UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

SUBSTÂNCIAS PSICOATIVAS NO TRÂNSITO: ESTUDO SOBRE FATORES DE RISCO E TECNOLOGIAS DE DETECÇÃO *IN LOCO*

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Orientador: Prof. Dr. Flavio Pechansky

Co-orientadora: Profa. Dra. Renata Pereira Limberger

Porto Alegre

Abril de 2017

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“Para todo problema complexo, existe uma solução simples, clara – e errada.”

Henry L. Mencken (1880-1956)

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RESUMO

O impacto do uso do álcool na condução de veículos automotores foi primeiramente evidenciado concomitantemente ao surgimento dos primeiros automóveis. Desde então, diversos estudos foram realizados a fim de identificar a relação entre o uso de álcool e a capacidade psicomotora de motoristas. Atualmente, já está bem estabelecido que dirigir veículos sob o efeito de álcool aumenta o risco de colisões no trânsito. Por outro lado, dados sobre o impacto de outras substâncias psicoativas (SPAs) além do álcool ainda são escassos na literatura, mesmo com o crescente relato de motoristas envolvidos em colisões no trânsito que testaram positivo para SPAs. No Brasil, poucos estudos foram realizados visando à detecção de SPAs no trânsito - porém, mesmo com poucos dados, já foi possível observar uma alta prevalência de uso de SPAs pelos condutores. Além disso, estudos internacionais apontam que condutores que dirigem sob o efeito de álcool e de outras SPAs possuem características específicas, como por exemplo, alto índice de recidiva e alta prevalência de transtornos pelo uso de substâncias. Apesar de o Brasil possuir legislação que proíba motoristas de dirigir sob o efeito de álcool e também outras SPAs, contamos apenas com o uso de etilômetros para a mensuração do uso de álcool como medida efetiva na testagem de motoristas em barreiras de fiscalização, sem nenhum dispositivo aprovado para SPAs. Assim, o objetivo desta tese foi investigar fatores de risco para colisões no trânsito envolvendo o uso de SPAs e avaliar dispositivos de detecção de SPAs que possam ser implementados na fiscalização de condutores brasileiros. O artigo 1 da presente tese é uma análise de dados secundários provenientes de um estudo multicêntrico que avaliou 765 usuários de crack, e teve como objetivo estimar a prevalência de dirigir sob o efeito de SPAs e de colisões

no trânsito na amostra, analisando se questões psiquiátricas e padrão de uso de SPAs estão relacionadas ao histórico de acidentalidade. O artigo 2 compreende uma revisão sistemática da literatura sobre a confiabilidade de dispositivos de triagem para a detecção de SPAs utilizando urina ou fluido oral como matrizes biológicas. O artigo 3 é uma avaliação de dois dispositivos de triagem para a detecção de cocaínicos, utilizando amostras de fluido oral doadas por usuários de cocaína ou crack recrutados em centros de atendimento para transtorno pelo uso de substâncias na cidade de Porto Alegre. Como resultados principais, encontrou-se uma alta prevalência de usuários de crack que relataram ter dirigido sob o efeito de SPAs e também uma alta prevalência do relato de colisões no trânsito após o uso de crack. Além disso, o uso de crack por mais de cinco anos - independente de comorbidades psiquiátricas ou consumo de outras SPAs - foi o único fator associado à maior prevalência de histórico de acidentalidade (RR=1.52, 95%IC: 1.02-2.75). De forma geral, os dispositivos de triagem avaliados pela revisão sistemática mostraram uma alta variabilidade nos dados de confiabilidade (sensibilidade, especificidade e acurácia), tanto para dispositivos de urina quanto para dispositivos de fluido oral. Especificamente, o dispositivo DDS2™ atingiu resultados superiores ao recomendado para os critérios de confiabilidade (>80%) para a análise de benzoilecgonina no ponto de corte de 10 ng/mL. Já o dispositivo *Multi-Drugs Multi-Line – Twist Screen Test Device*™ não atingiu esses parâmetros de forma concomitante para nenhuma das análises realizadas. Os resultados do presente trabalho sugerem que a população de usuários de crack é uma população de risco para colisões no trânsito. Além do uso prolongado de crack (que foi estatisticamente associado ao desfecho de histórico de acidentalidade), outros fatores, como o uso de múltiplas substâncias, prejuízo cognitivo e altos índices de impulsividade também podem estar indiretamente associados ao aumento do risco de colisões no trânsito nessa população. Devido à alta variabilidade dos

