

Using Animal Models to Identify Clinical Risk Factors in the Older Population Due to  
Alcohol Use and Misuse

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## Abstract

The number of people over the age of 65 years old is increasing and understanding health risks associated with the aged population is important. Recent research has revealed that alcohol (ethanol) consumption levels in older demographics remain elevated and often occurs in a dangerous binge pattern. Given ethical constraints investigating high level or binge pattern alcohol consumption in humans, animals models are often used to study the effects of ethanol. The current review highlights ongoing work revealing that aged rats are often more sensitive to the effects of acute ethanol compared to younger rats. In addition, the development of ethanol tolerance following chronic exposure may have a different temporal pattern in aged rats compared to younger rats. These differential age effects highlight clinical risk factors for alcohol misuse in the older population.

Alcohol (ethanol) is the most commonly used and misused drug in the world (Ferreira & Willoughby, 2008) with an estimated 2.3 billion people current alcohol drinkers in 2018 (Global status report on alcohol and health, 2018). The global health cost of alcohol misuse is tremendous and has been estimated to result in over 3 million deaths each year (World Health Organization, Alcohol Fact sheet, 2018) and over 95,000 deaths annually in the United States (Centers for Disease Control and Prevention, 2021). In addition to significant health consequences, alcohol misuse produces significant economic costs to the country and individual states (Sacks et al., 2015). Unfortunately, the negative consequences of alcohol consumption are increasing in most age demographics due to COVID-19 and the number of deaths related to alcohol use and misuse have increased in the first 18 months of the COVID-19 pandemic (White et al., 2022). Understanding the effects of alcohol consumption and identifying the mechanisms that are responsible for these effects are critical public health concerns. However, even though alcohol has a simple chemical structure, research has found that the drug produces its effects through a wide variety of mechanisms in the central nervous system including GABAergic (for review see Kumar et al., 2009), glutamatergic (for review see Bell et al., 2016; Johnson et al., 2020), serotonergic (for review see Lovinger, 1999), adenosine (for review see Nam et al., 2013), and dopaminergic (for review see Dahchour & Ward, 2022) systems to name several (for a general overview please see Vena et al., 2020; Elvig et al., 2021). These multiple mechanisms work in concert to impact complex behaviors such as motor movement (Dar, 2015), the rewarding properties of the drug (Martin-Fardon & Weiss,

2012), cognition (Van Skike et al., 2019) and anxiety-like behavior (Pandey et al., 2017). As such, having a complete understanding of the effects produced by alcohol has proven challenging.

The complexity in understanding alcohol's effects due to its numerous mechanisms of action is also confounded due to a wealth of research demonstrating that biological age is a critical factor in understanding how alcohol impacts behavior. Initially, the majority of research investigating the effect of alcohol occurred in adult subjects. Following the description of fetal alcohol syndrome (Jones & Smith, 1973), much work focused on, and continues to be focused on, the question of how alcohol impacts development during prenatal and/or early postnatal exposure. Groundbreaking work in the late 1990s spearheaded by Linda Spear and Ellen Whit began to focus on the issue of how biological age is a modifying factor in understanding the effects of alcohol. Specifically these researchers, and many others, focused on investigating differential effects of ethanol in adolescent animals compared to adult animals (Spear & Varlinskaya, 2005; Chin et al., 2010; Matthews, 2010; Witt, 2010; Spear, 2018; Crews et al., 2019). In general, this research has demonstrated that adolescent animals are significantly less sensitive to the effects of ethanol compared to adult animals when measured in a variety of either behavioral or electrophysiological measures.

