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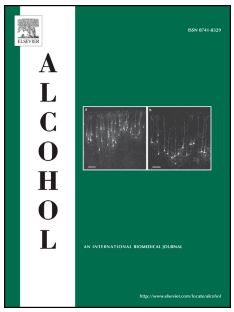

Special Issue on Alcohol Biosensors: Development, Use, and State of the Field:Summary, Conclusions, and Future Directions

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Special Issue on Alcohol Biosensors: Development, Use, and State of the Field: Summary, Conclusions, and Future Directions

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The goal of this special issue on alcohol biosensors was to draw attention to recent progress in this exciting area of alcohol research and to encourage more researchers to work in this understudied area. We sought to provide a range of research studies that offered novel contributions and advancements to the field that covered: a) development/testing of hardware, software, and other tools; b) methodology, protocols, and research designs integrating biosensors; and c) applications and outcomes of studies including biosensor data. In doing so, we chose to avoid review articles, as well as publications related to the criminal justice system use of this technology. Here we place these findings within the long-term context of the field, highlight the contributions the studies make to this literature, critique the current state of the field and recommend directions for future research, and offer considerations for investigators wishing to incorporate these tools into their work.

In the 1980s, sweat patches and alcohol vapor tests were first piloted as methods for collecting and quantifying the alcohol filtering through the skin via sensible (i.e., active through sweat glands) and insensible (i.e., passive diffusion through skin) processes (Phillips & McAloon, 1980). By the 1990s, researchers began publishing reports using transdermal alcohol sensors that are the basis of modern devices (e.g., Swift et al., 1992; Swift, 2000). Over the next decades, several devices (primarily Alcohol Monitoring System, Inc.'s Secure Continuous Remote Alcohol Monitor, SCRAM©, but also Giner, Inc.'s WrisTAS^{TM}) were shown to be effective devices for monitoring alcohol abstinence, but the field largely settled on abstinence as the primary outcome of these devices due to the large variability in the outcome measures across individuals, the bulkiness of the devices, and the lack of a vision for how these could be used more broadly to understand alcohol consumption and related behaviors. Now within the past ~5 years, there has been emerging recognition of the broader applicability of alcohol biosensor devices as mobile health technology tools for use by researchers, clinicians, and lay individuals as part of health monitoring and precision medicine programs. These advancements have been accelerated by pushes from NIH and NIAAA via Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, Requests for Applications (RFAs), as well as several Challenges and Broad Agency Announcement initiatives with DARPA, to make this a priority topic. Now, this rapidly growing field is making large strides that deserve highlighting via a special issue. In fact, when we first contemplated this special issue topic, the question was raised if it were too soon to produce a compilation of manuscripts addressing the use of biosensors beyond abstinence monitoring, and through this selection of eight manuscripts it has become clear that researchers are indeed advancing the utility of this methodology in important ways and using these devices to address a variety of research questions in novel ways.

Although the field is rapidly advancing and offers the promise of a mobile and passive approach to examining alcohol consumption and related behaviors in the field, we know that using transdermal measures has both benefits and drawbacks. As is noted throughout the manuscripts in this issue, barriers remain for the large-scale use of these devices that have yet to be fully addressed. These issues include: (1) device reliability,

accuracy, size, durability, and wearer ease and appeal; (2) the fact that raw transdermal alcohol concentration (TAC) data does not consistently correlate with breath and blood alcohol concentrations (BrAC and BAC) across individuals, devices, and environmental conditions, resulting in difficulty quantifying alcohol levels and time course of exposure; and (3) amount of burden for subjects to obtain readings and care for devices and for researchers to consolidate biosensor data and link it to other data.

In the rest of this summary and critique, we review the important take-away messages of each study in this special issue. We then discuss what this means for alcohol researchers who may wish to use these methods in their own work. We include recommendations as well as questions that remain to be resolved and topics requiring continued investigation.

