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Recommendations for Toxicological Investigation of Drug-Impaired Driving and Motor Vehicle Fatalities—2017 Update

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Abstract

This report describes the outcomes of a process undertaken to review and update the National Safety Council's Alcohol, Drugs and Impairment Division's recommendations for the toxicological investigation of suspected alcohol and drug-impaired driving cases and motor vehicle fatalities. The updates to the recommendations are made based on a survey of practices in laboratories in the USA and Canada performing testing in these cases, consideration of existing epidemiological crash and arrest data, current drug use patterns, and practical considerations of widely available technology platforms in laboratories performing this work. The final recommendations updates are derived from a consensus meeting of experts recruited from survey respondents and the membership of the National Safety Council's Alcohol, Drug and Impairment Division. The principal changes in this round of recommendations include removal of butalbital, phenobarbital, and phencyclidine from Tier I (mandatory) to Tier II (optional) due to changes in prevalence. In addition, buprenorphine, fentanyl, tramadol, and their metabolites were moved from Tier II to Tier I due to increased prevalence and concerns about their potential for causing impairment. In addition, screening and confirmatory cutoffs for the oral fluid scope were further refined. Other additions were made to the list of Tier II compounds including fentanyl analogs (e.g., acetylfentanyl, butyrylfentanyl, furanylfentanyl, etc), mitragynine, novel opioids (e.g., MT-45, U-47700), atypical antipsychotics, and novel benzodiazepines (e.g., clonazolam, flubromazolam, etc).

Introduction

Beginning in 2004, the National Safety Council's Alcohol, Drugs and Impairment Division (NSC-ADID) (previously the Committee of Alcohol and Other Drugs (CAOD)), started an initiative to standardize toxicology laboratory testing practices for cases involving driving under the influence of drugs (DUID), by surveying the testing

scope and analytical cutoffs being used for blood and urine drug testing by those laboratories. Based on the results of the survey and consensus input from a subsequent face-to-face meeting of a panel of forensic toxicologists, the first recommendations document was published in 2007, and represents a list of drugs which ought to be tested for in suspected impaired driving cases (1). Drugs and drug classes were included based on their known potential to cause impairment described in peer-reviewed traffic safety and human performance literature, the experience of laboratories participating in the survey, and data gathered from DUID arrests. The drugs of concern generally have pharmacological effects (central nervous system (CNS) depression, sedation, drowsiness, hyperstimulation, drug withdrawal, "risk-taking", hallucinations, mood alteration, etc.) that make them likely to have adverse effects on driving. Following publication of the 2007 recommendations, the 2009 National Academy of Sciences (NAS) Report was published (2). This report called for among other things, better standardization of approaches to forensic analysis, and consensus-based standards—a goal consistent with the development of the recommendations in the 2007 document.

In 2013, the NSC-ADID undertook an update to the 2007 recommendations using the same approach of a survey of laboratory practices, resources and drug prevalence, followed by a face-to-face consensus meeting of stakeholders from laboratories performing this type of forensic casework (3). In addition to an update of the scope for blood and urine testing, reporting thresholds for oral fluid drug testing in DUID cases were established. Further, drugs of concern were divided into two groups: Tiers I and II. While both groups are equally capable of causing impairment, Tier I drugs encompassed the most frequently encountered drugs found in DUID casework, and those which could be detected and confirmed with commonly available immunoassay and gas chromatography/mass spectrometry (GC/MS) instrumentation.

Tier II analytes were those that had limited or regional prevalence, were encountered less frequently, or required more advanced instrumentation such as liquid chromatography/mass spectrometry (LC–MS-MS) or liquid chromatography/high resolution mass spectrometry (LC–HRMS) not available in the majority of laboratories. The 2013 report required that to be compliant with the NSC-ADID recommendations, laboratories had to test for Tier I compounds at the recommended cutoffs. Tier II may or may not be included in the scope of testing depending on regional trends in DUID casework, as well as laboratory resources, staffing, availability of instrumentation/technology, and resources for method development and validation.

In 2016, the NSC-ADID, with support of the National Highway Traffic Safety Administration (NHTSA), requested another review of the recommendations for toxicology testing in impaired driving and motor vehicle fatality investigations in light of changes in available technology, and the increased popularity and rapidly changing landscape of novel psychoactive substances (NPS). These include compounds such as the synthetic cannabinoids, cathinones and “bath salts”, and novel opioids, especially analogs (4, 5). We describe the process through which the changes to the recommendations were made and detail the updated recommendations for drug testing in DUID and motor vehicle fatality cases.

