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Inhalation of Alcohol Vapor: Measurement and Implications

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Abstract

Decades of alcohol research have established the health risks and pharmacodynamic profile of oral alcohol consumption. Despite isolated periods of public health concern, comparatively less research has evaluated exposure to alcohol vapor. Inhaled alcohol initially bypasses first-pass metabolism and rapidly reaches the arterial circulation and the brain, suggesting that this route of administration may be associated with pharmacological effects that increase the risk of addiction. However, detailed reviews assessing the possible effects of inhaled alcohol in humans are lacking. A comprehensive, systematic literature review was conducted using Google Scholar and PubMed to examine manuscripts studying exposure to inhaled alcohol and measurement of biomarkers (biochemical or functional) associated with alcohol consumption in human participants. Twenty-one publications reported on alcohol inhalation. Fourteen studies examined inhalation of alcohol vapor associated with occupational exposure (e.g., hand sanitizer) in a variety of settings (e.g., naturalistic, laboratory). Six publications measured inhalation of alcohol in a controlled laboratory chamber, and 1 evaluated direct inhalation of an e-cigarette with ethanol-containing “e-liquid.” Some studies have reported that inhalation of alcohol vapor results in measurable biomarkers of acute alcohol exposure, most notably ethyl glucuronide. Despite the lack of significantly elevated blood alcohol concentrations, the behavioral consequences and subjective effects associated with repeated use of devices capable of delivering alcohol vapor are yet to be determined. No studies have focused on vulnerable populations, such as adolescents or individuals with alcohol use disorder, who may be most at risk of problems associated with alcohol inhalation.

Keywords

Ethanol Vapor; Alcohol Inhalation; Alcohol Without Liquid; Vaportini; Vaping

ALCOHOL USE IS a significant health problem that often co-occurs with other addictive disorders and mental health diagnoses (Bradizza et al., 2006; Falk et al., 2006; Grant et al., 2004; RachBeisel et al., 1999). While scores of human and animal studies have exhaustively characterized the behavioral and neurocognitive effects resulting from oral ingestion over a wide range of doses, the evaluation of effects from alternative routes of alcohol absorption has received comparatively little attention. Notably, alcohol inhalation in humans has been documented within contexts associated with incidental exposure (e.g., occupational or

environmental) as well as intentional, or inadvertent, exposure while using devices that deliver alcohol vapor.

Concerns about the negative health impact of exposure to inhaled alcohol have been present for decades (e.g., Lester and Greenberg, 1951). The majority of research on incidental exposure to alcohol vapor has largely focused on occupational exposure, namely healthcare professionals that frequently use commercial alcohol-containing products such as hand sanitizer; but emerging research suggests that another source of exposure to inhaled alcohol is from the use of e-cigarettes that contain ethanol (EtOH) in the “e-liquid.” E-cigarettes are battery-operated devices that use an electrical current to heat small metal coils that then generate aerosols from an e-liquid reservoir (i.e., tank or saturated wicking material). E-liquids typically contain a “base mixture” of glycerol and propylene glycol to which various flavoring ingredients and nicotine are added. In addition, EtOH is a variable, but frequent constituent of e-liquids (Cai and Kendall, 2009; Ellicott, 2009; Herrington and Myers, 2015; Tygat, 2007; Valance and Ellicott, 2008; Varlet et al., 2015) and alcohol has been detected in the aerosols produced from them (Herrington et al., 2015; Laugesen, 2008). Furthermore, some Internet-based e-cigarette forums include recipes that recommend alcohol as an ingredient in self-made e-liquids. Consequently, the fact many e-cigarette users are repeatedly inhaling variable levels of alcohol during routine e-cigarette use has potential health implications.

In addition, “alcohol vaporizers” that use heat or physical agitation to generate alcohol vapor or aerosols in an enclosed system that are then inhaled have periodically been publicized as a novel mode of recreational alcohol use (Le Foll and Loheswaran, 2014). For example, one such method known as “alcohol without liquid” used a nebulizer to mix alcohol and oxygen to create a mist (Lovell, 2004). Although the specter of a public health menace from inhaled alcohol use emerged with these early reports, widespread recreational use of inhaled alcohol or of other routes of administration failed to materialize and these alternative forms of alcohol use have largely been relegated to Internet-based curiosities (Stogner et al., 2014). Collectively, the absence of sustained, identifiable public health risks resulting from recreational or coincidental exposure to inhaled alcohol, combined with the absence of evidence for acute safety risks within extant literature on studies simulating occupational exposure, has resulted in an implicit presumption that inhaled alcohol poses negligible risks as compared to the well-established consequences of ingested alcohol. With that said, the scientific assessment of harm from inhaled alcohol is incomplete because it has been based upon comparisons to the effects of ingested alcohol and has relied on methods and assumptions that do not address more subtle behavioral, cognitive, and physical manifestations that may result from the possibly dissimilar pharmacodynamics of inhaled alcohol (Fig. 1).