resultados de confiabilidade dos dispositivos de triagem encontrados na literatura, e devido ao fato de que o uso desses dispositivos frequentemente implica em questões legais e morais dos sujeitos testados, aconselha-se que os dispositivos sejam avaliados quanto as suas capacidades analíticas e características práticas antes de serem implementados em qualquer contexto. Especificamente para a detecção de cocaínicos, o dispositivo DDS2™ apresentou melhores resultados quando comparado ao dispositivo MDML™. Entretanto, principalmente devido à alta prevalência de resultados falsos positivos, ressalta-se a importância da realização de testes confirmatórios sempre que a realização de testes de triagem tiverem finalidades forenses, como no caso do uso para fiscalização de trânsito.

Palavras-chave: trânsito; substâncias psicoativas; populações de risco; dispositivos de triagem; detecção de drogas.

ABSTRACT

The impact of alcohol use in driving abilities was initially described concomitantly to the development of the automobile. Since then, several studies were conducted aiming at the identification of the relationship between alcohol use and driving impairment. Currently, it is well established that driving under the influence of alcohol increases the risks of traffic crashes. However, data regarding the impact of psychoactive substances (PAS) other than alcohol are still missing in the literature, even with the increased report of drivers who have tested positive in traffic crashes. In Brazil, few studies were conducted aiming at the detection of PAS in traffic settings; however, even with little data, it is possible to describe a high prevalence of PAS use among drivers. Moreover, international studies suggest that drivers who drive under the influence of alcohol or other PAS present specific characteristics, such as high rates of recidivism and high prevalence of substance-use related disorders. Although Brazil has legislation that prohibits drivers to drive under the influence of alcohol and other PAS, we can only rely on the use of breathalyzers for the measurement of alcohol at the roadside. Therefore, the aim of the present thesis was to investigate risk factors for traffic crashes involving PAS use, and to evaluate point-of-collection testing devices for detection of PAS that could be implemented in the context of Brazilian traffic enforcement. The first paper is a secondary data analysis derived from a multicenter study which evaluated 765 crack-cocaine users; its main goal was to estimate the prevalence of driving under the influence of PAS and traffic crashes, and to ascertain psychiatric comorbidities and polydrug use related to the history of crashes. The second paper is a systematic review of the literature about the reliability of point-of-collection testing

devices for detecting PAS in urine and oral fluid. The third paper is an analytical evaluation of two point-of-collection testing devices for cocaine detection, using samples of oral fluid obtained from cocaine or crack-cocaine users recruited in substance abuse treatment centers in the city of Porto Alegre. We found a high prevalence of crack-cocaine users that reported driving under the influence of PAS, and a high prevalence of reported involvement in traffic crashes after crack-cocaine use. Besides that, crack-cocaine consumption for more than five years – independently of psychiatric comorbidities and other PAS use - was the single factor associated with higher prevalence of crash history (RR=1.52, 95%IC: 1.02-2.75). Overall, the point-of-collection testing devices evaluated in the systematic review showed high variability in the reliability results (sensitivity, specificity and accuracy), even for urine as for oral fluid analysis. Specifically, the DDS2™ mobile test system achieved results superior to that recommended for reliability measures (>80%) for the analysis of benzoylecgonine with the cutoff of 10 ng/mL. The Multi-Drugs Multi-Line – Twist Screen Test Device™ did not achieve these parameters in a concomitant way in any of the analysis performed. The results of the present study suggest that crack-cocaine users are a risky population for traffic crashes. Besides the longer use of crack-cocaine (which was statisticaly associated with the traffic crash outcome), other factors - such as use of several PAS, cognitive impairment and high levels of impulsivity could be indirectly associated with increased risk for traffic crashes among this population. Due to the high variability in the reliability measures of the point-of-collection testing devices found in the literature, and also due to the fact that the use of these devices frequently implies legal and moral aspects of the subjects being tested, it is recommended that these devices be evaluated for its analytical and practical capacities before they are implemented in any context. Specifically for cocaine detection, the DDS2™ mobile test system showed better results in comparison with the

