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Towards on-skin analysis of sweat for managing disorders of substance abuse

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A patient-centred system that leverages the analysis of sweat via wearable sensors may better support the management of patients with substance-use disorders.

The rise of substance-use disorders (SUDs) is a global public-health crisis. In the United States, the high prevalence of SUDs has been underestimated for a long time[1]. In fact, synthetic opioids have caused waves of deaths by overdose. Despite a wide range of treatment strategies for withdrawal from SUDs, relapses remain high[2], partly owing to craving. Craving is accompanied by physiological changes such as increased arousal and increased sweat rate as well as a loss of control.

Wearable sweat sensors can be used to measure sweat rates straightforwardly and continuously, and to provide non-invasive therapeutic drug monitoring for opioids and other substances[3,4]. In this Comment, we argue that a personalized digital-biomarker signature powered by a machine-learning model that leverages analysis of sweat in addition to physiological measures such as heart rate and core body temperature could support the management of the health of people with SUDs. To this end, we describe the translational development — from research into the relevant physiology to technology needs to clinical implementation — of such a sweat-based patient-centred sensing system.

Addiction is a complex chronic disorder that involves the dysregulation of underlying brain mechanisms and neural circuits[5]. When exposed to addictive substances, the brain adapts, which leads to the development and persistence of addictive behaviours. At the behavioural level, the hallmark is compulsive drug-seeking and drug-taking. The process starts when addictive substances activate the reward system[6]: a neural projection that extends from the midbrain to the ventral striatum and that primarily releases the neuromodulator dopamine. Physiologically, dopamine-releasing neurons become active when an unexpected reward is received, and such neural activation may facilitate the association of the reward with a conditioned stimulus[7]. Normally, once the reward becomes fully predicted, no dopamine is released on the further delivery of the reward. However, because of their sheer pharmacological power, addictive drugs override this resetting and generate a dopamine-induced 'learning' signal in such a way that any cue associated with the drugs becomes overvalued. The cellular substrate of these learning mechanisms involves changes in synaptic transmission[8]. Addiction is thus associated with long-lasting changes in synaptic plasticity (that is, the brain's ability to adapt and change in response to experience). It is ultimately such altered neural-circuit function that drives such compulsive behaviour. Moreover, stress and other fundamental brain functions that greatly impact addiction behaviour are upregulated during craving, leading to increased physiological arousal and ultimately to the increased excretion of sweat.

Sweat rates and molecular monitoring

When the body is stressed (physically or mentally), or when local sweat glands are stimulated by chemicals, the greatest amount of sweat generation takes place in eccrine sweat glands (located in the surface of the whole body). A much smaller amount is produced in apocrine and apo-eccrine glands (in the armpits and genital areas). The sweat glands show filtration of primary sweat and different types of substance resorption and secretion, with the latter two types of gland producing a protein-rich liquid (body odour) and the first mainly producing a watery liquid for evaporation and body cooling. Eccrine sweat production varies dramatically across the body surface, with the highest outputs on the forehead, spine and upper back[9].

The collection of sweat for regional quantification and analysis is carried out using technical absorbents or cotton absorbent pads that are applied briefly or continuously to the skin and subsequently weighed; the liquid is then extracted and analysed[10]. Alternatively, for whole-body analysis, a washdown procedure is used. In such a procedure, all sweat is collected by washing off the body with distilled water[11]. For the quantification of regional sweat production, sweat capsules perfused with dry air that capture all sweat can be used[12]. For the local analysis of sweat content, capillary systems can capture sweat and transport it to a reservoir containing a sensor. Whole-body sweat production can also be determined by weighing a person before and after sweating via a suitable precision scale (with error rates of less than 10 g per 150 kg).

Sweat production in a specific environment is mainly determined by metabolic and thermal loads, and it is strongly modulated by fitness, acclimatization, age and sex[13]. High fitness levels and acclimatization typically result in a higher sweat-rate capacity (although there are also non-responders). Children up to puberty have an underdeveloped sweating system; a reduction in capacity is also evident from middle age onwards, starting at the legs and arms, and reaching the torso. Although sex differences were described, they are typically confounded by differences in fitness, body mass and type of work.

Sweat contains proteomic, metabolomic and pharmacological information[14]. Many compounds of concern in SUDs — in particular, opioids, cocaine, amphetamines and Δ^9-tetrahydrocannabinol — are easily detectable in sweat[15]. Also, alcohol and other legally acquirable and potentially addictive substances are excreted into sweat[16]. With the ability to monitor many biomarkers in sweat (such as the stress hormone cortisol and the cytokines interleukin-6, interleukin-10 and tumour necrosis factor alpha[17]), a person's psychoneuroimmunological status — resulting from the interaction of their central nervous system, the endocrine system and the immune system — becomes continuously assessable on a molecular level, and could be used to estimate the

person's stress levels. Hence, sweat holds great promise as a matrix for the molecular monitoring of stress and drug metabolites in patients with SUDs.