Further exploration of the behavioral and pharmacological profile of inhaled alcohol use is particularly relevant for drugs of abuse, because the rate of delivery to brain receptor sites is positively correlated with their abuse potential and addiction risk (Allain et al., 2015). In well-controlled human laboratory studies, faster delivery of fixed doses of opioids, benzodiazepines, cocaine, and stimulants produce greater positive subjective drug effects (Marsch et al., 2001; de Wit et al., 1992). Preclinical studies suggest that greater

psychomotor sensitization and immediate early gene expression are potential mechanisms by which rate of delivery impacts the behavioral effects for drugs of abuse (Samaha et al., 2005). As with smoked drugs such as nicotine and cocaine, inhaled alcohol bypasses first-pass metabolism and, compared with other routes of administration, should rapidly reach arterial circulation in the brain. Consequently, inhaled alcohol may be associated with enhanced behavioral effects including increased risk of addiction. Indeed, in rodents, chronic exposure to alcohol vapor was found to be the most effective mechanism for inducing alcohol dependence (Gilpin et al., 2008). If similar effects are present in humans, inhaled alcohol may produce a “priming” effect for alcohol consumption when small doses of alcohol are rapidly delivered. To determine the influence of inhaled alcohol, it is helpful to first evaluate whether exposure to alcohol vapor can be detected via established alcohol biomarkers.

The purpose of this focused review is to (i) summarize the translational foundation of alcohol inhalation and evaluate possible effects of exposure in humans, (ii) establish the objective evidence for systemic alcohol absorption after human inhalation, and (iii) discuss the most common contexts of alcohol inhalation and their differential risk profiles.

ANIMAL MODELS OF EXPOSURE TO ALCOHOL VAPOR

Preclinical studies provide the best evidence to date for characterizing possible risks associated with inhalation of alcohol vapor. Compared with oral administration, EtOH vapor provides a faster, more reliable method of inducing alcohol dependence in animal models (e.g., Heilig and Koob, 2007; Koob et al., 2009; Martin et al., 2012; Sommer and Spanagel, 2013; for review, see Vendruscolo and Roberts, 2014). The use of alcohol vapor inhalation for the induction of dependence has several advantages over other methods of forced alcohol administration (e.g., oral gavage, intragastric intubation) such as precise control of the dose, duration, and pattern of exposure that correspond to key features of alcohol dependence including withdrawal severity and tolerance (Gilpin et al., 2008; Goldstein and Pal, 1971; Rimondini et al., 2003). In a seminal study, Rogers and colleagues (1979) compared alcohol exposure via an inhalation chamber, intubation, and liquid diet in rats. Of these, alcohol inhalation was the only method to safely induce tolerance and dependence by producing sustained blood alcohol levels above 100 mg/dl while permitting rats to move normally and match nutritional needs between the control and experimental groups (Rogers et al., 1979). In subsequent operant conditioning paradigms, rats permitted to self-administer EtOH vapor achieved sustained blood alcohol levels between 100 and 150 mg/dl that significantly reduced the severity and presence of withdrawal criteria (Roberts et al., 1996). Withdrawal-associated increases in operant self-administration of EtOH vapor in alcohol-dependent rats has also been shown to persist for 4 to 8 weeks after induction of dependence (Roberts et al., 2000). Another study comparing liquid diet and vapor inhalation in rats concluded both routes of administration consistently produced alcohol withdrawal; however, vapor inhalation, relative to the liquid diet, was associated with a greater peak and average severity of withdrawal symptoms and a higher average blood alcohol level at the time of withdrawal (217.8 mg/dl vs. 94.3 mg/dl, respectively) (Macey et al., 1996). Finally, self-administration of an alternative reinforcer (i.e., saccharin) in rodents exposed to intermittent vapor was not significantly different than no alcohol controls, suggesting that the motivational mechanisms

driving self-administration are likely specific to alcohol (Becker and Lopez, 2004; O'Dell et al., 2004).

Animal models using alcohol vapor have also contributed to our understanding of the impact of EtOH on the brain and other vital organs as well as in evaluating the mechanisms and efficacy of possible pharmacological interventions for chronic alcohol use. Alcohol vapor exposure in rodents results in alcohol-induced alterations in neural pathways that have been associated with alcohol use in humans such as dopamine (Budygin et al., 2007; Hirth et al., 2016), GABA (Roberto et al., 2004), glutamate (Rimondini et al., 2002; Roberto et al., 2006), and corticotrophin-releasing factors (Sommer et al., 2008; for review, see Heilig and Koob, 2007). Preclinical research using alcohol vapor to induce repeated cycles of intoxication and withdrawal has elucidated mechanisms critical to the development and evaluation of pharmacological intervention (Czachowski and Delory, 2009; Gewiss et al., 1991; Rimondini et al., 2002; for review, see Meinhardt and Sommer, 2015). For example, the administration of acamprosate blocks exposure-induced, but not basal, EtOH vapor intake and the resultant changes in gene expression mirror those in human models of alcohol dependence (Rimondini et al., 2002). Chronic intermittent EtOH vapor exposure in rats also produces widespread significant tissue injury including hepatic, pulmonary, and cardiovascular changes (Mouton et al., 2016). In sum, the use of alcohol vapor to induce dependence in preclinical models is an effective approach for evaluating motivational, biological, and pharmacological factors associated with chronic alcohol use and intoxication.