MDML™ device. However, primarily because of the high prevalence of false positive results, we highlight the need for confirmatory analysis in all cases where the screening tests would have forensic purposes, such as in the traffic enforcement context.

Keywords: traffic; psychoactive substances; risky populations; point-of-collection testing devices; drug detection.

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LISTA DE ABREVEATURAS E SÍMBOLOS

BZE – Benzoilecgonina

COC – Cocaína inalterada

CONTRAN - Conselho Nacional de Trânsito

CT – Colisões no trânsito

DRUID – Projeto *Driving under the Influence of Drugs, Alcohol and Medicines*

FCR – Fatores comportamentais de risco

FI – Fator de impacto

FO – Fluido oral

FP – Falso-positivo

MDMA – Metilenodioximetanfetamina

MDML^{TM} - *Multi-Drugs Multi-Line – Twist Screen Test Device*^{TM}

MS – Ministério da Saúde

OMS - Organização Mundial da Saúde

PIB – Produto interno bruto

ROSITA - *Roadside Testing Assessment*

SPAs – Substâncias Psicoativas

TUSP – Transtornos relacionados ao uso de substâncias psicoativas

SUMÁRIO

1 INTRODUÇÃO

1.1 Trânsito e seu impacto social

A mobilidade urbana está diretamente relacionada a determinantes sociais e de saúde em uma população [1,2]. Assim como outros países em desenvolvimento, o Brasil tem observado um aumento constante em sua taxa de motorização nos últimos quinze anos, com uma frota atual de 56,8 milhões de automóveis [3]. Nesse sentido, a crescente motorização tem impactado em diversas esferas que vão além da própria mobilidade urbana, como por exemplo problemas relacionados à obesidade, saúde mental, qualidade de vida, poluição do ar e inclusão social, entre outros [1,4,5]. Além destes, os diversos prejuízos decorrentes de colisões no trânsito (CT) também são consequências importantes relacionadas à expansão da motorização nos grandes centros urbanos.

Segundo a Organização Mundial da Saúde (OMS), as lesões provocadas no trânsito constituem um dos maiores desafios da atualidade, e são, muitas vezes, negligenciadas no âmbito das políticas de saúde pública [6,7]. Diversas evidências apontam que as CT são responsáveis por enormes repercussões econômicas, sociais e psicológicas, exigindo esforços concentrados em busca de ações preventivas e de fiscalização eficazes [7,8]. Segundo dados internacionais, as CT ocasionam um total de 1,25 milhões de mortes por ano, sendo a principal causa de mortalidade de indivíduos entre 19 e 25 anos e a nona principal causa de mortalidade entre todas as faixas etárias [6,7]. Além disso, mais de 60% das CT estão concentradas em apenas dez países (em ordem decrescente por número absoluto de mortes): Índia, China, Estados Unidos, Rússia, Brasil, Irã, México, Indonésia, África do Sul e Egito; países que, juntos, englobam 56% da população

mundial. Levando em consideração as condições socioeconômicas dos países, observa-se que 90% das CT ocorrem em regiões de baixa e média renda, que totalizam 54% da frota de veículos e 82% da população mundial. Ainda, as taxas de mortalidade por CT são mais altas em países de baixa renda (24,1 por 100.000 habitantes) do que países com renda média (18,4 por 100.000 habitantes) e renda alta (9,2 por 100.000 habitantes) [7]. De uma forma geral, o "fardo" desproporcional que os motoristas de risco geram a estas nações – em especial aos motoristas que não apresentam risco - tanto do ponto de vista econômico, como social, legal e de saúde, justifica sobremaneira a atenção dada a esta questão.