Wearable sensors

Wearable sensors of sweat leverage its ready availability and its rich molecular composition[18]. Fully integrated wireless systems can monitor sweat rate and a broad spectrum of molecular analytes[19,20]. These systems integrate miniaturized iontophoresis modules for the on-demand, steady and automatic sweat induction during daily activities[21,22], as well as microfluidic setups for sweat sampling and for the in-situ analysis of the secreted sweat (which can also be thermally induced or exercise-induced) with high temporal resolution and minimal evaporation.

Wearable sweat-rate sensors most commonly incorporate interdigitated electrodes placed inside a microfluidic channel; the electrodes change impedance as sweat flows over them[23] (sweat has a higher dielectric strength than air). Although simple, this approach is limited by the total volume that the device can collect. In fact, the effectiveness of sweat-rate monitoring ceases once the sweat-sampling microchannel is filled. Alternatively, a pair of vertically mounted electrodes connected to an outlet of sweat-sampling microfluidics can be used to detect the frequency of sweat-droplet generation within the space between the electrodes, thus providing an indirect measure of the sweat rate[24]; the flow rate can then be calculated from differences between upstream and downstream temperatures, measured via a thermal actuator and a pair of thermistors[25].

A variety of wearable electrochemical and optical sensors, mostly relying on enzymes and ionophores, can be used to monitor metabolites, ions, nutrients, hormones, proteins, and many substances and drugs in sweat[18–21] within the micromolar-to-millimolar range. Increasing efforts have been directed towards the development of wearable sensors that leverage bioaffinity receptors (particularly antibodies, aptamers and molecularly imprinted polymers) coupled with nanomaterials (such as laser-engraved graphene and gold nanoparticles) to enable the detection, at ultralow levels, of clinically relevant biomarkers (in particular, nutrients and C-reactive protein) in sweat[21,22].

The integration of sensors and vital-sign sensors in wearables opens up further possibilities for personalized medicine. For example, multimodal cardiometabolic monitoring has been realized by combining sweat sensors with heart-rate sensors and blood-pressure sensors into a single wearable system[26]. Such networks of wearable sensors, which generate a massive amount of physiological data that call for the use of machine-learning models to recognize patterns and relationships in the datasets, may aid the understanding of health conditions and facilitate the discovery of new biomarkers of health or disease[27].

Implementation

Pharmacological agonist therapy and cognitive behavioural therapy can be used to support patients during withdrawal from SUDs. Treatment in an in-patient detoxification setting provides a transient well-controlled and guided environment in the short term. However, in out-patient settings, exposure to conditioned behavioural patterns, social pressures and stress leads to a higher risk of relapse[28].

Craving during withdrawal (often triggered by exposure to person-specific variables; Fig. 1) is a main driving force for relapse. The identification of triggers is crucial for providing patients with strategies for coping with the exposure to them. However, trigger identification is not always feasible, as the complex context of everyday life may render it too difficult to understand the underlying causalities. In fact, triggers are often not at all obvious, which diminishes the feeling of control. Because increased sweat rates are a common physiological reaction during craving, sweat rates make for a useful biomarker for the monitoring of withdrawal from SUDs and thus for the identification of triggers.

The clinical gold standard for assessing sweat rate in the context of craving for opioids makes use of the 11-item clinical opioid-withdrawal scale. Specifically, patients are asked to assess their own sweating by choosing one of the following: subjective report of chills or flushing, flushed or observable moistness on the face, beads of sweat on brow or face, or sweat streaming off the face. In general, the self-assessment of one's own sweat rate is difficult as, for example, sweat volumes at rest are usually very small (39–217 g m^{-2} h^{-1}; ref. 29). However, gravimetrical analysis — the physiological laboratory gold standard for quantifying sweat rate — is neither continuous nor easily applicable outside a laboratory setting; this is one main reason why sweat rates are an underrated symptom in SUDs.