Devices:
Brief Overview/Current State: To obtain drinking data in a manner requiring less participant burden, passive alcohol biosensors have been developed that only require participants to wear them while drinking. Among these devices, the most well-developed have been those measuring transdermal alcohol concentration (TAC), the amount of alcohol diffusing through the skin. A number of TAC devices have been available to researchers for over a decade, and others are under development to be commercially available (see Luczak et al., 2018).

New Contributions of Special Issue Articles: Wang et al. (2018) reviewed two transdermal alcohol devices in early stages of development, but as with many start-up companies, at the time of publication only one of these companies (BACtrack®) remains viable. The concepts and physiology of the body's processing of alcohol is well understood and can be captured through numerous detection modalities (e.g., chemical, enzymatic), but to produce a wearable device to measure and collect these data is not as simple. Commercial alcohol biosensor devices must be reliable, precise, durable, easy to maintain and care for, quantifiable, inexpensive, and visually appealing to the wearer, and ideally waterproof. Research devices need to be reliable, quantifiable, precise, and in many cases less punitive in appearance, but could require greater burden for care and maintenance.

In the Kinnamon et al. (2018) article we see that additional alcohol substrates may be useful measures of longer-term alcohol use. Ethyl glucuronide is one of these alcohol substrates, along with ethyl sulfate. Other substrates like fatty acid ethyl esters, phosphatidyl ethanol, acetaldehyde adducts may also be promising. A major future step forward as the field expands might be the development of sensors that could measure the intermediate alcohol metabolite acetaldehyde. Acetaldehyde is a known carcinogen and also thought to be associated with some of alcohol's pathological effects (Baan et al., 2007), therefore sensors that can capture acetaldehyde exposure following alcohol consumption can provide crucial and hitherto unknown information on its role in alcohol-related pathology. In addition, software innovations could integrate the detection of multiple analytes and their temporal trajectories to provide even more metrics of alcohol exposure. After all, the alcohol concentration in body fluids is the primary determinant of

its physiological and behavioral pharmacological effects.

Remaining Issues/Future Directions: Primary issues with device development that remain include miniaturization, adherence/slippage from skin that affect accuracy, high failure rates and unreliability, and the need for waterproofing. However, the ease of removal also is a component that is not necessarily beneficial for the researcher or clinician, although the small and unobtrusive size is probably a plus for almost all participants in terms of wearability and the potential for reduced stigma (Barrio et al., 2019). Finally, to become a standard of measurement, there is a need to solve issues of the complex pharmacokinetics of alcohol, substantial variability across individuals, and delay and attenuation across individuals. The articles by Fairbairn et al. (2018) and Sirlanci et al. (2019) in this special issue show that these problems are not only tractable but also provide a model that could enable the accurate quantification of alcohol consumption and exposure from any transdermal sensor in current or future development.

This special issue focused exclusively on transdermal measurement as this is the alcohol biosensor domain where the greatest strides have been made. However, we also note that several other non-invasive methodologies including chemical, electronic, infrared, and photothermal devices are being investigated as possible real-time alcohol monitors, as well as microneedle technology, a more invasive technique to record alcohol concentration below the surface of the skin (Mohan et al., 2017). There are now novel biosensors that can measure alcohol at other sites and location on the body beyond the wrist or ankle. These include sensors on the tooth, on patches that include microneedles, or iontophoresis methods that can be applied on any part of the body (e.g., as tattoos) and also embedded into textiles (for e.g., headbands or socks; see Kim et al., 2019).

Data Manipulation, Consolidation, Cleaning:

Brief Overview/Current State: The need to consolidate large amounts of data and to adapt these data into meaningful metrics is critical. A number of physical/physiological-based models, statistical algorithms, and integrative software systems are being created to consolidate biosensor data (e.g., peak levels, duration of drinking, absorption and elimination rates), and to convert TAC data into interpretable quantitative estimates of BrAC/BAC. Some of these models are applicable to any biosensor device that measures alcohol content in body-water on or in the body, thus broadening their utility to numerous hardware technologies.