Além do alto índice de mortalidade, cerca de 20 a 50 milhões de pessoas sobrevivem a CT com traumatismos, gerando também altos índices de morbidade [7]. Fora isso, diversos estudos apontam para uma alta prevalência de transtornos mentais, como depressão, ansiedade e transtorno de estresse pós-traumático, entre indivíduos que sofreram CT [9–11]. O impacto econômico das CT também é de extrema relevância, já que estudos sugerem que os custos mundiais decorrentes dessas colisões são superiores a 518 milhões de dólares por ano. Em países de baixa e média renda, estima-se que os custos econômicos derivados deste tipo de acidente sejam superiores a 5% do produto interno bruto (PIB) [7].

Segundo o Departamento de Informática do Sistema Único de Saúde (Datasus), do Ministério da Saúde (MS), os acidentes de transporte terrestre no Brasil são responsáveis por aproximadamente 43 mil mortes por ano, representando uma das principais causas de mortalidade no país. Apenas no ano de 2014, ocorreram mais de 170 mil CT em rodovias federais, acarretando um custo de 12,3 bilhões de reais. Nessa esfera, 64,7% dos custos estão associados às vítimas das colisões, como cuidados com a saúde e perda de produção devido às lesões ou morte, e 34,7% associados aos veículos, como danos materiais e perda de cargas [8,12].

Além disso, enquanto alguns países como a Austrália, os Estados Unidos e a Noruega evidenciam uma diminuição do número de vítimas de CT, dados apontam que as estatísticas brasileiras aumentaram nos últimos anos, passando de 18 mortes por 100 mil habitantes em 2000 para 22,2 mortes por 100 mil habitantes no ano de 2014 [13]. Assim, o Brasil apresenta taxas de mortalidade muito maiores que a média das Américas (15,9 por 100 mil habitantes), estando próximo ao registrado nos países africanos, considerados os mais letais no trânsito, com uma média de 26,6 vítimas para cada 100 mil habitantes.

1.2 Fatores e comportamentos de risco para CT

Uma enorme magnitude de fatores contribui para a incidência de CT, o que implica na ampla complexidade dessa problemática. No final da década de 60, o pesquisador William Haddon Jr. desenvolveu uma matriz teórica visando à criação de um modelo dinâmico que guiasse o processo de intervenções para reduzir as CT e/ou lesões decorrentes das mesmas (**Tabela 1**). Ele definiu três fases temporais que envolvem as CT: período pré-acidente, acidente e período pós-acidente [14]. O resultado dessa matriz é utilizado até hoje dentro das práticas de segurança no trânsito.

Tabela 1 Matriz Haddon para prevenção de acidentes e lesões de trânsito.

	FATORES		
FASE	**Humano**	**Veículo**	**Ambiente**
Pré-acidente (evitar acidente)	- Informação; - Atitudes; - Uso de SPAs; - Fiscalização.	- Condições do veículo (freio, eixo, velocidade, faróis).	- Condições da via; - Condições do tempo; - Sinalização; - Políticas de segurança.

Acidente (evitar/diminuir lesões durante o acidente)	- Uso de cinto de segurança, capacete, e outros equipamentos de segurança; - Uso de SPAs; - Atitudes.	- Dispositivos de segurança; - Design do veículo.	- Objetos de proteção a CT na via.
Pós-acidente (manutenção da vida)	- Primeiros socorros; - Acesso a médicos; - Idade, condições de saúde.	- Facilidade de acesso; - Risco de fogo.	- Facilidade de resgate; - Qualidade do atendimento médico.

