Title

Noninvasive skin swab analysis detects environmental drug exposure of pharmacy staff.

Journal

Clinical and Translational Science, 17(10)

Authors

Thompson, Samantha

Abelyan, Samvel

Panitchpakdi, Morgan

et al.

Publication Date

2024-10-01

DOI

10.1111/cts.70022

Peer reviewed

Received: 13 March 2024 | Revised: 4 August 2024 | Accepted: 12 August 2024

DOI: 10.1111/cts.70022

BRIEF REPORT

Noninvasive skin swab analysis detects environmental drug exposure of pharmacy staff

Samantha Thompson | **Samvel Abelyan** | **Morgan Panitchpakdi** | **Jasmine Zemlin** | **Sydney Thomas** | **Haoqi Nina Zhao** | **Pieter C. Dorrestein** | **Shirley M. Tsunoda**

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, USA

Correspondence
Shirley M. Tsunoda, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, 9500 Gilman Drive, MC 0657, La Jolla, CA 92093-0657, USA.
Email: smtsunoda@health.ucsd.edu

Abstract

The skin is complex with multiple layers serving protective, regulatory, and detective functions. The skin hosts chemicals originating from consumption, synthesis, and the environment. Skin chemicals can provide insight into one's daily routine or their level of safety in a work environment. The goal of this study was to investigate the utility of noninvasive skin swabs to detect drugs in a pharmacy setting and to determine whether drugs are transferred to the skin of pharmacy staff. To answer this question, skin swabs were collected from healthy pharmacy staff workers and healthy non-pharmacy individuals and analyzed via untargeted liquid chromatography–tandem mass spectrometry (LC–MS/MS). Drugs were annotated through library matching against the GNPS community spectral library. We then used questionnaire data to exclude medications that participants took orally or applied topically and focused on the drugs participants were exposed to in the work setting. Overall, pharmacy staff had a higher number and variety of medications on their skin as compared with healthy individuals who did not work in a pharmacy. In addition, we identified some chemicals such as *N*,*N*-Diethyl-metatoluamide on a large number of subjects in both experimental and control groups, indicating environmental exposure to this compound may be ubiquitous and long-lasting.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Noninvasive skin swabbing has been shown in previous studies to detect drugs and drug metabolites. Previous studies have also shown that chemical contamination occurs in healthcare settings.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can noninvasive skin swabs detect drug exposure in pharmacy providers? What classes of compounds do pharmacy workers get exposed to in their daily environment?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Healthcare professionals may be exposed to a multitude and variety of different chemicals that they handle. These chemicals can be monitored using noninvasive skin swabs. Gloves may or may not protect individuals depending upon the chemical and the circumstances. Systemically administered drugs are also detected in noninvasive skin swabs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results from this study demonstrate that a method using noninvasive skin swabs and nontargeted metabolomics can detect drugs and chemicals in the environment. These results may provide initial guidance for continuous monitoring of environmental drug exposure. This may also lead to enhanced guidance and monitoring of healthcare personnel particularly who handle hazardous compounds.

INTRODUCTION

The skin surface is a matrix for monitoring chemicals exposed to the environment. Chemicals present on the skin originate from many sources, including human metabolism, microbes, behaviors, food, personal care products, the environment, and drugs.[1,2] In fact, studies show that our daily routines leave chemicals on the skin surface originating from our surroundings.[3,4] Individuals working in environments surrounded by chemicals may be more vulnerable to their effects. For example, individuals working in pharmacies handle an estimated 250 prescriptions per day, not including chemicals from cleaning supplies or shipping containers.[5] The impact of these chemical exposures on health is currently unknown.