Research understanding the effects of ethanol in prenatal, early postnatal, adolescent, and adult animals have been informative and provided important mechanisms underlying these differential behavioral effects. Recently, research efforts have begun to focus on investigating the behavioral effects produced by ethanol in aged animals. This expansion of focus has occurred for good reasons as outlined by several

papers in the present special issue. For example, the average age of the population in most, if not all countries, is increasing. Specifically, by the year 2050, it is predicted that the number of people over the age of 60 years old will increase from 900 million people to approximately 2.1 billion people (The World Population Prospects, 2015). Older individuals use healthcare more than younger individuals as measured by dollars spent (Lassman et al., 2014) and consequently, the increase in the population age threatens to overwhelm health care systems by producing a “silver tsunami” (Tampi et al., 2015) due to older adults needing medical care. It is therefore important to not only identify factors that negatively impact the health of older adults, but also determine how age alters neurological mechanisms thereby producing these effects. Stated directly, investigating and understanding the health risks of older adults is a critical public health care issue.

Recent research has demonstrated that aged adults, similar to younger adults, frequently consume alcohol and the consumption pattern is often in a dangerous binge pattern (Blazer & Wu, 2009; Laberge et al., 2020; Breslow et al., 2017; Han et al., 2019; Calvo et al., 2020). In fact, alcohol consumption in the aged population is becoming more problematic over time. Specifically, compared to younger drinkers, the percentage increase in older adults who consume alcohol is greater than that found in younger populations (Keyes et al., 2019). Furthermore, older females without children have the largest increase in heavy drinking of all demographics (McKetta & Keyes, 2019). It is therefore critical to investigate the effects of alcohol consumption in the aged population.

Due to ethical constraints, in addition to clinical studies using human subjects, animal subjects are being used to investigate the effects of ethanol in older subjects. In addition, recent studies have begun to identify potential mechanisms in the CNS of aged animals that may cause differential effects of ethanol in aged subjects compared to younger subjects. In the following review, we will discuss recent behavioral data highlighting differential effects of ethanol in aged animals compared to younger animals. In addition, we will attempt to place this framework within known clinical risk factors to the aged population. Finally, we will briefly identify needed areas for research to further understand how ethanol impacts the older population.

The overarching conclusion of our work investigating the effects of ethanol in aged animals compared to younger animals is that the normal aging process increases the sensitivity of the animal to ethanol in most behavioral measures. In addition, the increased sensitivity to ethanol in aged subjects is not solely due to altered ethanol metabolism and therefore likely involves central nervous system mechanisms. Finally, the increased sensitivity to ethanol in the aged population produces clinical health risks that may be life-threatening.

Acute ethanol administration produces a constellation of effects that are dose-dependent. These effects include increases in the “loss of righting reflex”, also commonly referred to as sleep time (the length of time an animal is unconscious and laying on its back following a high dose ethanol challenge), impairments in motor coordination and movement termed ataxia, decreases in core body temperature termed hypothermia, impairments in specific types of cognition including changes in hippocampal dependent learning and memory, and alterations in anxiety-like behaviors.

Ethanol exposure affects most of these behaviors greater in aged animals compared to younger animals, and, each behavior has clinical health implications in humans.

Therefore it is important to understand how ethanol impacts the aged subject to gain therapeutic treatments and educational information to protect the older population.

Loss of Righting Reflex: Loss of righting reflex (LORR) is a standard technique that measures sensitivity to high dose ethanol (Majchrowicz, 1975) by determining 1. The length of time needed for a rat to lose consciousness and remain in a supine position; 2. The length of time needed for a rat to regain consciousness, or regain the righting reflex, and roll over onto all four paws (typically determined in our lab as occurring 3 times in a 60-second time period); 3. The blood ethanol level at which animals regain the righting reflex. Sensitivity is defined as longer LORR and/or a lower blood ethanol concentration upon regaining the righting reflex. An acute ethanol challenge results in aged rats having a significantly longer loss of righting reflex compared to adults and adolescent animals (Ornelas et al., 2015; Gano et al., 2017; Perkins et al., 2018). The specificity in LORR supports the hypothesis that the increased sensitivity in aged animals to ethanol involves a CNS mechanism as demonstrated by the fact that the time needed for losing the righting reflex is not significantly different by age (Gano et al., 2017; Perkins et al., 2018) and aged animals regain the righting reflex at significantly lower blood ethanol levels (Perkins et al., 2018). In addition, with the exception of peak blood ethanol levels following a 3.0 g/kg ethanol injection (Perkins et al., 2018), blood ethanol levels are mostly similar between different ages (Ornelas et al., 2015; Gano et al., 2017; Perkins et al., 2018). Finally, the strain of the animal does not appear to impact the increased sensitivity in aged animals to the

loss of righting reflex, in that similar results are found using Sprague Dawley rats (Ornelas et al., 2015) and F344 rats (Gano et al., 2017; Perkins et al., 2018).