Fonte: adaptado de Haddon Jr, 1968 [14].

Dentre esses fatores, a OMS, em 2016, destacou seis importantes elementos de caráter comportamental dos usuários das vias que devem ser amplamente abordados e fiscalizados a fim de reduzir a incidência de CT e lesões decorrentes no mundo: velocidade de tráfego; uso de capacetes por motociclistas; dirigir sob o efeito de álcool e outras SPAs; uso de cinto de segurança; uso de acento especial para crianças; e fatores de distração durante a condução de veículos (ex: uso de celular, fones de ouvido) [7]. De acordo com a literatura, os fatores comportamentais de risco (FCR) são responsáveis por cerca de 90% das CT [15–18]. Logo, diversos FCR - como o excesso de velocidade e uso de SPAs, são amplamente investigados e abordados dentro das políticas públicas por se tratarem de causas preveníveis e por constituírem fatores importantes no aumento de risco e/ou gravidade de colisões, lesões e morte no trânsito [19–22].

1.3 Uso de SPAs por condutores

O uso de álcool e outras SPAs por condutores e demais usuários das vias tem sido considerado um dos principais FCR, com estudos evidenciando que cerca de 10 a 44% dos motoristas envolvidos em CT estão sob o efeito de alguma SPA [23]. Nesse sentido, dirigir sob a influência do álcool é um risco conhecido e investigado desde o surgimento dos primeiros

automóveis [24,25]. Por outro lado, o impacto do uso de outras SPAs além do álcool por motoristas e demais usuários das vias começou a ser investigado a partir dos anos 60, e, por isso, muitas informações ainda não estão bem consolidadas. Entretanto, cabe salientar que o reconhecimento dessa problemática em níveis mundiais tem gerado o aumento do interesse de pesquisadores, profissionais da saúde e gestores públicos, fazendo com que mais estudos estejam sendo realizados dentro dessa temática.

Informações sobre a prevalência de uso de SPAs além do álcool por motoristas ainda são muito inconsistentes, principalmente devido ao fato de que muitos países não realizam essa testagem de forma sistemática. De maneira geral, levantamentos apontam que cerca de 1 a 15% dos motoristas dirijam sob o efeito de SPAs [26]. Na Europa, um estudo multicêntrico revelou que aproximadamente 7,5% dos motoristas parados em barreiras de fiscalização testaram positivo para álcool e/ou outras SPAs, com grande diferenças quanto às substâncias detectadas e suas prevalências entre os países participantes do estudo [27]. Nesse sentido, diversos autores apontam que o padrão do uso de SPAs por condutores reflete o padrão do uso de SPAs na população geral de cada região [13,28]. Nos Estados Unidos, dados oriundos do último Levantamento Nacional de Segurança no Trânsito, realizado entre os anos de 2013 e 2014, mostraram que 22,5% dos motoristas abordados nas rodovias durante os finais de semana testaram positivo para pelo menos uma SPA, com um aumento significativo da prevalência de motoristas positivos para substâncias ilícitas entre os anos de 2007 e 2013-2014 (12,4% e 15,1%, respectivamente) [29]. Já na Austrália, dados apontam que cerca de 2,3 a 3,8% dos motoristas abordados em barreiras de fiscalização testam positivo para SPAs, entre os quais as classes de substâncias mais frequentemente encontradas são o ecstasy e os canabinóides [30–33].