Environmental substances and xenobiotics can be detected on the skin using noninvasive skin swabbing. This novel technique pairs rapid, noninvasive sampling with untargeted LC–MS/MS analysis to broadly screen for compounds and their byproducts without a prior knowledge of the expected chemicals.[6,7] Recent studies have shown the clinical utility of skin swabbing and mapped the relationship of drug and metabolite detection on the skin to blood concentrations.[1,8,9]

Pharmacy personnel constantly interact with a multitude of medications in the workplace. These can range from oral tablets to topical creams/solutions to intravenously administered compounds including chemotherapy and other substances that have known effects on reproductive and cellular health. In addition, medications handled in an institutional setting may be touched by various healthcare workers – from the person unpacking the medication to the technician compounding it, the pharmacist verifying the medication, the person delivering the medication, the nurse administering it, and the person emptying the trash. Transference of the medication and its potential effects could occur at any point in this drug distribution process. The goal of this initial pilot study was to demonstrate the feasibility of using noninvasive skin swabs to detect chemical transference in a pharmacy setting.

METHODS

We conducted a prospective, controlled two-group-comparison study of 46 individuals that was approved by the Office of IRB Administration at UC-San Diego, protocol #210420. Inclusion criteria included healthy individuals with no chronic medical conditions aged ≥18 years, and able to follow study requirements. The experimental group included individuals who were regularly exposed to a pharmacy setting, such as pharmacists, pharmacy interns, and pharmacy technicians ($n = 21$). The control group included individuals without regular exposure to a pharmacy setting and who did not share a household with a pharmacy employee ($n = 25$). Participants were excluded if they were taking any prescription medications (excluding birth control), had loss of skin integrity on the desired swab locations, or were pregnant or breastfeeding at the time of enrollment.

After giving informed consent, participants completed a questionnaire with the following information: name, date of birth, sex assigned at birth, topical and oral medication history (OTC and prescription), place of work (including the specific area within the pharmacy for the experimental group), and their practice of glove wearing (experimental group only). All study participants were subject to noninvasive swabbing using cotton swabs that were pre-cleaned and pre-soaked in 1:1 ethanol and water. Swabs were applied to the front (palm) and back of both hands as well as the forehead at the end of their work day. The same two investigators applied moderate pressure to each skin site using a circular motion for 30 s. Swabs

were stored at −80°C in a 96-well DeepWell plate prior to undergoing extraction. Swabs were submitted to untargeted LC–MS/MS analysis and analyzed using the GNPS ecosystem which includes a drug-specific spectral library. Detailed swab preparation, LC–MS/MS, and data analysis methods are included in the supplemental methods section (Data S1).

RESULTS

The experimental group was composed of 21 healthy individuals (11 females) aged 24–82 years who were employed by UC-San Diego Health (16), CVS (3), or Rite Aid (2) pharmacies. Individuals worked as pharmacists, interns, compounding technicians, or infusion technicians. The control group was composed of 25 healthy, non-clinically active faculty and students (11 females) at UCSD aged 18–62 years who had not been exposed to a pharmacy setting or individuals employed in a pharmacy setting (Tables S1–S3). There were significantly more medications found on the skin of the experimental group compared with the control group ($p = 0.00026$). Table 1 presents the variety of medications found on the hands/forehead of experimental and control group participants. For a complete list of all the molecules detected from this study refer to Table S4.

The GNPS molecular networking analysis resulted in a 4.65% annotation rate and identification of various detected drugs and drug metabolites based on MS/MS spectral similarity. Using the drug and drug suspects spectral library, one metabolite of sulfamethoxazole and two suspects of terbinafine were additionally annotated (Figure S1). Of the drugs identified, most unique annotations were found on the skin of individuals who actively worked in a pharmacy setting when compared with the control group (Figure 1a). The classes of drugs that were annotated included ACE inhibitors, antibacterials, antifungals, antiseptics, β-blockers, vasodilators, and topical drugs. Testosterone, gabapentin, and progesterone metabolites were only found in the control group, which may result from endogenous metabolism rather than medication exposure. Topical compounds such as *N*,*N*-Diethyl-meta-toluamide (DEET) had spectral matches observed in participants of both groups. Propranolol, a β-blocker, was detected solely in the

TABLE 1 Medications detected on the skin of the experimental versus control.