The analysis of sweat via wearables allows timely and meaningful updates to at-risk patients about sudden changes in the sweat rate associated with triggers and cravings. The warnings may be feasible even before clinical manifestation and perception by the patient if the sensors prove to be sufficiently sensitive. This would allow the biosensing system to predict, identify, detect and quantify early warning signs of craving with the help of a 'stress meter' (Fig. 1). The obtained information can be forwarded to connected applications, which automatically activate appropriate digital countermeasures to prevent exposition to stressful situations, to directly guide the person on how to cope with stressful situations that might lead to relapse, and to reduce stress and pressure through cognitive behavioural therapy.

The sweat rate is influenced by factors such as physical stress and mental stress. The sensitivity of sweat rate as a standalone biomarker may be low, owing to the fact that an increased sweat rate may result from environmental factors or from exertion. However, by integrating additional sensors that measure heart rate, activity, core body temperature and the environment, sweat-rate changes can be interpreted and placed in context. Also, shaking or tremor — a common symptom of withdrawal — can be assessed using simple accelerometry[30]. Therefore, when it comes to the identification of triggers and to monitoring episodes of craving, a holistic interpretation of continuous sweat analysis combined with biophysical measurements may provide a straightforward assessment with high sensitivity.

The molecular monitoring of sweat may have further promising implementations for the general management of SUDs. During pharmacological agonist treatment, drug concentrations can be monitored non-invasively, daily and independently of any healthcare facility. With the help of machine-learning algorithms, automated sensor-data interpretation based on predefined lower and upper concentration margins could display concentrations of substances of concern in sweat via a 'substance meter'. This could help to prevent pharmacological misdosing (and hence the subsequent risk of craving episodes) and to identify the intake of further (wanted or unwanted) substances. Additionally, monitoring stress markers such as cortisol and cytokines could provide insights into an individual's psychoneuroimmunological status on a day-to-day basis, thus supporting the monitoring and assessment of the individual's general stress levels. Moreover, machine-learning algorithms could be used to recognize patterns and concentration signatures of such biomarkers, and correlate them with the individual