INHALED ALCOHOL IN HUMANS: POSSIBLE REINFORCING EFFECT

Although alcohol vapor is arguably the most effective method of inducing a state of dependence in animal models, there is a paucity of research on the behavioral and pharmacological profile of inhaled alcohol in humans. A cursory Internet search typically yields multiple news articles, instructional blogs, and user-uploaded videos of consumer and commercial devices that are designed to deliver alcohol vapor for recreational use. Most appear to be targeted to young adults and often include anecdotal evidence of a rapid “high” that quickly subsides. Additionally, patterns of use closely resemble binge drinking where the device is used frequently for a short period of time to achieve subjective levels of intoxication. Despite the digital presence of alcohol vaping devices and media reports of increasing use, no studies have directly compared behavioral and pharmacological profiles of oral and inhaled routes of alcohol administration in humans. As such, the relative reinforcing strength of vaporized alcohol transmitted to the brain via arterial uptake is largely unknown. By analogy, arterial levels of inhaled nicotine are reported to be as much as 10-fold higher than concurrent venous concentrations in blood (Benowitz, 2008; Hukkanen et al., 2005). Thus, the immediate impact of inhaled alcohol on brain sites of action may be out of proportion to those predicted from blood alcohol content (BAC) measurements.

Although oral and inhaled alcohol use likely entail differences in pharmacodynamics, human neuroimaging studies using oral and/or inhaled alcohol as conditioned reinforcers reveal meaningful similarities in cue reactivity in response to small doses of alcohol. Oral

administration of just 1 ml of preferred brand of alcohol to humans during an fMRI scan is associated with increased craving and activation in reward-related regions of the brain, including the nucleus accumbens, amygdala, precuneus, dorsal striatum, and insula (Claus et al., 2011; Filbey et al., 2008; Ray et al., 2014). Furthermore, activation of these regions is positively associated with alcohol use disorder severity (Claus et al., 2011). Alcohol odors have also been used as conditioned reinforcers in human fMRI studies by forcing air into a closed container of alcohol that volatilizes alcohol into a nasal cannula attached to the participant (Lowen and Lukas, 2006; Lukas et al., 2013; Schneider et al., 2001). Exposure to inhaled alcohol, relative to neutral odors, has been associated with brain activation in the nucleus accumbens, amygdala, and ventral tegmental area (Kareken et al., 2004; Schneider et al., 2001). Thus, exposure to even a small amount of alcohol or inhalation of vaporized alcohol has analogous and potentially additive effects on brain regions known to be involved in the development and maintenance of addiction.

ACUTE BIOCHEMICAL AND FUNCTIONAL BIOMARKERS FOR ALCOHOL EXPOSURE

A biomarker is an objectively measured characteristic that is evaluated as a therapeutic indicator of a pharmacologic response to intervention or a diagnostic indicator to assess the risk or presence of a disease (Biomarkers Definitions Work Group, 2001; Gutman and Kessler, 2006). As inhaled alcohol is likely associated with low levels of alcohol exposure and not necessarily associated with chronic alcohol consumption, the current review will focus on the biomarkers of acute alcohol exposure (see Ingall, 2012).

Acute Biochemical Biomarkers

Two direct biochemical markers that have been used to study the bioavailability of inhaled alcohol are breath alcohol and the urinary alcohol metabolites, ethyl glucuronide (β -D-6-glucuronide or EtG) and ethyl sulfate (EtS).

Breath/Blood Alcohol Content

In both forensic and clinical settings, breath alcohol content (BrAC) is accepted as a valid estimation of BAC (Jones, 1993; Martin et al., 1984). The pharmacodynamic profile of ingested alcohol is well established. The principle effects (i.e., subjective, motor, cognitive) of acute alcohol exposure are most evident in the rising BAC curve (Friel et al., 1995; Wilkinson, 1980); moreover, individuals are typically more responsive to changes in BAC than to the absolute level of BAC (Martin et al., 2006). Although the pharmacodynamics of inhaled alcohol have not been established, it is possible that inhalation of alcohol vapor may correspond to low levels of total exposure that share features of the rising curve after acute oral alcohol exposure. Alterations in alcohol-specific motivational and attention processes are also evident at low BAC levels, including increasing craving and attention to alcohol-related stimuli (Schoenmakers et al., 2008). Collectively, these studies highlight the clinical importance of even a low dose of oral alcohol, particularly in the rising BAC curve, and possible shifts in motivation that are evident after exposure to relatively small amount of alcohol.

Ethyl Glucuronide and Ethyl Sulfate

Two additional direct biochemical biomarkers are EtG and EtS (Jatlow and O'Malley, 2010; Wurst et al., 2015). While they are only minor metabolites of EtOH, accounting for less than 0.1% of total EtOH dispersion (Helander et al., 2009), both EtG and EtS can detect alcohol a few hours after exposure (Wurst et al., 2006; Zimmer et al., 2002) and remain detectable for days depending upon the dose (Helander and Beck, 2005; Jatlow et al., 2014; Wurst et al., 2015). Particularly relevant to alcohol inhalation, EtG and EtS are effective at confirming that alcohol has been absorbed even in the absence of a positive BAC.

Acute Functional Biomarkers

The primary action of ingested alcohol is dose-dependent central nervous system depression exemplified by functional changes in multiple cognitive and motor domains (Little, 1991). Much of the existing literature on functional biomarkers has focused on deficits at or above the legal limit for intoxication (i.e., 80 mg/dl); but deficits in reaction time, response inhibition, working memory, and visuo-motor control are observable at BAC under the traditional cutoff for intoxication (for review, see Brick and Erickson, 2009; Chamberlain and Solomon, 2002). A review of over 100 studies on low-dose alcohol exposure suggested that functional impairment of skills related to driving begin with any departure from a BAC of zero (Moskowitz and Fiorentino, 2000). All of the above studies are based on oral ingestion and subsequent peripheral (venous) measurement or estimation of BAC, which may not be the most effective for quantifying alcohol after inhalation. Although the impairments associated with low-level alcohol exposure may not be sufficient to endanger personal safety (e.g., driving under the influence), subjective effects and functional impairments associated with alcohol consumption could trigger alcohol-specific expectancies that may increase reactivity to alcohol cues and motivate drinking behavior.