Methods

This project and survey was approved by the Arcadia University Institutional Review Board (IRB) under project number 885920–1.

Toxicology survey

The 2016 toxicology laboratory survey was created using SurveyMonkey® (San Mateo, CA), and the questionnaire was developed by the authors of this report to include questions related to agency type, caseload, laboratory management and resources, staffing, availability and the use of various technologies for screening and confirmation, matrices accepted by the laboratory (i.e., blood, urine and/or oral fluid), prevalence of drugs encountered in DUID and motor vehicle fatality cases (aggregated), compliance with the previously published NSC-ADID recommendations, and the scope of testing and screening and confirmation cutoffs currently in use in the laboratory for this testing.

Laboratories were selected for participation in the survey from databases of professional organizations, specifically the American Board of Forensic Toxicology (ABFT), the Society of Forensic Toxicologists (SOFT), the International Association for Chemical Testing (IACT), and the American Academy of Forensic Sciences (AAFS), as well as those laboratories providing support for the Fatality Analysis Reporting System (FARS) at the NHTSA.

Following a screening invitation email to confirm that the laboratories performed testing of impaired or fatally injured drivers and their willingness to participate, invitations with a link to the survey were sent to a total of 102 laboratories. Laboratories were given 2 weeks to respond, then received follow-up calls to encourage completion of the survey. A total of 70 toxicology laboratories throughout the USA and Canada ultimately provided sufficiently complete information to be included in the survey data compilation and analysis. Survey data were analyzed using Microsoft Excel (Redmond, WA).

Consensus meeting

A subset of the survey respondents (n = 18) and the authors were invited to participate in a face-to-face consensus meeting in November 2016, in Philadelphia, PA. Participant selection was designed to provide diversity of experience and perspective including geographic location, agency type (see acknowledgments), and workload. States represented were AL, AZ, CA, CO, FL, GA, ID, MD, MI, MS, MT, NH, NY, PA, RI, SC, TX, VA, WA and WI. These participants provided additional detailed survey information on the screening and confirmation cutoffs used in their individual laboratories. The consensus group reviewed the results of the toxicology survey and the follow-up survey, and current peer-reviewed literature on drugs encountered in DUID casework. The group then performed a line-by-line review of the 2013 recommendations using a modified Delphi method, specifically addressing questions of the current appropriateness of the screening and confirmation targets and cutoffs, and the designation of drugs as Tiers I or II compounds.

Results

Toxicology survey

A total of 70 participants completed the survey. Full results of the survey are available on the Center for Forensic Science Research and Education’s (CFSRE) website (https://www.forensicscienceeducation.org/wp-content/uploads/2016/04/Full-Survey-Report.pdf). Survey participants represented state (50%), county (26%), private (7%), regional (6%), municipal (6%), university (1%) and hospital (4%) laboratories. Of the 70 responding laboratories, 90% reported testing blood samples; 68% tested urine, and 1% tested oral fluid. Enzyme-Linked Immuno-Sorbent Assay (ELISA) was the most frequently reported

method for screening for drugs in blood in DUID cases, being used in 74% of laboratories, followed by GC/MS (50%), LC–MS-MS (39%), Enzyme Multiplied Immunoassay Technique (EMIT) (11%); and LC/HRMS (11%). The most common method used for urine screening was ELISA (49%); GC/MS (37%); LC–MS-MS (29%); EMIT (27%); and LC/HRMS (9%). For confirmation and quantitation of drugs in blood, 87% of laboratories reported using GC/MS followed by LC–MS-MS (81%). For confirmation of drugs in urine, GC/MS was used by 77% of laboratories, followed by LC–MS-MS (54%).

Compliance with the scope of testing and cutoff limits from the 2013 recommendations showed that 17% of the laboratories met or exceeded all of the recommendations, while an additional 52% reported they are partially in compliance and actively developing or validating methods to meet the remaining recommendations. Twenty percent of the survey respondents reported they do not believe that some of the compounds are applicable for their laboratory due to low local rates of prevalence of specific compounds. Compliance trends showed that for drugs where the cutoff limits had not changed between the 2007 and 2013 recommendations, rates of compliance had remained about the same or improved. Cutoff limits that had been lowered over that period of time showed lower rates of compliance, suggesting that laboratories have not yet been able to revalidate their methods to attain this increased requirement for sensitivity. Reasons for lack of compliance were reported as being due to lack of staffing, instrument capacity, instrument technology, analyst time, budget or that the cutoff limits were not relevant for the laboratory.