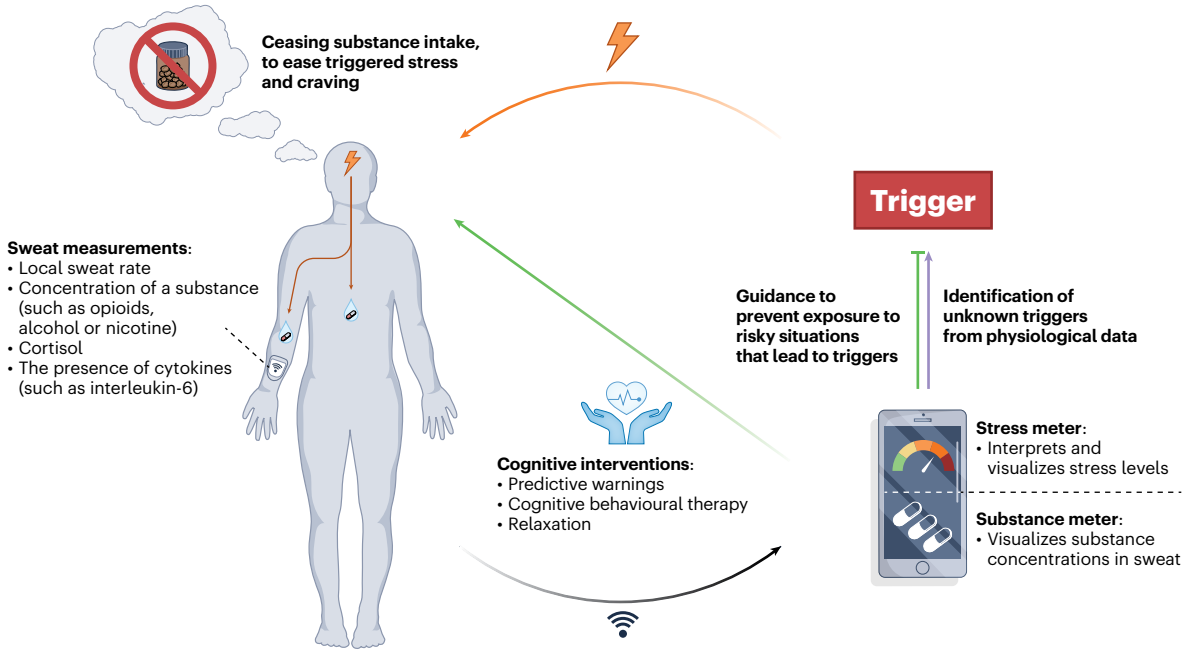

Fig. 1 | Wearable sweat analysis for the management of SUDs. Foreseeable or unforeseeable triggers[36] cause craving symptoms and distress (orange arrow), and a subsequent strong desire to take in the addictive substance (for example, an opioid). When the substance is not available, a strong physiological arousal leads to increased sweating. A skin patch that can locally monitor the sweat rate and the concentration of drugs and their metabolites and send the information to a connected device (black arrow) would allow for real-time data analysis and interpretation. Integrating the device with digital health applications and digital therapeutics would allow for better direct support to patients, for example, via cognitive behavioural interventions that can ease the stress (green arrow), prevent trigger incidents (green inhibitor) and help identify unforeseen triggers (violet arrow). Wearable sweat analysis would enable frequent measurements of physiological state, the identification of triggers and the delivery of support, as well as the provision of information about the general experience of craving over the course of one day, one week and one month[37]. Measurements of physiological state and of the concentration of drugs and their metabolites in sweat may need to be conducted only once a day, and longitudinal data would allow to ascertain whether the wearable device can be effectively used to detect triggers and to limit cravings to better manage SUDs.

response and the environment of the wearer. For example, the early onset of elevated levels of cortisol and cytokines can precede a craving or a relapsing episode. With enough data, the wearable device could make predictions and provide real-time intervention personalized to the patient. This health information could then be integrated into the stress meter. The molecular analysis of sweat could thus allow for the monitoring of compliance with pharmacological agonist treatments, assure abstinence from unwanted substances and assess an individual's general stress levels.

The ability to cross-connect wearable sensors with applications and portable devices would allow for the implementation of digital therapeutics and management tools for the personalized support of patients in everyday life. Such an automated, continuous and personalized patient-management system could lead to several favourable outcomes: a pharmacological agonist-therapy dosage regimen based on measured sweat concentrations in a semi-closed-loop approach could be adapted day-by-day; if a trigger and/or craving are detected or identified, applications could expediently support patients in managing risky situations and complex real-life environments; applications promoting relaxation could help reduce everyday stress and pressure; digital cognitive behavioural therapy could be set up to empower patients to cope with the challenges of SUD withdrawal in their lives; and strategies for digital guidance could be implemented to provide support in the case of an emergency.

Patient-centred healthcare

Successful implementation of innovative healthcare solutions requires collaboration and the delivery of mutual value across the complex web of stakeholders in the world of healthcare. However, the roles and power dynamics of stakeholders are shifting, owing to changes in healthcare delivery and development in order to meet sustainability goals and to create an equitable healthcare system. The stakeholders include patients, caregivers, healthcare providers, regulators, governments, insurance companies, communities, pharmaceutical firms, technology organizations and academic institutions (Table 1). It is important that the different needs and aims of each stakeholder are thoroughly addressed. The increase in innovative digital health tools makes a move towards 'Health 4.0' possible, a term indicating universal digital integration occurring in all healthcare sectors and that refers to the delivery of true 'smart' health[31]. In Health 4.0, the role of the patient changes to that of an empowered citizen. The inclusion of individuals in the management, decisions and ownership of their own health creates both opportunities and challenges. Including the patient's voice at all stages of therapy produces a life-cycle development[32] that is mature and ongoing. Early and systematic partnership with patients with regard to medical devices and digital innovation creates better trust, adherence and the persistence of solutions[33].

Careful identification of the correct cohort at the different stages of development is achieved by meaningful expectation management,

Table 1 | The involvement and goals of stakeholders of wearable sweat-analysis systems for managing SUDs

Stakeholders	Involvement	Goals
Patients and caregivers	Provide a lived experience, particularly during craving episodes and relapse	A personalized solution that allows most patients to overcome SUDs by breaking the cycle of addiction
Policymakers	Deliver secure and sustainable public healthcare	A fully validated medical device that enables compulsory, evidence-based clinical guidance for managing SUDs
Developers of biosensor technology	Develop biosensing systems	An accurate, precise and validated biosensing system for the monitoring of the rates of sweat production and of substances of concern, cortisol and cytokines in it
Healthcare professionals	Indicate and guide treatments, such as pharmacological agonist therapy and cognitive behavioural therapy	Better patient care through the early detection and identification of triggers, the monitoring of substance concentrations, and personalized and automated interventions
Academic institutions	Foster innovation, for example, by supporting the exploration of new sweat biomarkers	New monitoring approaches, such as automatized warnings of increased arousal or stress, or the early identification of triggers, are successfully investigated in clinical trials
Payers	Financially support withdrawal programmes	An affordable and reimbursable medical device that is used by patients and that reduces healthcare costs
Public-health officials	Assess and mitigate the societal impact of SUDs	Timely, cost-effective and sustainable support to address relapse

by planning, and by defining the scope of work for individuals and patient-advocacy organizations while respecting their capacities and independence. Arriving at meaningful inclusion requires solutions to actively address the unmet needs of a community. People who are living with addiction are a vulnerable population. Partnership with vulnerable communities requires the development of a safe and trustful space for transparent discussion, built on a foundation of authentic healing relationships[34], and the inclusion of addiction community leaders and people recovered and recovering from addiction[35].