New Contributions of Special Issue Articles: Roache et al. (2018) applied novel criteria for determining drinking episodes from SCRAM device data. This work builds on their prior work and also that of Barnett et al. (2014; 2015), recognizing the need for different thresholds for researchers than for use in the criminal justice system where the priority must be to minimize false positives. In research, a set of indices that attempt to maximize both sensitivity and specificity have greater value for detecting drinking episodes of low and moderate consumption (e.g., <5 standard drinks). This new set of criteria resulted in the detection of almost one-third more drinking episodes than the SCRAM criteria for the justice system. Their approach provides a better indicator of

drinking (vs. abstinence) for use by researchers wishing to understand abstinence and low-level drinking in addition to heavier drinking. In addition, the removal of outliers from possible environmental contaminants highlights the importance of processing of biosensor data prior to using the data to address research questions.

In Fairbairn et al. (2018), data collected on participants in both the laboratory and the field were used to examine two methods for estimating BrAC from the SCRAM device TAC data. These two methods both applied the same underlying physics- and physiology-based models to link BrAC to TAC (Rosen et al., 2014), but the method for calibrating the models were based either (1) on individual data obtained by simultaneously obtaining BrAC and TAC data from that person (Luczak & Rosen, 2014), or (2) on population data obtained from a larger sample to estimate parameters that apply to the larger population (Barnett et al., 2015). Results indicated strong associations between daily self-reported drinking and offered promise for using a population-based approach to this estimation procedure.

Sirlanci et al. (2018) advance the population-based methods used in Fairbairn et al. (2018) to estimate BrAC and BAC from TAC data. This novel method uses population-level data to determine model parameter values in a random differential equation. These models were integrated into the *BrAC Estimator* software to produce new software output features including credible bands around the BrAC/BAC estimated curves. This study provides initial proof-of-concept for this approach and represents a major step forward in the ability to produce quantitatively and temporally accurate estimates of BrAC from TAC data.

Remaining Issues/Future Directions: One crucial difference between devices and software is the ability to track an interpretable measure of alcohol concentration in real-time. Although this is almost mandatory for commercial devices to be appealing to lay users, this is not necessary for researchers, and may even be preferable to be hidden from the wearer. Continuous feedback on estimated BAC or BrAC may alter behavior, be seen as an incentive for additional drinking, or mix expectancies and responses to alcohol in ways that become difficult to parse. However, the research community must also take into consideration that alcohol research itself will begin to change with the availability of such tools beyond research and clinical fields.

Applications in the alcohol research field:

Brief Overview/Current State: The use of wearables to measure consumption in clinical trials of treatments for AUD can be broadly classified into two categories. The first category comprises contingency management studies wherein the absence of detection of alcohol, indicating abstinence, is incentivized with monetary rewards, thus motivating patients to maintain sobriety during treatment. The application of these studies in alcohol research was limited by the detection of alcohol or its metabolites in breath, blood or urine, which was only possible for 24-48 hours. The use of wearable biosensors to provide passive, objective tracking of alcohol use was leveraged in early studies to demonstrate their feasibility and application in alcohol treatment research (Dougherty et al., 2015; Barnett et al., 2017). These studies primarily used the SCRAM

device, which has a high threshold for detecting abstinence from alcohol, primarily for legal purposes. However, efforts have been made to quantify the use of the SCRAM to detect various thresholds for drinking and to distinguish false positive measures, which can be limiting in clinical treatment research.

New Contributions of Special Issue Articles: In this issue, two papers highlight the utility of incorporating wearables for monitoring alcohol consumption in community treatment settings. Alessi et al. (2019) applied SCRAM to detect alcohol consumption in an outpatient clinic as part of two cohorts with a high degree of compliance with wearing the sensor and providing self-report drinking data. Rash et al. (2018) applied SCRAM to detect alcohol consumption in a sample of heavy drinkers in a soup kitchen setting, which also highlights the feasibility and the utility of incorporating wearable sensors in interventional research in this understudied population. The careful incorporation of wearable sensors in alcohol treatment interventions along with diligent follow-up and care management can greatly enhance the ability to conduct research on interventions in these otherwise challenging populations.