Drug name (cosine[a])	Number of experimental	Number of control	Class
Lisinopril (0.76)	4	0	ACE Inhibitor
Amiodarone (0.97)	1	0	Antiarrhythmic
Trimethoprim (0.80)	5	0	Antibacterial
Cefazolin (0.91)	1	0	Antibacterial
Sulfamethoxazole (0.97)	1	0	Antibacterial
Terbinafine (0.99)	1	0	Antifungal
Chlorhexidine (0.95)	3	0	Antiseptic
Buspirone (0.93)	2	0	Anxiolytic
Propranolol (0.95)	6	0	β-blockers
Atenolol (0.86)	2	0	β-blockers
Metoprolol (0.97)	1	0	β-blockers
Ketamine (0.94)	2	0	General Anesthetic
Ethinyl estradiol (0.83)	5	5	Hormone
17.alpha.-Ethinylestradiol (0.82)	3	7	Hormone
Testosterone (0.96)	0	1	Hormone
6.beta.-Hydroxymedroxyprogesterone 17-acetate (0.75)	0	3	Steroid
Cortisol (0.83)	1	0	Steroid
DEET (0.99)	17	24	Topical
Cilostazol (0.97)	1	0	Vasodilator
Total	56	40	

[a]Cosine – the cosine value of each drug allowed us to identify the strength of the match.

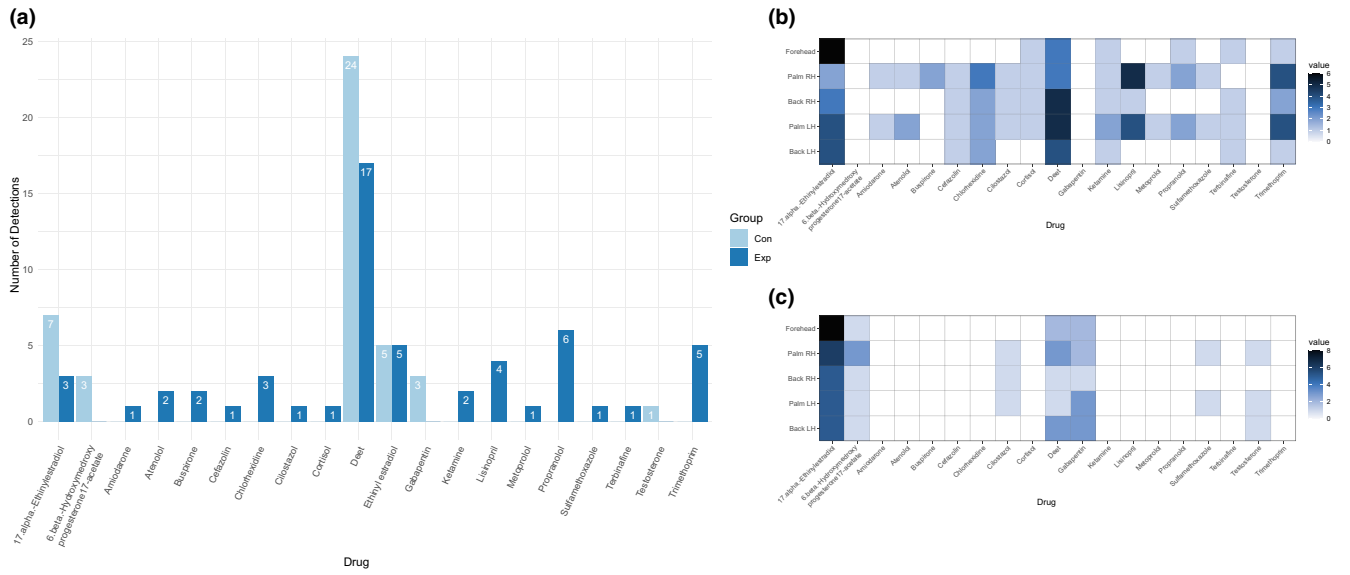

FIGURE 1 Detections of drugs on the skin. (a) Barplot with counts of annotated drugs detected from metabolomic analysis of skin swabs using GNPS molecular networking. Heatmaps highlighting spectral matches of experimental (b) pharmacy-setting exposed individuals and (c) non-exposed individuals group across various sample sites. Values indicate the number of times a drug was uniquely detected per sample in each site. The *y*-axis represents sample sites that were swabbed on all participants, and the *x*-axis represents detected drugs identified and annotated using the GNPS molecular networking platform and MS/MS spectral matching.