Development and validation of digital biomarkers

Newly established digital biomarkers could be used for remote monitoring and for additional information in clinical trials, yet also for disease monitoring and decision-making. New guidelines for establishing digital biomarkers were released by the Clinical Trials Transformation Initiative in collaboration with healthcare authorities, academic partners and industry (https://go.nature.com/42YLL3O). In essence, the guidelines pose that clinical relevance needs to be established, that stakeholders should be included and that clinical application in early phase clinical trials is recommended, so as to demonstrate fit-for-purpose design. Early interactions with healthcare authorities will help to establish novel digital biomarkers as contributing added value in the monitoring and treatment of SUDs. The use of algorithms, machine learning or artificial intelligence (AI) tools can facilitate the use of software as a medical device, with meaningful consequences for product development.

Regulatory challenges

The type of device discussed in this Comment is an in-vitro diagnostic medical device under Regulation (EU) 2017/746 (IVDR). It combines software and wearable sensors (a 'smart' textile) to analyse sweat and to provide health data. The primary purpose of the device aligns with that of in-vitro diagnostic devices providing physiological or pathological information, as defined by IVDR, Chapter 1, Article 2. To bring innovation to the market, connecting academic research with regulatory compliance from the very beginning is mandatory (this would go beyond European Union regulations such as IVDR 2017/746). To succeed, the final product must be compliant with International Organization for Standardization (ISO) standards ISO 20916 for clinical performance studies using specimens from human subjects, ISO 14971 for risk management, IEC 62366 for human factors engineering, ISO 62304 for software development and ISO 10993 for biological evaluation. Also, design, development and prototype production must be aligned with ISO 13485 requirements (https://www.iso.org).

If 'principles of AI' are leveraged for the device, the European Union's General Data Protection Regulation demands that users, especially patients, should be informed about automated decision-making processes. Also, the United States Food and Drug Administration emphasizes clinical validity, data separation and algorithm transparency. Dealing with the ever-changing nature of 'AI driven' algorithms requires compliance with two key documents: *Software as a Medical Device Pre-Specifications* and an *Algorithm Change Protocol* (https://go.nature.com/4c59OlI). If these documents are missing at the time of initial approval, subsequent changes may require time-consuming and costly resubmission.

To unlock the potential of wearable sweat analysis, researchers should adhere to the regulatory standards and address the challenges of AI and communicating effectively. Compliance with the European Union's General Data Protection Regulation and Medical Device Regulation/IVDR, and with the United States Food and Drug Administration requirements, will ensure user awareness and acceptance by the competent authorities.

Outlook

The continuous monitoring of substances and metabolites in sweat has been hindered by insufficient sensor stability, by interpersonal variations in the generation of sweat and in the levels of relevant biomarkers in it, and by poor correlations between their concentration in sweat and blood. A wearable sensor for use in the context of SUDs would ideally be composed of a sweat-rate sensor and an array of molecular sensors for the detection of multiple biomarkers, with personalized calibration. Such a wearable sensor would be integrated with sensors for the simultaneous monitoring of heart rate, blood pressure and skin conductance, and be coupled with machine-learning models for accurate data analysis. Currently, no research-grade devices fulfil all these criteria.

Yet commercially available technology for wearable sweat-rate measurements (such as the Gx Sweat Patch from Epicore Biosystems; https://www.epicorebiosystems.com/gx-sweat-patch) allows for the objective and continuous assessment of sweating, a main symptom of

SUDs. Thorough clinical investigation should reveal the full potential of wearable sweat analysis. For this to happen, a wide range of stakeholders — patients, caregivers, policymakers, developers, healthcare professionals, academic institutions, payers and public-health officials (Table 1) — should be involved in the medical device development process, from the design of the device to its validation to the assessment of its use by patients. Device design should take a patient-centred approach and leverage healthcare considerations, particularly reductions in the time for patients to access support, and the resources available to support services to address the underlying causes of vulnerable populations. When a vulnerable patient leaves the safety of sheltered treatment, the device should act as the 'counsellor' in their pocket. Successful adoption of the technology will require users to be empowered in the management of their recovery.

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Competing interests

The authors declare no competing interests.

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