Chronic exposure to ethanol often produces tolerance, or a reduction in the behavioral effect under investigation following a drug challenge, and can be investigated using the LORR. We have conducted two studies that have revealed chronic ethanol administration produces tolerance to the loss of righting reflex in aged subjects, which may be different than that found in younger subjects. For example, we administered low to moderate ethanol doses (1.0 g/kg or 2.0 g/kg ethanol or saline control) to adolescent, adult, and aged male Sprague Dawley rats in a chronic binge-like fashion and then approximately three-weeks following the chronic intermittent treatment administered a high dose (3.0 g/kg) ethanol challenge. Aged animals chronically administered the low to moderate doses of ethanol and then challenged with the high dose ethanol injection showed ethanol tolerance as evidenced by reduced sleep times. However, the tolerance to the high dose challenge following the chronic low dose ethanol treatment was not seen in adolescent or adult animals (Matthews et al., 2019). We have also investigated if chronic intermittent ethanol exposure during adolescence alters LORR to an ethanol challenge late in life. Once again, it appears tolerance to high dose ethanol as measured by loss of righting reflex exists and can last for a majority of the animals' lifespan. Specifically, if adolescent animals are exposed to high dose ethanol (5.0 g/kg ethanol) in a chronic binge fashion during adolescence and then allowed to age until ~17 months, tolerance to a high dose challenge as measured by loss of righting reflex still persists (Matthews et al., 2017).

Clinically, consumption of high dose alcohol can produce unconsciousness that can lead to life threatening consequences. The present data in aged rats demonstrates that older people without a long history of alcohol consumption may be at a greater risk of serious health consequences if the drinking approaches a binge level of consumption (4+ drinks in females or 5+ drinks in males that raise the blood ethanol level to 80 mg/dl in two hours). Furthermore, if consumption takes place in a mixed aged group where younger individuals are not as impacted by the alcohol consumption level, older individuals may be at a greater risk due to social pressure to consume alcohol at higher levels. Finally, research has shown that most people begin consuming alcohol as adolescents (Haighton et al., 2016) often in a binge pattern (US Department of Health and Human Services, 2019). Such consumption patterns may produce long-lasting tolerance that impacts future drinking patterns in older populations, leading to additional dangerous behaviors.

Ataxia: Acute ethanol exposure produces impairments in motor coordination in animals (for review see Dar, 2015) and body posture and sway in humans (Mills & Bisgrove, 1983). In animal models, ataxia can be measured using a variety of different techniques including the accelerating rotarod and aerial righting reflex. The accelerating rotarod requires subjects to locomotor on a rotating rod that slowly accelerates in speed and the dependent measure of ataxia is either the time spent on the rod or the speed at which the subject falls off the rotating rod. The aerial righting reflex capitalizes on the natural reflex of rodents to rotate in the air when released over foam pads to land on its paws. Ethanol impairs performance in both tasks indicating ethanol-induced ataxia (Bogo et al., 1981; Frye et al., 1981; Rustay et al., 2003). Similar