The second category of treatment research includes clinical trials of novel pharmacotherapeutic agents for AUD. In this line of research, novel medications are tested across phases of development to evaluate their effect on alcohol consumption and related outcomes. As descried in the article by Roberts and McKee (2018), wearables combined with additional mobile assessments such as ecological momentary assessment (EMA) can provide critical real-word evidence in studies where alcohol consumption is the primary outcome. These studies can be broadly categorized as: (1) studies examining how a medication might attenuate alcohol response, and here the approach would be to measure these responses during naturally occurring drinking episodes where the response measures can be assessed using smartphone and other mobile health (mHealth) means, and the drinking itself can be measured using the biosensor; (2) studies examining reduction of alcohol consumption which would be assessed in natural settings, using the biosensor and possibly additional wearables that assess drinking topography and patterns; and (3) studies examining effects on cue-reactivity to alcohol – again these can be assessed during exposure to cues (e.g., alcohol, stress, etc.) in natural settings both in the absence and presence of alcohol, and outcomes measured using smartphones and sensors.

In confirmatory clinical trials testing the efficacy of new medications, the FDA approved outcomes include measures such as % no drinking days and % no heavy drinking days, typically assessed by self-report. As one can expect with the development of more quantitative and reliable technology, these measures can be assessed using wearables. In addition, the use of sensors and wearables can provide extremely valuable secondary data to better understand and interpret these medication effects. These data may include drinking topography, craving, subjective and objective measures of alcohol response, as well as other factors such as mood, medication compliance, and the environmental variables including location, social context, outlet density, etc. As highlighted by Roberts and McKee, this will provide some distinct advantages over simply obtaining self-reporting drinking data retrospectively. Additionally, the data are

passively and objectively recorded, and the assessments can be tied to critical events like relapse, binging, craving, cues, etc. Finally, the ability to remain connected with patients via these devices can also improve compliance, enable monitoring of adverse events, facilitating multi-site studies, and reduce burden on patients and staff.

Remaining Issues/Future Directions: With all the innovations and developmental advances, there is an evolving need to better understand for whom and under what conditions this type of data collected is more valuable. A recent study suggests important benefits to the incorporation of transdermal sensors into treatment research programs, including its utility as an objective measure of relapse and tighter control of monitoring by treatment providers (Barrio et al., 2019). However, this research will require a number of studies across a number of samples representing the range of potential treatment populations to determine the applicability and utility of these sensors.

In addition, alcohol biosensors can be integrated into larger-scale personal health data collection systems. Sensors that capture movement of the hand and gestures can also be combined with biosensors to get measures of drinking topography/patterns. This further can be combined with EMA measures in sophisticated ways to provide additional self-reported information, and can also be combined with other physiological sensors that measure gait, heart rate and variability, skin blood flow etc. to provide a multidimensional and ultimately accurate, reliable and robust measure of alcohol consumption.

Researcher considerations/recommendations:
We hope that this collection of papers will become a valuable resource for the alcohol research community. We believe these articles touch on a number of applications and advancements, but also serve as a warning and risk assessment for researchers to weigh when considering whether or not to use such approaches in their own work.

(1) Researchers should weigh the costs and benefits of using biosensor devices and seek to obtain data at the required resolution to address their research questions. What is gained from this method versus cost in terms of effort and expense? Can this approach answer research questions in ways that other methods cannot? The answers to these questions will depend not only on the aims of the study, but also the sample under investigation. Biosensor devices and techniques are not a magic bullet, but they certainly can address some limitations that exist in the field.