Participants were asked about their practices in testing for Tier II compounds. The 2013 recommendations listed 50 Tier II compounds that may be emerging, or have regional but not national prevalence in DUID populations (3). Of the 70 responding laboratories, 81% test for some Tier II compounds.

The 10 most frequently encountered drugs reported by the participating laboratories as appearing in their 10 most frequently detected drugs is shown in Table I.

Finally, the survey asked participants to provide any additional drugs for inclusion in Tier I of the updated recommendations. The top three suggestions were fentanyl and analogs, buprenorphine, and etizolam. Other suggestions included designer/synthetic opioids, designer benzodiazepines, mitragynine, synthetic cannabinoids, tramadol, trazodone, antipsychotics, cannabidiol, cannabinol, chlorpheniramine, difluoroethane, diphenhydramine, gabapentin, ibogaine, ketamine, metaxalone, NBOMes, promethazine, quetiapine, risperidone, zaleplon and zopiclone.

Table I. Number of laboratories reporting this compound/class in their 10 most frequently detected ($n = 70$)

Compound	Frequency
Alprazolam/alpha-hydroxyalprazolam	65
THC and metabolites	63
Oxycodone	57
Morphine	48
Methamphetamine	46
Cocaine and metabolites	46
Clonazepam/7-aminoclonazepam	41
Diazepam/Nordiazepam	40
Amphetamine	36
Hydrocodone	36
Diphenhydramine	22
Zolpidem	18
Fentanyl	18
Lorazepam	18
Methadone	16
Codeine	15
Carisoprodol/Meprobamate	14
6-Acetylmorphine	13
Citalopram	9
Tramadol	9
Hydromorphone	9
Gabapentin	5
Trazodone	4
Oxazepam	3
Fluoxetine/Norfluoxetine	3
Phencyclidine (PCP)	3
Temazepam	3
Cyclobenzaprine	2
Dihydrocodeine	2
Oxymorphone	2
MDMA	1
Amitriptyline	1
Butalbital	1
Topiramate	1

Recommendations

Based on the above considerations and deliberations, Table II shows the updated recommended scope and cutoffs in ng/mL for screening and confirmation in blood, urine and oral fluid for Tier I drugs. Changes made from the 2013 recommendations were as follows. Butalbital and phenobarbital were moved from Tiers I to II for all matrices due to low prevalence in DUID cases, and in consideration of the need to apply laboratories' limited resources to substances of greater prevalence and concern. Phencyclidine was also demoted from Tiers I to II to reflect its generally low prevalence except in certain-specific geographic regions. Buprenorphine (and its metabolite norbuprenorphine), fentanyl, tramadol (and its metabolite O-desmethyltramadol) were promoted from Tiers II to I for all matrices, due to increased prevalence observed by those laboratories performing testing for them, and their known potential for impairment.

Some changes were made to the cutoffs for other drugs. In blood, screening cutoffs of 10 ng/mL for low dose benzodiazepines (alprazolam, clonazepam and lorazepam) and 50 ng/mL for the remaining higher dose benzodiazepines were affirmed. The screening cutoff for oxymorphone was eliminated under the assumption that laboratories would predominantly be screening for oxycodone by ELISA.

In urine, the screening cutoff was specified for the inactive tetrahydrocannabinol (THC) metabolite 11-nor-carboxy-delta-9-tetrahydrocannabinol (carboxy-THC) only, assuming laboratories will be screening using ELISA. There was some discussion about the possibility of raising the urine screening and confirmation thresholds to concentrations that would rule out the possibility of passive exposure (6). Ultimately, the authors determined that in those jurisdictions where urine is still an acceptable matrix for impaired driving investigations, that the presence of cannabinoid metabolites would be assessed in the context of other information including driving performance, demeanor, performance in field sobriety or psychophysical tests, making passive exposure less of a concern, since probable cause for collection of the sample requires that there is some objective evidence of impairment. Impairment