to the effects of high dose ethanol on loss of righting reflex, aged rats have significantly greater levels of ataxia following acute ethanol administration compared to younger animals. For example, aged rats require significantly greater heights to right themselves in the aerial righting task compared to adult or adolescent animals when tested with either low doses of ethanol (1.0 g/kg) or moderate doses of ethanol (2.0 g/kg) (Van Skike et al., 2010; Novier et al., 2013). In addition, similar doses of acute ethanol will produce significantly greater ataxic effects in aged rats compared to younger rats when subjects are tested on the accelerating rotarod task (Novier et al., 2013; Ornelas et al., 2015). Furthermore, the significant increase in ethanol-induced ataxia in aged animals is not completely due to differential blood ethanol levels in animals of different ages, as determined by partial clearance curves and analysis of covariance between ataxic impairment and blood ethanol levels (Van Skike et al., 2010; Novier et al., 2013; Ornelas et al., 2015). Interestingly, the increased motor impairment produced by an acute ethanol challenge in aged animals as measured with the aerial righting reflex did not show tolerance. Specifically, when animals were first exposed to ethanol in a chronic intermittent fashion and then challenged with an acute ethanol injection, similar levels of ataxia were found (Matthews & Mittleman, 2017).

The clinical health implications for increased ataxia following low to moderate ethanol exposure in the aged subjects are readily apparent. Specifically, falling is a significant health-risk factor for the aged. In fact, in 2019, over 3 million hospital visits in the aged population were due to falling and resulted in over 34,000 deaths in people aged 65 and older, which was the leading cause of injury or death in this age group (<https://www.cdc.gov/falls/index.html>). Given the reported levels of alcohol consumption

in the aged population and preclinical data revealing that similar levels of ethanol exposure increase deficits in motor function, it is critical that health education that is focused on the risk factors of ethanol exposure and mobility in the aged be enhanced. Furthermore, chronic intermittent ethanol exposure did not produce tolerance to the effect of an ethanol challenge when measured by the aerial righting reflex (Matthews & Mittleman, 2017). This lack of tolerance could produce further health risks as it relates to falling. Namely, older adults with a history of alcohol consumption may develop tolerance to some effects of alcohol but may not develop tolerance as readily to the motor impairing effects of the drug. Further work is needed to determine if such risk factors help explain the high number of yearly deaths due to falling in aged adults.

Hypothermia: Dangerous reductions in core body temperature are a significant health risk for the older population (for review see CDC, MMWR, March 05, 2003, 53(8), 172-173). Understanding risk factors beyond general ambient air temperature is important to protect the older population from frostbite or death resulting from hypothermia. Acute ethanol exposure produces hypothermia in both humans and animal models (Abel & York, 1979; Brassler & Spear, 2002; Freund, 1973; Ristuccia et al., 2007; Silveri & Spear, 2000; York, 1982; Ward & Cowley, 1999). Furthermore, it has been found that ethanol exposure interacts with advanced age to increase the hypothermic responses to ethanol. Specifically, low doses of acute ethanol exposure (1.0 g/kg, i.p.) does not produce differential hypothermia between aged, adult, or adolescent male rats, but higher acute doses of ethanol (3.0 g/kg i.p.) produce significantly greater hypothermia in aged male rats compared to adult or adolescent rats (Watson et al., 2020). Furthermore, when core body temperatures are different

between aged and adult animals 180-minutes post ethanol administration, blood ethanol levels are not significantly different between the two ages. This suggests the increased hypothermia in aged animals is not simply due to altered liver function producing differential blood ethanol levels. The increased risk for hypothermia in aged populations highlights the need for education concerning alcohol consumption and cold weather in aged adults, specifically in locations where cold weather and alcohol consumption frequently occur.

Cognition: It has long been shown that in adult rodents, ethanol will selectively impair some types of learning and memory, while either sparing or facilitating other types of learning and memory. For example, acute ethanol will impair hippocampal dependent spatial reference memory (Matthews & Best, 1995; Matthews et al., 2002; Acheson et al., 2001) and hippocampal dependent spatial working memory (Hoffmann & Matthews, 2001). Furthermore, ethanol will impair contextual learning (Melia et al., 1996) and trace classical conditioning (Weitemier & Ryabinin, 2003). Conversely, ethanol spares nonspatial, cue based learning. In fact, if tasks are constructed in such a way that the cue based (or nonspatial task) is actually a correct response, ethanol can facilitate performance in these tasks (Matthews et al., 1999). Finally, it has been shown that ethanol alters the electrophysiological properties of neurons in the hippocampus, in that it temporarily decreases the “spatial specificity” of hippocampal place cells (Matthews et al., 1996; White & Best, 2000). This work has been exhaustively reviewed (Van Skike et al., 2019).

