and providing evidence that smoking exacerbates progression of the AD pathology. Of note, acute nicotine exposure has been shown to increase connectivity between cortical regions, and nicotine administration to unmedicated non-smokers with major depressive disorder normalizes dysfunctional cortico-striatal communication (Janes et al., 2018); however, nicotine addiction was specifically associated with dorsal anterior cingulate cortex-dorsal striatum circuitry, and this was not found following acute exposure (Hong et al., 2009). These results highlight an important dissociation in neural circuitry regarding nicotine's acute versus chronic addiction-relevant effects. Further, these studies highlight that animal studies are needed to systematically map neural circuitry of nicotine addiction during aging and with age-related neurodegenerative disease.

As mentioned above, nicotine exerts its primary reinforcing actions through agonist actions at nAChRs. Nicotine maintains self-administration behavior through activation of high-affinity β_2 subunit-containing nAChRs localized on dopamine-containing cell bodies in the ventral tegmental area (VTA), and by altering glutamatergic and GABAergic tone in the VTA (Mansvelder et al., 2002). The result of this activity is increased levels of extracellular

dopamine in a key node of the reward pathway, the nucleus accumbens (Pontieri et al., 1996). Further, accumbens cholinergic interneurons are distributed throughout the striatum and provide most of the cholinergic innervation to this region (Woolf and Butcher, 1981), which is heavily associated with reward (Scofield et al., 2016). Additionally, striatal accumbens cholinergic interneurons contain ACh and provide cholinergic modulation of striatal dopaminergic transmission (Lester et al., 2010) as well as co-release of ACh and glutamate (Kljakic et al., 2017). Striatal ChIs also express AMPA- and NMDA-type ionotropic glutamate receptors (Deng et al., 2010; Standaert et al., 1999) as well as subtypes of nAChRs (Gotti et al., 1997). Recent studies have examined the role of these cells in modulating cocaine-related behaviors (Witten et al., 2010), and illustrate an important role of cholinergic signaling in addiction-motivated behaviors. Although the focus on the cholinergic system within the fields of addiction and pathological aging diverge regarding the different cholinergic cells within the brain, based on what we know so far, chronic nicotine exposure via smoking activates both striatal accumbens cholinergic interneurons as well as cholinergic cells originating in the basal forebrain. Additionalstudies are needed to (1) fully map the neural circuitry of nicotine use in older animals, and (2) decipher the role of the cholinergic system in aging populations who smoke and/or have other SUDs.

Nicotinic receptors have known interactions with E2, as E2 can alter expression of specific nAChR subtypes (Morley et al., 1983). Further, nicotine has been shown to inhibit estrogen response elements, and this is reversed by nAChR antagonists (Shingo et al., 2000). ERs can co-localize with nAChRs on various cell types including astrocytes and neurons (Hosli and Hosli, 1999; Hosli et al., 2001; Hosli et al., 2000). As well, E2 has been shown to interact with α4 subunits of α4 and β2-containing nAChRs, thus potentiating the response to nicotine (Jin and Steinbach, 2011). As mentioned above, β2-containing nAChRs within the nucleus accumbens are critical for nicotine's reinforcing effects (Picciotto et al., 1998), thus raising the possibility that E2 interacts with dopaminergic signaling within key reward regions such as the nucleus accumbens in a sex-specific manner. Given that levels of E2 markedly fluctuate during the menopause transition, and then significantly decline by postmenopause, it is likely that nAChR function is impacted during this critical reproductive system transition, and that this, in turn, affects treatment outcomes for smoking and pathological aging in women.

Conclusions

This review has discussed several arenas in which smoking and aging-related diseases may interact, all of which have translational impacts on public health. Here, we have highlighted areas where smoking status should be taken into account, including but not limited to HT, aging, and AD clinical trials, and have identified a large gap in smoking clinical trials which do not typically include individuals beyond 60 years of age and significantly underrepresent women. Importantly, this is also applicable to clinical studies for other SUDs such as cocaine (Larowe et al., 2013) and opioid use disorder (Huhn et al., 2019). Further, this review identified that the majority of studies with a focus on aging/addiction interactions have been centered on smoking status (Beydoun et al., 2014; Copeland et al., 2017; Fillit et al., 2008; Kivipelto et al., 2005; Meyer et al., 1999; Otuyama et al., 2019), although some have examined alcohol use (e.g., Emmanuel et al., 2003). Given the large focus of NIH on

the opioid epidemic, as well as the push to fund opioid-specific research by the HEAL initiative (Collins et al., 2018), it is important to take aging and lifetime use of all drugs of abuse into account, as this is likely an important factor impacting treatment outcomes for both SUDs and aging-related diseases. To this end, the National Institute on Drug Abuse and the National Institute on Aging have issued a joint notice of special interest for research in the areas of cannabis, prescription opioid, or prescription benzodiazepine use in older adults (over 50 years of age; see NOT-DA-20-014). This is an important first step towards integrating these two fields of research, but much work is needed at both the clinical and preclinical levels of analysis. Here we have focused specifically on two exemplar mechanistic areas which may interact in aging populations with comorbid smoking and aging-related pathologies, as well as with normal aging-related processes more generally such as with menopause. This is notable because pathological aging does not reflect the majority of individuals, and thus research is needed in both normal and pathological aging domains. There is virtually no preclinical work examining neural mechanisms of addiction in aged animals, which represents a large gap in our understanding of the neurobiological underpinnings of aging and addiction. Of note, longitudinal studies of animal self-administration are needed to model human patterns of drug intake into older age, which raises issues of feasibility regarding catheter patency maintenance and cost of housing animals over extended periods of time. Given these putative limitations, paradigms that do not require long-term catheter patency such as conditioned place preference, or models that do not incorporate longitudinal study design, may be initially needed to model specific aspects of addiction in aging animals and lay an initial scientific framework. Even while acknowledging these limitations, research is needed to fill this critical gap between the fields of research.

Throughout this review, we have highlighted female-specific conditions which may impact treatment outcomes in a sex-specific fashion. Specifically, we have focused on the menopausal transition, as this may be a critical time period for women in which the variability and eventual precipitous loss of ovarian hormones interacts with disease progression and may hinder treatment outcomes for pathological aging and/or smoking. The mandate by the National Institutes of Health to incorporate both sexes into research (Clayton, 2016; Miller et al., 2017; Tannenbaum et al., 2016) will yield important advancements in understanding the impact of cycling ovarian hormones and loss thereof, as well on exogenous hormone regimens, on neurobiology and behavior. This is imperative to promote translational science with informative value for public health issues, such as aging and addiction in women.

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