Table II. 2017 Recommended scope and cutoffs in ng/mL for screening and confirmation in blood, urine, and oral fluid for Tier I compounds (all concentrations are in ng/mL)

Drug	Blood		Urine		Oral Fluid	
	Screen	Confirm	Screen	Confirm	Screen	Confirm
DRE category; cannabis						
THC	–	1	–	–	4	2
Carboxy-THC	10	5	20	5	–	–
11-OH-THC	–	1	–	–	–	–
DRE category; CNS stimulants						
Methamphetamine	20	20	200	50	20	20
Amphetamine	20	20	200	50	20	20
MDMA*	–	20	–	50	20	20
MDA*	–	20	–	50	20	20
Cocaine*	–	10	–	20	20	8
Benzoylecgonine	50	50	150	50	20	8
Cocaethylene	–	10	–	20	–	8
DRE category; CNS depressants						
Carisoprodol	500	500	500	500	100	100
Meprobamate*	–	500	500	500	100	100
Zolpidem	10	10	20	20	10	10
Low Dose Benzodiazepines	*10*	–	*50*	–	*5*	–
Alprazolam	–	10	–	50	–	1
Alpha-Hydroxyalprazolam	–	–	–	50	–	–
Clonazepam	–	10	–	50	–	1
7-Aminoclonazepam	–	10	–	50	–	1
Lorazepam	–	10	–	50	–	1
High Dose Benzodiazepines	*50*	–	*100*	–	*5*	–
Diazepam	–	20	–	50	–	1
Nordiazepam	–	20	–	50	–	1
Oxazepam	–	20	–	50	–	1
Temazepam	–	20	–	50	–	1
DRE category; narcotic analgesics						
Codeine*	–	10	–	50	–	5
6-Acetylmorphine	–	5	–	10	–	2
Buprenorphine	1	0.5	5	1	1	0.5
Norbuprenorphine	–	0.5	–	1	–	0.5
Fentanyl	1	0.5	1	0.5	1	0.5
Hydrocodone*	–	10	–	50	–	5
Hydromorphone*	–	5	–	50	–	5
Methadone	50	20	300	50	25	10
Morphine	10	10	200	50	10	5
Oxycodone*	10	10	100	50	10	5
Oxymorphone*	–	5	–	50	10	5
Tramadol	100	50	100	50	50	10
O-desmethyltramadol	–	50	–	50	–	10

*For laboratories screening by immunoassay, the compounds marked should have cross-reactivity equal to at least 80% of the relevant target compound of the designated immunoassay, for example, if MDMA is intended to be detected on the methamphetamine immunoassay, it must have a cross-reactivity of 80% on that assay.

from recent cannabis use cannot reliably be determined solely from a positive urine test for a THC metabolite. In its 2013 recommendations, the authors acknowledged that urine is a specimen best suited to demonstrate historical drug use or exposure, rather than impairment proximate to the time of driving, and for that reason is a less reliable specimen than blood or oral fluid in the context of an impaired driving or motor vehicle fatality investigation. The authors of the current recommendations feel similarly that urine is an inferior specimen to blood or oral fluid, and for this reason should be interpreted with caution.

Screening cutoffs for 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) in urine were removed given that most laboratories will be screening for these drugs using the amphetamine and methamphetamine ELISA kits. A screening cutoff of 2 ng/mL was added for zolpidem as several ELISA kits are now available for zolpidem and use a 20 ng/mL calibrator for urine. As with blood, the screening cutoff requirement for oxymorphone was removed because most laboratories will be using the oxycodone ELISA for this screen.

Laboratory-based oral fluid drug testing for DUID is still in very limited use, as only one laboratory in this survey reported validated oral fluid drug tests. Point of contact devices are increasingly being used in the field, however. A requirement to confirm Carboxy-THC in oral fluid was removed as concentrations are typically in the picogram per milliliter range and below the detection capabilities of most laboratories. Target cutoff concentrations for opioids in oral fluid were reduced