Few studies have examined the effect of acute ethanol exposure on cognition in aged animals. What has been found suggests that the basal cognitive ability of the

animals is critical to understanding the effect of acute ethanol on learning and memory. In our first study investigating the effects of acute ethanol in aged and adult animals, we concluded that acute ethanol produces a significantly greater effect in aged animals compared to adult animals (Novier et al., 2013). In this study, we trained animals in the spatial version of the Morris water maze task and then challenged them with either ethanol or allopregnanolone, a neurosteroid that mirrors many of the effects of ethanol in cognitive tasks (Matthews et al., 2002; Rabinowitz et al., 2014) and *in vivo* electrophysiological studies (Tokunaga et al., 2003). Acute ethanol produced significantly greater spatial memory impairments in aged animals compared to adult animals when latency to the escape platform was the dependent variable. However, when swim pathlength to the escape platform was analyzed, only a main effect of ethanol dose was found (Novier et al., 2013). This mixed effect, a significantly greater effect in swim latency but not swim pathlength, suggests the effect of acute ethanol on some forms of cognition are not as clear cut as seen with LORR, ataxia, or hypothermia. We further explored the effect of acute ethanol on cognition by first having animals of various ages learn the spatial version of the water maze task and then separating them into either “cognitively spared” or “cognitive impaired” subjects based on their baseline learning and only testing the cognitively spared animals. Acute ethanol administration did not produce a significantly greater spatial memory impairment in cognitively spared aged animals that were the same age as those tested by Novier et al., 2013 (~19 months of age) but did produce a significantly greater impairment when cognitively spared subjects were between 29 and 33 months of age (Matthews et al., 2020). The results of these two studies are interesting because they reveal that rats in

the “early stages of aging” category (~18 to 20 months) have selective effects following acute ethanol administration. Namely acute ethanol impairs motor coordination, hypothermia, and sleep time more in “early aged” animals compared to younger animals but hippocampal-dependent learning and memory is not altered in early aged animals compared to younger animals. In addition, the results highlight the importance of determining baseline cognition prior to administering ethanol challenges in learning and memory tasks that use aged subjects.

Most individuals begin alcohol consumption as adolescents and much research has demonstrated that adolescent ethanol exposure produces long lasting behavioral and neurobiological effects (see Crews et al., 2019 for review). To investigate if adolescent ethanol exposure impacts cognition late in life, we undertook a longitudinal study design where male Sprague-Dawley rats were treated with ethanol, or water as a control, during adolescence and then tested on a variety of behaviors over the next ~17 months of life (Matthews et al., 2017). Adolescent ethanol exposure produced subtle cognitive deficits that lasted through the lifespan but also, and somewhat surprisingly, produced an exaggerated impairment to an acute ethanol challenge late in life (post-natal day 531). In an additional study, either adult or aged male rats were exposed to ethanol in a chronic fashion via liquid diet for seven weeks before undergoing a variety of tests including spatial learning in the Morris water maze followed by an ethanol or allopregnanolone challenge (Novier et al., 2016). Chronic ethanol exposure via liquid diet produced subtle, but significant, impairments in spatial memory in aged and adult rats, but allopregnanolone only impaired spatial memory in the adult but not aged animals. These data suggest aging and ethanol consumption may differentially impact

GABA<sub>A</sub> receptors, thereby producing differential age effects in the allopregnanolone challenge.