(2) It is also important to consider that the types of outcome measures obtained from biosensors are more nuanced than commonly used calendar methods that are standard in alcohol research. The outcomes obtained also may have different meaning and relevance when obtained under naturalistic conditions versus in laboratory settings. For example, as consumption fluctuates with multiple peaks and declines over the course of a natural drinking event, knowing the time of peak BrAC may become less informative than measures capturing the area under the drinking curve, total drinks consumed, total time of consumption, or total time above an estimated threshold. In some studies, however, knowing the maximum estimated BrAC while driving is a crucial research

question, lending more importance to the timing of drinking levels in relation to specific behaviors. Other studies may be focused on understanding rates of consumption, which has recently come into focus as a vulnerability factor for alcohol use disorders (Gowin et al., 2018). Again, as in the cases above, what we learn from such studies may shed light on risk factors that has not been apparent without such fine-grained knowledge of consumption patterns and levels.
(3) Another question as we look ahead in this field is learning more about how well we can estimate BrAC or BAC from transdermal data. How good can we get in terms of quantifying range of error? What individual and environmental factors affect TAC? And will it eventually be possible to obtain estimates of BrAC/BAC from TAC in real time? Forecasting models of weather and of traffic have improved dramatically over recent years, due in large part to machine learning techniques analyzing huge stores of data and revealing patterns previously unidentified. If we obtain similar amounts of data (or generate it via simulation), this may also be possible in this field. Once individuals can view their BrAC/BAC in real time, many of the prevention efforts we make as researchers and clinicians will be viewed in a whole new light with accurate knowledge of personal alcohol levels informing decisions and behavior.

(4) More needs to be done to understand reactivity, i.e., the effect of the wearable sensor itself on behavior. Self-monitoring of health behaviors, both at the clinical practice level and at the individual consumer level, has become increasingly more prevalent, and large amounts of data, both behavioral as well as physical/biological (such as heart rate, step counts, etc.), are being gathered in natural settings. This type of digital phenotyping, usually done passively, can drive changes in behavior and it is not difficult to envision the effect of continuous monitoring of alcohol exposure on consumption in individuals being monitored. Knowing one's BAC or BrAC in real-time may not lead to decreased alcohol consumption or reduced likelihood of driving after drinking, with personal motives for monitoring drinking levels varying across individuals. It would therefore be extremely relevant for researchers to examine this phenomenon, and potential underlying determinants on drinking behavior.

(5) At the technical and technological level, other relevant considerations include the integration of alcohol measurement with other apps and devices that obtain biological signals such as heart rate and skin conductance, behavioral signals such as those collected via EMA surveys, and environmental data such as GPS, humidity, and ambient temperature. These data are gathered both passively and actively, and can represent a major "big data" challenge in terms of collection, integration, analysis, and interpretation. Ultimately the goal of these efforts is to incorporate this digital phenotyping to better understand the underlying disorder and develop personalized interventions for prevention and treatment.

(6) Finally, to move this field forward, it is critical for researchers to be highly transparent and to report as complete a picture as possible of their methods, data capture results, and successes and failures. It is not enough to show high quality data obtained on a few participants and omit information regarding device and data capture failure rates, participant tampering or inadvertent damaging of equipment, and researcher inability to

determine drinking episodes from sensor data or to reconcile data from multiple sources. Such information provides crucial information for determining the utility of these devices and methods in their current state and to track progress (or stalemate) in the field (Luczak et al., 2015; Marques & McKnight, 2009). Much work needs to be done before alcohol biosensors reach their full utility, but the articles presented in this issue demonstrate that the field is moving forward productively and in the right direction.

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Highlights

We highlight the novel contributions of the 8 articles in this special issue to this exciting area of alcohol research

We discuss remaining issues and future directions for alcohol biosensor a) devices, b) data manipulation, consolidation, and cleaning, and c) applications in the field.

We provide 6 considerations/recommendations for researchers utilizing alcohol biosensors.

We note that continued work is needed to maximize the utility of these devices and methods, with the articles presented in this issue demonstrating that the field is moving forward productively and in the right direction.