MATERIALS AND METHODS

Literature searches were performed in PubMed and Google Scholar using the following search terms: "alcohol OR ethanol AND inhalation OR vapor," without any restrictions on date of manuscript publication. Potential studies were limited to those with human participants that included both exposure to inhaled alcohol and measurement of biomarkers (biochemical or functional) associated with alcohol consumption. Upon completion of literature search, the reference sections of identified articles and reviews (e.g., Stogner et al., 2014) were used to locate additional studies that met inclusion criteria.

RESULTS

A total of 21 publications met criteria to be included in the review. A summary of findings can be found in Table 1. Fourteen studies examined inhalation of alcohol vapor associated with occupational exposure (e.g., hand sanitizer) in a variety of settings (e.g., naturalistic, laboratory). Six publications measured alcohol inhalation of alcohol in a controlled laboratory chamber, and 1 evaluated direct inhalation of an e-cigarette with EtOH-containing e-liquid.

Occupational Exposure via Hand Sanitizers

One possible complicating factor when studying hand sanitizer use is the ability to isolate inhalation of alcohol vapor, and not dermal resorption, of alcohol. To address this, a double-blind, randomized, 3 times crossover study included either dermal application of 74.1% EtOH, 10% 2-propanol, or a combination of both, to the participant's back (thus reducing opportunity to inhale alcohol vapor) (Kirschner et al., 2009). All 3 conditions resulted in undetectable BAC suggesting that increases in alcohol biomarkers are unlikely to result from transdermal resorption. To determine whether use of hand sanitizer presents an opportunity for inhaled alcohol exposure, 1 study used a specialized apparatus that measures alcohol vapor in the breathing zone (150 cm) above individuals exposed to 3 ml of hand sanitizer (Bessonneau and Thomas, 2012). Results suggest that alcohol levels within the breathing zone peaked around 1.3 to 1.4 mg/dl after 30 seconds of exposure and 1.8 to 2.0 mg/dl after 40 seconds of exposure. Assuming an average breathing frequency, the authors calculated that after 30 seconds and 90 seconds of hand disinfection, the total inhaled dose of EtOH were 74.9 mg and 328.9 mg, respectively (Bessonneau and Thomas, 2012). Therefore, although transdermal alcohol absorption remains a possibility, it is more likely that the positive tests for alcohol biomarkers after hand sanitizer use reviewed below are due to inhalation of alcohol vapor and not dermal resorption of alcohol.

Healthcare workers have been the focus of many studies because infection control plans encourage the repeated use of alcohol-based hand sanitizers. To evaluate whether a naturalistic exposure to alcohol-containing hand sanitizers results in an increase in alcohol biomarkers, Hautemaniere and colleagues (2013a) repeatedly measured alcohol concentrations present in blood, breath, and urine at the beginning of a work shift and 4 hours later. Participants were asked to maintain their typical frequency of hand sanitizer use during the course of the study. Four hours into a shift, EtOH was not detectable in blood or urine; however, mean alcohol in inhaled air was 46.2 mg/m³ and expelled air contained 0.003 mg/dl of alcohol up to 2 minutes after exposure (Hautemaniere et al., 2013a). In a similar study with a larger sample of 86 healthcare workers tested before and after a 4-hour shift, alcohol was not detected in blood and urine, but approximately one-third of healthcare workers demonstrated an elevated mean expired EtOH level of 0.008 mg/dl within 2 minutes of exposure (Ahmed-Lecheheb et al., 2012). Furthermore, another study found a significant positive correlation between the amount of hand sanitizer used and EtOH concentration in inhaled air, suggesting that increased sanitizer use will increase inhaled alcohol exposure (Hautemaniere et al., 2013b).

Another set of experimental studies have evaluated direct biomarkers for alcohol exposure after replicating various recommended hand-sanitizing procedures in the laboratory. With notable exceptions (Miller et al., 2006), multiple studies have reported increases in BAC after exposure to alcohol vapor during hand-sanitizing protocols modeled from clinical settings. For example, Kramer and colleagues (2007) evaluated 3 hand rubs (95, 85, and 55% EtOH) in hygienic (4 ml applied 20 times) and surgical (20 ml applied 10 times) hand disinfection. The highest median blood levels of EtOH 30 minutes postexposure in the hygienic (2.1 mg/dl) and surgical (3.0 mg/dl) conditions were low, but still demonstrate a small dose-dependent increase in blood EtOH levels after exposure to alcohol vapor from

hand sanitizer (Kramer et al., 2007). Additional studies using other hand-sanitizing protocols that mimic healthcare settings have reported consistent increases in BAC (Below et al., 2012; Brown et al., 2007) and BrAC (Ali et al., 2013; Brown et al., 2007) with the median BrAC at times exceeding the legal limit (119 mg/dl after 3.0 ml) (Ali et al., 2013). Taken together, these results suggest that incidental exposure to alcohol vapor from hand sanitizer corresponds to inconsistent or extremely small increases in BrAC and BAC biomarkers.