Clinical implications of the effect of acute ethanol and cognition are several. Older adults generally experience reductions in cognitive function that increase with age (see Foster this issue). Interaction of age and alcohol use can cause additional impairments in cognitive function in the aged populations that can result in significant health and personal risk, such as over/under medication taking and/or financial loss. Furthermore, alcohol use across the lifespan has recently been identified as a significant factor leading to the development of dementia, including Alzheimer's Disease (Schwarzinger et al., 2018). As such, it is critical that additional research be conducted on the impact of acute, chronic, and lifetime ethanol exposure in animal models on cognitive function late in life.

Anxiety: Alcohol can impact the expression of anxiety in a bi-directional manner. Following an acute exposure alcohol can be anxiolytic, that is it can result in a reduction in self-reported anxiety in humans and produced behavioral changes that are interpreted as reducing anxiety in animal models. Following withdrawal from chronic exposure to ethanol, an increase in anxiety in humans is reported and behavioral changes in animal models occur that are interpreted as producing an anxiogenic effect (see Eckardt et al., 1998 for an exhaustive review of this early work).

We have conducted two studies that investigate the effect of chronic ethanol exposure on anxiety-like behavior in aged animals. Firstly, chronic ethanol exposure via liquid diet for seven weeks increased anxiety-like behavior in aged male rats compared to control aged male rats, as evidenced by significant decreased open arm entries,

decreased open arm time, and increased closed arm time in the elevated plus maze. In addition, the pattern of behavior in chronic ethanol exposed aged rats appeared different than the pattern of behavior in chronic ethanol exposed adult rats. However, differential exposure levels in the liquid diet procedure precluded our ability to directly compare increased anxiety-like behavior in the two ages (Novier et al., 2016). To overcome the differential intake of ethanol via liquid diet in our previous study, we administered ethanol in a chronic intermittent fashion via intraperitoneal injections to adolescent, adult, and aged male rats and measured a variety of behaviors including anxiety-like behavior on the elevated plus maze (Matthews et al., 2019). In this experiment, no difference in anxiety-like behavior was found between animals of different ages administered ethanol. Additional research using other models of anxiety-like behavior in rodents (open field, zero maze, light dark box) are needed to more fully ascertain if differences exist between aged animals and younger animals as it relates to the effect of chronic ethanol on anxiety-like behaviors.

Continuing to investigate the effect of ethanol in aged animals on measures of anxiety-like behaviors are critical, as these measures have strong clinical implications. Considering stress reduction has been reported as a cause of alcohol consumption (Pohorecky, 1981) and perceived levels of stress increase later in life as people age (Osmanovic-Thunstrom et al., 2015) it is possible that ethanol consumption levels are rising in the aged population due to increases in stress, either real or perceived. Future research is needed to address this critical health question.

Future directions: The majority of the studies reviewed in this article use only male rodents as subjects. This is an obvious, glaring weakness of the studies and

highlight the need for studies that include sex as a factor. Secondly, there is a need for longitudinal studies that investigate the effect of ethanol exposure across the lifespan. Such studies should include exposure prenatally and/or early postnatally, during adolescence and/or throughout the lifespan. Studies such as these are labor intensive, but critical and currently are often not done. As outlined in the Foster paper (this issue) studies that collect data in adulthood and then speculate conclusions to the aged time period are insufficient substitutes. Third, studies addressing ethanol self-administration in aged rats are currently lacking. Such studies are needed. Finally, additional studies are needed to identify potential neurobiological mechanisms that produce the altered behavioral effects reported in this and other papers in this issue. Studies of each of these types are currently being conducted in our laboratory.

Conclusion: Biological age has long been a critical factor in understanding the effect of alcohol on behavior. Recently it has become clear that investigating aged subjects is also foundational to understanding the effects of both acute and chronic alcohol. Targeted studies have demonstrated that aged rodents are significantly more sensitive to the effects of ethanol compared to younger animals in most tasks. In addition, the clinical implications of the increased sensitivity are important for understanding the health risk factors of the older population. Given the significant increase in the aged population in most, if not all countries in the world, additional research is needed to better understand how alcohol impacts the aged population compared to adults and adolescents.

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