experimental group. Propranolol was detected on the left and right palm swabs of five individuals, suggesting contamination through handling of the drug; in addition, propranolol was found on the forehead of a study participant who reported taking propranolol. More medications were discovered on pharmacy staff who were not wearing gloves compared with those wearing gloves (Table S4).

The presence of drugs identified by spectral matching was detected across five different sample sites. The largest amount of unique spectral matches of drugs was detected in samples of the left and right palms of the experimental participants (Figure 1b). The forehead and back left-hand sites contained the fewest number of drugs found, but resulted in the highest number of matches for their available drug detections. Ethinyl estradiol had the highest value of spectral matches in the forehead, followed by the back of the left-hand site. β-blocker drugs (metoprolol, propranolol, atenolol) were only found on the palms of either hand. Topical drugs such as DEET were found in all hand sites, but also the forehead of study participants.

DISCUSSION

Our study demonstrated that noninvasive skin swabs coupled with nontargeted metabolomic analysis have the potential to detect environmental drug exposure. There were significantly more therapeutic agents detected on the skin of the experimental group compared with the control group (Table 1) suggesting that pharmacy workers are exposed to medications that they are handling. The medications detected varied in therapeutic class, chemical structure, and workplace location. The majority of medications were detected on the palms and backs of the hands reflecting the major source of contact with medications (Figure 1b,c). Importantly, some medications were discovered on the forehead due to topical administration or drug absorption and secretion after ingestion.

One major class of medication exposure observed in the experimental group was antibiotics consisting of sulfamethoxazole, cefazolin, and trimethoprim. Workplace antibiotic exposure could have deleterious consequences if these antibiotics are absorbed systemically. For example, occupational penicillin dust was shown to confer penicillin resistance in pharmacy workers.[10] Interestingly, nurses exposed to antibiotics on surfaces at work and in the air showed high levels of exposure using normal preparation techniques but reduced exposure with Tevadaptor® closed-system drug transfer device (CSTD).[11] Additionally, antibiotics not only disrupt gut microbial communities in individuals taking them, but they have also been shown to affect individuals sharing a household.[12,13]

Three beta-blockers were detected on the skin of six participants in the experimental group: propranolol, atenolol, and metoprolol. Propranolol was detected on the hands and forehead of one participant in the experimental group who reported taking propranolol at the time of this study. Our previous study has shown that

orally administered diphenhydramine and metabolites can be detected on the skin using our nontargeted metabolomics pipeline and that the appearance on the skin lags behind blood concentrations by 1.5 h or more.[8] All other incidences of drug exposure on skin were in participants in the experimental group with no history of taking these medications. Lisinopril, an ACE inhibitor commonly used for hypertension was detected on the skin of four participants in the experimental group. It is not known whether occupational exposure to these antihypertensive agents has any clinically significant effect on these individuals.