In contrast, a number of studies have evaluated EtG and EtS levels after exposure to alcohol vapor. For example, in a simulation of a typical clinical shift, individuals used 3 ml of 96% EtOH sanitizer 4 times an hour for 8 hours and then provided repeated urine samples over 24 hours (Arndt et al., 2014). Use of sanitizer was associated with elevated EtG levels up to 2,100 ng/ml and individuals who were exposed only to alcohol vapor demonstrated concentrations between 600 and 800 ng/ml (Arndt et al., 2014). Notably, application of hand sanitizer under an exhaust fan (i.e., no vapor) resulted in undetectable EtG, further supporting the likelihood that positive biomarkers are a result of alcohol inhalation and not dermal resorption. In another study, daily pre- and posturinary analyses revealed that use of 1 ml of 62% EtOH hand sanitizer every 5 minutes for a 10-hour period on 3 consecutive days resulted in positive EtG levels in 90% of participants with a mean EtG of 278 ng/ml (range = 0 to 2,001 ng/ml). Positive urine EtS was present in 72% of the sample with a mean value of 9 ng/ml (range = 0 to 84 ng/ml) (Reisfield et al., 2011). Several other studies report detectable EtG and EtS after exposure to alcohol vapor from hand sanitizer (Arndt et al., 2012; Jones et al., 2006; Rohrig et al., 2006; Rosano and Lin, 2008) with reported average peak concentrations sometimes exceeding clinical thresholds commonly used to indicate alcohol consumption (Skipper et al., 2009). Therefore, in contrast to BAC, urine EtG may at least for a short period time document systemic exposure to alcohol after incidental exposure to EtOH vapor from hand sanitizer.

Other Occupational Exposure to Alcohol Vapor and Laboratory Alcohol Vapor Chambers

Compared with the numerous studies on biochemical biomarkers associated with exposure to alcohol vapors from hand sanitizer, we identified only 6 studies that explored possible functional biomarkers associated with direct exposure to inhaled alcohol. One study measured environmental air concentration of isopropanol in a printing works while measuring corresponding isopropanol concentration in alveolar air, blood, and urine of workers (Brugnone et al., 1983). This occupational exposure resulted in detectable levels in alveolar air (range 4 and 437 mg/m³), but not in blood or urine. While 1 study reported no detectable increases in blood EtOH content after exposure to vaporized EtOH (1,000 parts per million [ppm]) (Campbell and Wilson, 1986), 2 other studies combined alcohol vapor exposure with light exercise and reported increases in blood, urine, and BrAC after exposure to 142 ppm of 2-propanol vapor (Ernstgard et al., 2003) and a dose-dependent increase after exposure to 3 concentrations (0, 100, 200 ppm) of methanol (Ernstgard et al., 2005). Another study reported that exposure to 6 EtOH concentrations (125 to 1,000 ppm) in an inhalation chamber resulted in peak BAC of 0.3 (men) and 0.27 (women) mg/dl after 4 hours in the highest concentration (Dumas-Campagna et al., 2014). Finally, associations between BrAC and performance on neuromotor tasks, including reaction time, body sway, postural tremor, and velocity of hand movements, were evaluated during 6 hours of EtOH inhalation

at 4 concentrations: 0, 250, 500, and 1,000 ppm (Nadeau et al., 2003). Results demonstrated negative BrAC in all conditions except for a negligible increase after 3 and 6 hours at the highest concentration and neuromotor effects were largely nonsignificant at all concentrations. This study was limited in that the total sample consisted of only 5 males and neuromotor tests were associated with high variability (Nadeau et al., 2003). Assessment of BAC/BrAC has been established after oral ingestion of alcohol, but arterial or brain levels may prove more relevant. If true, even a modest BAC or detectable EtG in a larger sample could potentially reflect functional impairment.

Alcohol Inhalation via E-Cigarette

A recent study measured motor performance and urine EtG after inhaling from an e-cigarette filled with e-liquids that contained high or low alcohol concentrations (Valentine et al., 2016). The e-liquids used in an e-cigarette contain numerous chemicals which have as-yet-unknown toxicities. Ethyl alcohol (alcohol) is one such constituent, but has received little scientific interest in this context (Hutzler et al., 2014; Varlet et al., 2015). The study evaluated the acute effects of puffing from commercially available e-liquids containing 23% or trace (<0.4%) alcohol in young adult social drinkers who also smoke cigarettes. While no differences in subjective drug effects were observed between alcohol conditions, puffing from an e-liquid with 23% alcohol was associated with diminished performance on the Purdue Pegboard Dexterity Test, a test known to be sensitive to alcohol exposure (Breckenridge and Berger, 1990; Buddenberg and Davis, 2000; Marczinski et al., 2012; Tarter et al., 1971). Further, in 3 of the 8 subjects with undetectable baseline urine EtG levels, just 1 test session of puffing from the e-cigarette with 23% alcohol resulted in positive EtG levels (average 371 ng/ml) verifying systemic exposure (Valentine et al., 2016). Importantly, the results may underestimate the intensity of exposure that could result after repeated, heavy e-cigarette use with alcohol-containing e-liquid.