Table III. Recommended compounds for Tier II

Recommended compounds for Tier II	
DRE category; cannabis	DRE category; CNS depressants (contd.)
Synthetic cannabinoids	Novel benzodiazepines
DRE category; CNS stimulants	Phenytoin
Cathinones	Pregabalin
Methylphenidate	Topiramate
Mitragynine	Tricyclic antidepressants
DRE category; CNS depressants	Valproic acid
Atypical antipsychotics	Zopiclone
Barbiturates	DRE category; narcotic analgesics
Carbamazepine	Fentanyl analogs
Chlordiazepoxide	Novel opioids
Chlorpheniramine	Tapentadol
Cyclobenzaprine	DRE category; dissociative drugs
Diphenhydramine	Dextromethorphan
Doxylamine	Ketamine
Gabapentin	PCP
Gamma-hydroxybutyrate (GHB)	DRE category; inhalants
Hydroxyzine	Inhalant class
Lamotrigine	DRE category; hallucinogens
Mirtazapine	Hallucinogens

typically by half to improve likelihood of detection. Buprenorphine and its metabolite norbuprenorphine, and fentanyl were all added with screening cutoffs of 1 ng/mL, and confirmation cutoffs of 0.5 ng/mL. Tramadol and its metabolite O-desmethyltramadol were added with recommended screening and confirmation cutoffs for tramadol of 50 and 10 ng/mL respectively in oral fluid (7). The authors recommend that more data be collected concerning drug concentrations in oral fluid of impaired drivers to allow further review of the proposed cutoffs in the future.

Since the goal of these recommendations is standardization of practices in an effort to improve the quality of aggregated data from DUID testing laboratories and to detect concentrations of drugs in the range typically encountered in DUID investigations, laboratories are generally encouraged to establish cutoffs at the concentrations indicated in Table II. However, if existing validations or local conditions dictate, the authors concurred that laboratories meeting or exceeding the targets identified in Table II would be considered in compliance with the recommendations. This will be clarified in future surveys.

The drugs and drug classes represented in these revised scopes can be detected using commonly available immunoassay kits, with ELISA being the recommended format for blood. The panel should include ELISA assays for cannabis, methamphetamine, amphetamine, cocaine/metabolite, benzodiazepines, carisoprodol, zolpidem, opiates, oxycodone, fentanyl, buprenorphine, tramadol and methadone. Care should be taken with the benzodiazepine ELISA, since these assays frequently have low rates of cross-reactivity with potent short-acting benzodiazepines lorazepam and clonazepam. Customized calibrators with lower cutoffs should be evaluated by laboratories using ELISA kits whose manufacturers use diazepam or oxazepam as a calibrator.

Table III shows the revised recommended list of compounds for Tier II. Fentanyl, buprenorphine, and tramadol were promoted to Tier I. Meperidine and propoxyphene were removed from Tier II due to their discontinued availability in the USA. Modafinil, citalopram, clonidine, desipramine, doxepin, fluoxetine, olanzapine, paroxetine, phenazepam, quetiapine, risperidone, sertraline, trazodone, triazolam, venlafaxine, zaleplon, LSD and psilocybin were removed from Tier II due to lack of prevalence. Fentanyl analogs (e.g., acetylfentanyl, butyrylfentanyl, furanylfentanyl, etc), mitragynine, novel opioids (e.g., MT-45 and U-47700), atypical antipsychotics, novel benzodiazepines (e.g., clonazolam, flubromazolam, etc.) were added to Tier II. The individual tricyclic antidepressants desipramine, imipramine, amitriptyline and nortriptyline were consolidated into the class of tricyclic antidepressants. The general class of synthetic cannabinoids is still included for Tier II, however, as this class of drugs changes very rapidly, the specifically targeted compounds should be determined based on local prevalence.

Conclusions

Efforts to promote standardization of the scope of analysis and cutoffs for drug testing in suspected impaired driving and motor vehicle fatality cases have shown progress in terms of the increased numbers of laboratories either now meeting the recommended cutoffs and scope, or working to implement the 2013 recommendations. The benefits of having greater standardization between laboratories in terms of scope and sensitivity, include greater likelihood of detection of drugs in impaired drivers, better support for the International Association of Chiefs of Police Drug Recognition Expert (DRE) program that targets many of these drugs, and higher quality consolidated data for epidemiological and public health studies. The biggest challenges and obstacles the laboratories face with implementation of the recommendations are limited staffing, instrument resources, analytical sensitivity and time.

The NSC-ADID intends to repeat the survey and update the recommendations in 2020, and the recommendations are being considered as the basis for development of a standard under the National Institute of Standards and Technology (NIST) Organization of Scientific Area Committees (OSAC) in forensic science.

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