Ketamine, a rapid-acting general anesthetic, was found in two individuals working as pharmacy delivery personnel. This was likely from handling the IV bags containing ketamine without glove protection. Ketamine may be harmful in the recreational use setting but has not shown reports of fatalities or overdoses in a clinical setting.[14] It has been shown to cause double vision as well as neurological and cardiovascular effects.[15] Ketamine exposure has been observed in other health settings with a risk of systemic absorption from contact with the injection solution as detected in hair samples of veterinarians. Hair follicle levels in veterinarians partially overlapped with those seen in individuals convicted of driving under the influence of drugs and alcohol (ketamine included with other drugs).[16]

Gloves appeared to protect individuals from drug detection, although this was not absolute. We identified fewer medications on the skin of staff who routinely wore gloves as protection. Eleven individuals in the experimental group were wearing gloves while handling drugs. Of those 11, three still showed the drugs ketamine and cefazolin on the skin. Of the 10 individuals in the experimental group who reported not wearing gloves, 8 had multiple drugs on their skin (Table S4). While gloves may protect against environmental drug exposure, they do not appear to provide absolute protection from all chemicals. We analyzed the data after excluding the presence of hormones since we were unable to differentiate endogenous vs. exogenous origin. We also excluded DEET from this analysis because it was so ubiquitous in both experimental and control individuals that we hypothesized that this was an environmental contaminant present in both groups. Further explanation can be found in the supplemental discussion section. Ultimately, after controlling for hormones and DEET, more drugs were discovered on the skin of individuals not wearing gloves compared with those wearing gloves ($p = 0.00009$, z-test). Based upon the data in our study, it may be important for pharmacy workers to have minimal direct contact with medications. Implementing such practices as wearing gloves and/or appropriate PPE for all inpatient and outpatient shifts, unit dose medications in the outpatient setting, and washing hands after every exposure to medication would be a large administrative and logistical burden. Future studies should address if this is reasonable to implement.

An important question to be answered in future studies is whether any of these chemicals are absorbed with the potential to cause deleterious effects. One study specifically looked at irinotecan and its metabolites in the blood of pharmacy staff inside and outside the compounding room.[17] Multiple individuals demonstrated irinotecan in plasma, mainly in individuals who did not compound the drug. Recently, it was reported that topical agents like sunscreen can be absorbed systemically in much higher concentrations than previously thought.[18] In summary, our study illuminates the exposure of certain drugs and chemicals to individuals working in a pharmacy, particularly in individuals not wearing gloves. Pharmacy workers should be aware of the potential risk of drug contamination to their skin and take appropriate measures to mitigate this exposure.

There are several limitations to our study. Some of the variability in our results could have been due to differences in skin swabbing technique. Although swabbing was standardized to try to minimize this limitation, there is a possibility that the pressure and size of the swabbing area could have varied which may have affected the amount of drug detected via our untargeted methods. Additionally, we are limited by the number of drugs and metabolites that are detectable with positive-ionization mass spectrometry and publicly available spectral libraries such as GNPS for annotation (2266 MS/MS spectra for 1004 drugs in the drug library). Thus, there may be many more drugs and chemicals contaminating the skin of pharmacy workers. In addition, it is possible that other routes may contribute to this exposure such as inhalation from IV reconstitution or automatic dispensing in the pharmacy setting.[19,20] Noninvasive skin swabbing may be a useful method to determine environmental and occupational exposure to drugs and chemicals. Understanding the impact of these workplace and environmental exposures on the individual is important, particularly for chemicals with known hazardous potential.

ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST STATEMENT

PCD is an advisor and holds equity in Cybele and Sirenas and a Scientific co-founder, advisor and holds equity to Ometa, Enveda, and Arome with prior approval by UC-San Diego. PCD also consulted for DSM animal health in

2023. All other authors declared no competing interests for this work.

ORCID

Jasmine Zemlin https://orcid.org/0000-0003-0713-9956
Sydney Thomas https://orcid.org/0000-0001-8261-1195
Haoqi Nina Zhao https://orcid.org/0000-0003-3908-630X
Pieter C. Dorrestein https://orcid.org/0000-0002-3003-1030
Shirley M. Tsunoda https://orcid.org/0000-0002-3974-8038

REFERENCES

Reference 20 has been cited in supporting information.