DISCUSSION

The current review of the literature highlights that biomarkers of alcohol exposure in humans are measurable after inhalation of alcohol vapor, but at levels that are generally considered subthreshold for legal intoxication based on oral ingestion of alcohol. Thus, it is not surprising that inhalation of alcohol vapor is commonly perceived as innocuous; however, the acute pharmacodynamics of inhaled alcohol are presently unknown. Guided by preclinical and addiction literature, it is possible that inhaled alcohol is especially reinforcing due to immediate and rapid transmission to the brain. As such, the usual methods of quantifying alcohol exposure (i.e., BAC and BrAC) may be largely irrelevant to the behavioral and pharmacological impact of inhaled alcohol. That is, compared with oral consumption of alcohol, a “hit” of alcohol to brain is not likely to produce analogous BAC levels that are associated with well-characterized impairments in cognitive and motor performance. The most sensitive biomarkers for alcohol inhalation seem to be EtG (and/or EtS), and the presence of EtG confirms that some amount of alcohol has been absorbed and metabolized. With that said, the literature reviewed above generally reflect very low levels of exposure (e.g., alcohol vapor from hand sanitizer) that may not reflect the levels or exposure resulting from the recreational inhalation of alcohol.

Recreational use of alcohol vapor is most likely to resemble a binge-like pattern where inhalation occurs repeatedly in short bursts (e.g., e-cigarette inhalation, recreational alcohol vaping). Based on animal literature highlighting that intermittent, relative to continuous, EtOH vapor exposure results in rapid increases in self-administration and greater overall intake (O'Dell et al., 2004; Rimondini et al., 2002), the reinforcing effect of taking “hits” of alcohol vapor may be greater than, or serve to enhance, oral ingestion. Furthermore, akin to oral alcohol use, the volume of alcohol inhaled may be a critical factor in determining the clinical effect of repeated exposure over the course of day. Therefore, positive biomarkers found in the above studies, especially EtG, may significantly underestimate the clinical significance of recreational alcohol vapor exposure. It may also be possible that home-made vaporizers, relative to commercial products, may deliver higher volumes of alcohol vapor, potentially resulting in greater levels of alcohol exposure. Additional research is needed to characterize the consequences of different methods of alcohol inhalation (e.g., deliberate vaping, inadvertent exposure) and, perhaps, the likely pharmacokinetics of brain exposure as reflected by arterial levels. The behavioral consequences of alcohol inhalation also need to be better defined and measured after repeated intentional exposures that simulate recreational binge patterns of use.

Overall, the immediate safety concerns for inhaled alcohol may be relatively minor. However, there may be specific contexts of use that are more likely to result in acute behavioral effects such as while using high-powered electronic cigarette designs in combination with high-alcohol-content e-liquids. The psychomotor impact of repeated intentional inhalation of alcohol vapor has not been comprehensively studied in a controlled laboratory setting. Such studies are needed to determine whether the amount or frequency of inhaled alcohol poses similar risks to complex tasks, such as driving. Safety concerns aside, the clinical significance of inhaled alcohol is likely to dependent on the specific populations or individuals exposed. For example, subtle changes in interoceptive states resulting from inhaled alcohol may serve as conditioned reinforcers for alcohol use, regardless of whether they are consciously perceived or attributed to the inhalation of alcohol. Therefore, it is noteworthy that the existing studies on inhaled alcohol deliberately exclude vulnerable populations such as those with alcohol use disorder.

Prior research in clinical populations has suggested that reactivity to drug cues can be consciously perceived via controlled processing or subject to automatic processing that is unavailable to introspection (Ryan, 2002). Drug expectancy plays a critical role in the generation of craving such that an individual can experience craving after becoming aware of drug-related stimuli or interpreting a state (e.g., physiological arousal) as representing a need for drug use. Exposure to the odor of a preferred alcoholic beverage is an example of a consciously perceived drug cue that can readily generate craving and motivate drinking behavior. Exposure to “preattentive,” or subliminal, drug cues, is also associated with increased craving, motivation for drug seeking behavior, and activation of reward-related limbic brain regions (Childress et al., 2008; Franken et al., 2000; Wetherill et al., 2014; Young et al., 2014). Compared with similarly masked control images, alcohol cues that were presented for 30 ms were associated with deceleration of heart rate in heavy drinkers that is thought to be indicative of an orienting index for the automatic analysis of a stimulus (Ingjaldsson et al., 2003b), and this effect was more pronounced within “high cravers”

(Ingjaldsson et al., 2003a). Additionally, exposure to subliminal alcohol-related, but not nonalcoholic, words resulted in activation of alcohol expectancy-consistent aggressive behavior (Friedman et al., 2007; Subra et al., 2010) and cognitive impairment (van Koningsbruggen and Stroebe, 2011). Thus, it may not be important that incidental or inadvertent (e.g., e-cigarettes) exposure to alcohol vapor results in biomarkers above or even near to legal limits; instead, the level of absorption after inhaling alcohol may only need to be sufficient to produce interoceptive or subjective states that have previously been associated with oral alcohol intoxication. Therefore, exposure to even small amounts of alcohol vapor by individuals in recovery from alcohol use disorders may facilitate relapse via reinforcement of alcohol-related expectancies that increase craving and/or attention to alcohol cues.

An alternative scenario is that exposure to alcohol vapor may influence the susceptibility to problematic or habitual oral alcohol use. The etiology of alcohol use disorders is complex and believed to be associated with a host of individual factors such as positive family history of alcohol problems, age of alcohol use onset, and co-occurring mental health and substance use disorders (for review, see Moss et al., 2007; de Wit and Phillips, 2012). In general, subjective positive effects resulting from initial drug use are believed to play a key role in escalation of problematic use and the development of drug use disorders (de Wit and Griffiths, 1991) and measures of drug liking have been posited to be both sensitive and reliable indicators of likelihood of abuse (Carter and Griffiths, 2009; Griffiths et al., 2003; McColl and Sellers, 2006). For example, evidence suggests that positive effects of nicotine are associated with abuse liability and increased smoking behavior while a sensitivity to negative or aversive subjective effects of nicotine may prevent both the initiation of tobacco product use as well as the amount of nicotine intake in established tobacco users (Carter et al., 2009; Hu et al., 2011; Jensen et al., 2015; Sartor et al., 2010). The neuropharmacological and behavioral effects of oral alcohol intoxication in heavy drinkers are believed to be multifaceted and include concurrent dimensions of reinforcement and punishment (Ray et al., 2009). Models that describe the development of alcohol use disorders are equally complicated with some highlighting increased experience of reinforcing effects of alcohol (e.g., Newlin and Thomson, 1990) and others emphasizing a reduced sensitivity to unpleasant effects of alcohol (e.g., Schuckit, 1994). Consistent with anecdotal and proposed behavioral and pharmacological consequences of inhaled alcohol, successive “hits” of alcohol may result in more reinforcing positive effects, and absent or attenuated aversive effects, when compared to oral alcohol consumption. As such, similar to the proposed etiology of nicotine addiction (Fowler and Kenny, 2014; Laviolette and van der Kooy, 2003; Riley, 2011), the potential for inhalation of alcohol vapor to influence susceptibility to the development of habitual alcohol use may be a function of the relative balance between inhaled alcohol’s positive and negative/aversive effects and is likely moderated by established risk factors for problematic drinking (e.g., positive family history).

Exposure to subthreshold doses of inhaled alcohol may also maintain or facilitate development of addiction to other substances, most notably nicotine. The frequent covariation of alcohol use and cigarette smoking is well documented with about 20% of those dependent on tobacco also dependent on alcohol, and with half of those who are alcohol dependent also being dependent on nicotine (Falk et al., 2006; Grant et al., 2004).

Use of alcohol and nicotine together may lead to a greater reinforcement than either substance alone. Indeed, co-administration of subthreshold doses of nicotine and alcohol induces dopamine release in the nucleus accumbens, a region implicated in the reinforcing effects of drugs of abuse (Tizabi et al., 2007). In human laboratory studies, acute alcohol administration increases urges to smoke, smoking behavior, and satisfaction from smoking in both heavy and light smokers (Kahler et al., 2014; King et al., 2009; McKee et al., 2006; Sayette et al., 2005). Collectively, numerous studies across varying levels of analysis indicate that the development of nicotine addiction may be facilitated by the use of combustible tobacco products or e-cigarettes that also contain alcohol. Considering the rapid rise in e-cigarette use, particularly among adolescents (Bunnell et al., 2015), more research on the prevalence and patterns of alcohol absorption from e-cigarette use, and on the biological effects of co-administered nicotine and alcohol, is needed to understand the influence of inhaled alcohol vapors from e-cigarette use on the development of nicotine addiction, especially in specific populations with increased vulnerability.

CONCLUSIONS AND FUTURE RESEARCH

This review of the current literature evaluating inhaled alcohol use has revealed a predominate focus on the inhalation of alcohol vapor from hand sanitizer use, a ubiquitous behavior in the healthcare worker population. When using standards established by decades of research on oral ingestion, exposure to alcohol vapor is often assumed to pose a negligible risk. However, many studies have reported that inhalation of alcohol vapor can result in measurable biomarkers of alcohol exposure, most notably EtG and/or EtS documenting systemic alcohol exposure by the inhalation route. Importantly, the acute behavioral consequences and subjective effects of repeated exposure using devices capable of delivering alcohol vapor await further characterization. Finally, inhalation exposure may also be especially important in individuals with an alcohol use disorder, or those at risk of developing alcohol use disorder for whom priming doses of alcohol, as might occur with inadvertent inhalation via e-cigarettes or from other sources, may lead to greater craving and further alcohol use.

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Fig. 1.
Comparison of oral and inhaled alcohol absorption, metabolism, immediate effects, and acute biomarkers.

Table 1.