1. Jarmusch AK, Elijah EO, Vargas F, et al. Initial development toward non-invasive drug monitoring via untargeted mass spectrometric analysis of human skin. *Anal Chem*. 2019;91:8062-8069.
2. Bouslimani A, Melnik AV, Xu Z, et al. Lifestyle chemistries from phones for individual profiling. *Proc Natl Acad Sci USA*. 2016;113:E7645-E7654.
3. Gong M, Zhang Y, Weschler CJ. Measurement of phthalates in skin wipes: estimating exposure from dermal absorption. *Environ Sci Technol*. 2014;48:7428-7435.
4. Weschler CJ, Nazaroff WW. SVOC exposure indoors: fresh look at dermal pathways. *Indoor Air*. 2012;22:356-377.
5. Safety in the Retail Pharmacy. (2014). Accessed March 1, 2024. https://psnet.ahrq.gov/perspective/safety-retail-pharmacy
6. Wang M, Carver JJ, Phelan VV, et al. Sharing and community curation of mass spectrometry data with global natural products social molecular networking. *Nat Biotechnol*. 2016;34:828-837.
7. Want EJ. LC-MS untargeted analysis. *Methods Mol Biol*. 2018;1738:99-116.
8. Panitchpakdi M, Weldon K, Jarmusch A, et al. Non-invasive skin sampling detects systemically administered drugs in humans. *PLoS One*. 2022;17. doi:10.1101/2021.11.22.469638
9. Bittremieux W, Advani RS, Jarmusch AK, et al. Physicochemical properties determining drug detection in skin. *Clin Transl Sci*. 2022;15:761-770.
10. Farshad AA, Enferadi M, Bakand S, Jamshidi Orak R, Mirkazemi R. Penicillin dust exposure and penicillin resistance among pharmaceutical workers in Tehran, Iran. *Int J Occup Environ Health*. 2016;22:218-223.
11. Sessink PJM, Nyulasi T, Haraldsson ELM, Rebic B. Reduction of contamination with antibiotics on surfaces and in environmental air in three European hospitals following implementation of a closed-system drug transfer device. *Ann Work Expo Health*. 2019;63:459-467.
12. Chopyk J, Cobián Güemes AG, Ramirez-Sanchez C, et al. Common antibiotics, azithromycin and amoxicillin, affect gut metagenomics within a household. *BMC Microbiol*. 2023;23:206. doi:10.1186/s12866-023-02949-z
13. Abeles SR, Jones MB, Santiago-Rodriguez TM, et al. Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome*. 2016;4:39. doi:10.1186/s40168-016-0187-9
14. Cope RB. The potential for occupational exposure of veterinarians to ketamine resulting in positive drug tests. *Aust Vet J*. 2018;96:59-61. doi:10.1111/avj.12676
15. Béchet V, Benoist H, Beau F, et al. Blood contamination of the pharmaceutical staff by irinotecan and its two major metabolites inside and outside a compounding unit. *J Oncol Pharm Pract*. 2022;28(4):777-784. doi:10.1177/10781552211012059
16. Matta MK, Zusterzeel R, Pilli NR, et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA*. 2019;321:2082-2091.
17. Corsello SM, Bittker JA, Liu Z, et al. The Drug Repurposing Hub: a next-generation drug library and information resource. *Nat Med*. 2017;23(4):405-408. doi:10.1038/nm.4306
18. Bittremieux W, Avalon N, Thomas S, et al. Open access repository-scale propagated nearest neighbor suspect spectral library for untargeted metabolomics. 2022. doi:10.1101/2022.05.15.490691
19. Aron AT, Gentry EC, McPhail KL, et al. Reproducible molecular networking of untargeted mass spectrometry data using GNPS. *Nat Protoc*. 2020;15:1954-1991.
20. Merel S, Snyder SA. Critical assessment of the ubiquitous occurrence and fate of the insect repellent N,N-diethyl-m-toluamide in water. *Environ Int*. 2016;96:98-117.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thompson S, Abelyan S, Panitchpakdi M, et al. Noninvasive skin swab analysis detects environmental drug exposure of pharmacy staff. *Clin Transl Sci*. 2024;17:e70022. doi:10.1111/cts.70022