Summary of Literature Review of Inhaled Alcohol

Article	Type of alcohol	Source of alcohol	Method of exposure	Study design	Biomarkers for alcohol exposure	Main finding
Ahmed-Lecheheb and colleagues (2012)	70% EtOH	Hand-sanitizing gel	Sanitizer: 3 ml several times over 4-hour shift	Naturalistic	BrAC; urine and plasma levels of EtOH, acetaldehyde, and acetate	↑ BrAC in 33% of participants
Ali and colleagues (2013)	62% EtOH	Hand-sanitizing gel	Sanitizer: 3 groups with varying amounts and drying procedures	Between subjects; 3 conditions: 1.5 ml with hand rubbing, 1.5 ml no rubbing, 3.0 ml no rubbing	BrAC	↑ BrAC (median, dose dependent)
Arndt and colleagues (2012)	30% propan-1-ol; 45% 2-propanol	Hand-sanitizing gel	Sanitizer: 5 individuals applying every 15 minutes for 8 hours	Within subjects: 2 conditions: 2 individuals present in room but did not apply sanitizer (inhaled only)	EtG	↑ EtG in 6 of 7 including both participants in inhaled only condition
Arndt and colleagues (2014)	96% EtOH	Hand-sanitizing gel	Sanitizer: 3 ml 4 times per hour for 8 hours	Between subjects; dermal and inhalation versus inhalation only	EtG	↑ EtG 6 hours after exposure
Below and colleagues (2012)	70% propan-1-ol; 63.14% propan-2-ol; 45% propan-2-ol with 30% propan-1-ol	Hand-sanitizing gel	Sanitizer: 10 surgical hand rubs (4 ml repeated 5 times) over 80 minutes	Between subjects; dermal and inhalation of 3 sanitizers	Plasma propanol levels	↑ In median propanol from dermal and inhalation
Brown and colleagues (2007)	70% EtOH or 70% isopropanol	Hand-sanitizing gel	Sanitizer: 1 squirt (1.2 to 1.5 ml) every 2 minutes	Naturalistic	BrAC, serum	↑ BrAC in 30% of participants within 2 minutes of exposure
Brugnone and colleagues (1983)	Occupational exposure to isopropanol	Isopropanol concentration in air	Air sample before shift, 30 minutes later, and hourly for next 7 hours	Naturalistic	Isopropanol in alveolar air, BAC, and urine	↑ Alveolar concentration that correlated with environmental air, not detected in blood or urine
Campbell and Wilson (1986)	1,000 ppm of EtOH air concentration	Inhaled alcohol	Inhaled alcohol for 3 hours	Case study, time series; blood assessed throughout 3 hours	BAC	No increases in EtOH blood content
Dumas-Campagna and colleagues (2014)	125 to 1,000 ppm of EtOH air concentration	Inhaled alcohol	Inhaled alcohol for 4 hours in each condition	Within subjects; exposed to 5 concentrations over 6 days (excluding exercise condition)	BAC	Detectable BAC in all conditions with highest in 1,000 ppm after 4 hours (0.30 mg/dl)
Ernstgard and colleagues (2003)	142 ppm of 2-propanol air concentration	Inhaled alcohol	Inhaled alcohol over 2 hours during light physical exercise	Within subjects; propanol and clean air exposures	BAC, urine, BrAC	↑ 2-Propanol in BAC, urine, and blood up to 6 hours after exposure
Ernstgard and colleagues (2005)	0.100,200 ppm of methanol	Inhaled alcohol	Inhaled alcohol over 2 hours in each condition with light physical exercise	Within subjects; exposed to 3 concentrations	BAC, urine, BrAC	Dose-dependent increase in methanol in BAC, urine, and BrAC

Article	Type of alcohol	Source of alcohol	Method of exposure	Study design	Biomarkers for alcohol exposure	Main finding
Hauteamier and colleagues (2013a)	70% EtOH	Hand-sanitizing gel	Sanitizer: used ad libitum over the course of a 4-hour shift	Naturalistic	BrAC, urine, and plasma levels of EtOH, acetaldehyde, and acetate	↑ BrAC within 2 minutes of exposure
Jones and colleagues (2006)	62% EtOH	Hand-sanitizing gel	Sanitizer: 0.5 g once per hour for 8 hours	Time series; urine assessed throughout 8 hours and next morning (18 hours)	EtG, EtS	↑ EtG and EtS
Kramer and colleagues (2007)	95, 85, and 55% EtOH	Hand-sanitizing gel	Sanitizer: 4 ml applied for 10 seconds repeated 20 times or 20 ml for 3 minutes repeated 10 times	Within subjects; 3 conditions: 55, 85, and 95% EtOH with 2 exposure durations	Blood levels of EtOH and acetaldehyde	Dose-dependent increase in median blood EtOH concentration
Miller and colleagues (2006)	62% EtOH	Hand-sanitizing gel	Sanitizer: 5 ml applied 50 times over 4 hours	Within subjects; pre-post, repeated application	Plasma levels of EtOH	No increases in plasma EtOH levels
Nadeau and colleagues (2003)	0 to 1,000 ppm of EtOH air concentration	Inhaled EtOH	Inhaled EtOH for 6 hours at each level	Within subjects; exposed to 4 concentrations (in ppm) over 4 days	Plasma levels of EtOH	Increases in plasma EtOH to 0.443 mg/dl at highest concentration (1,000 ppm)
Reisfield and colleagues (2011)	62% EtOH	Hand-sanitizing gel	Sanitizer: 1 pump (~1 ml) every 5 minutes for 10 hours	Repeated measures; sanitizer procedure repeated for 3 days	EtG, EtS	↑ EtG in all but 1 participant
Rohrig and colleagues (2006)	62% EtOH	Hand-sanitizing gel	Sanitizer: applied 15 minutes for 4 hours	Between groups; sanitizer applied at various frequencies	EtG	↑ EtG in 1 participant in the most frequent application group
Rosano and Lin (2008)	61% EtOH	Hand-sanitizing gel	Sanitizer: 1 ml applied 20 times during 8 to 12 hours	Within subjects; comparing EtG after hand sanitizer and oral EtOH challenge	EtG	↑ EtG in next day urine in 90% of sample
Skipper and colleagues (2009)	62% EtOH	Hand-sanitizing gel	EthGel applied 2 squirts on hands every 4 minutes for 1 hour	Between groups; 4 conditions: control, skin exposure, vapor exposure or both	BrAC, EtG	↑ EtG with gel exposure, especially vapor
Valentine and colleagues (2016)	23.5% EtOH	Electronic cigarette "liquid"	E-cigarette: Two 20-minute ad lib smoking sessions	Within subjects; pre-post smoking e-cigarette in high and low EtOH content	BrAC, EtG, EtS	No elevated BrAC, 38% of participants positive for EtG after high EtOH exposure

BrAC, breath alcohol content; BAC, blood alcohol content; EtG, ethyl glucuronide; EtS, ethyl sulfate; EtOH, ethanol; ppm, parts per million.