No Brasil, apesar das altas taxas de CT, poucos estudos foram realizados visando à investigação do uso de SPAs por condutores, com um foco maior sendo dado para motoristas profissionais [34–37]. Entre motoristas de caminhão, o uso de substâncias estimulantes é frequente, com estudos relatando uma prevalência de compostos anfetamínicos (CAs) na urina de motoristas parados em rodovias variando de 3 a 10% [38–40]. Nesse sentido, o uso de estimulantes por motoristas profissionais parece estar associado ao percorrimento de longas distâncias [41] e trabalho noturno ou em turnos irregulares [37]. Levando em consideração a população geral de motoristas brasileiros, estudos nacionais realizados pelo nosso grupo revelaram que cerca de 5,6 a 8,3% dos condutores abordados em pesquisas realizadas nas rodovias que cruzam as capitais federais testaram positivo para álcool e/ou outras SPAs [42,43]. Dentre as SPAs testadas, encontrou-se uma maior prevalência de estimulantes (3,4%), benzodiazepínicos (1%) e canabinóides (0,5%) [43]. Estudos apontam que essas prevalências são geralmente superiores em períodos noturnos, finais de semana ou em regiões perto de bares e casas noturnas, com um estudo revelando que cerca de 11% dos motoristas abordados na saída de pontos de venda de álcool na cidade de Porto Alegre testaram positivo para pelo menos uma SPAs na análise de fluido oral (FO) [44,45] .

Além dos dados obtidos com motoristas abordados de forma randômica em barreiras de fiscalização, diversos estudos realizam a investigação do uso de SPAs em indivíduos envolvidos em CT [46]. Nesse contexto, dados mundiais revelam que cerca 5-25% dos motoristas envolvidos em CTs possuem amostras de sangue positivas para alguma SPA além do álcool [28]. No Brasil, um estudo realizado na cidade de Vitória evidenciou que 44,8% das vítimas fatais envolvidas em CT - incluindo motoristas, passageiros e pedestres, obtiveram resultados positivos para álcool e outras SPAs. Dentre as SPAs, a cocaína foi a substância mais detectada, onde 12% dos indivíduos apresentaram resultados positivos [47]. Resultados similares foram encontrados em uma

amostra de motociclistas envolvidos em CT na cidade de São Paulo onde, dos 232 sujeitos avaliados, 15,5% testaram positivo para SPAs, sendo cocaínicos e canabinóides as classes de SPAs mais prevalentes [48]. Em Porto Alegre, um estudo realizado nas emergências da cidade revelou que cerca de 13% dos motoristas atendidos devido a CT obtiveram resultados positivos para canabinóides e 8,4% para cocaínicos. Esse mesmo estudo também revelou que motoristas com problemas relacionados ao uso de SPAs tinham 5,2 vezes mais chances de se envolver em CT relacionadas ao uso de SPAs do que motoristas sem problemas [49].

O reconhecimento e a investigação das populações de risco para CT também se tornou um fator importante dentro do desenvolvimento de políticas públicas de prevenção. Nesse sentido, estudos que investigaram motoristas que dirigem sob o efeito de SPAs evidenciaram que estes possuem características bastante específicas, como por exemplo alto índice de recidiva [50–52] e alta prevalência de transtornos psiquiátricos, principalmente os relacionados ao uso de substâncias psicoativas (TUSP) [42,53–57]. Ainda, evidências sugerem que populações de usuários de SPAs possuem maior envolvimento em CT do que a população em geral [58,59]. Um estudo realizado com sujeitos com TUSP em Londres revelou que mais de 80% deles dirigiu sob o efeito de SPAs e mais de 40% se envolveu em CT no ano anterior ao estudo [60]. Outro estudo, avaliando indivíduos usuários de heroína, revelou que cerca de 32% dos sujeitos reportaram ter se envolvido em CT quando sob o efeito de SPAs na vida [61]. Da mesma forma, estudos com usuários de cocaína também demostraram altas prevalências de histórico de CT [62,63]. Entre as principais causas levantadas para essa alta prevalência dentro dessas populações está o fato de que indivíduos com TUSP possuem uma menor percepção de risco quanto ao uso de drogas e consequente prejuízo psicomotor, são mais impulsivos e possuem prejuízos na tomada de decisão [28,64–66]. Por outro lado, alguns estudos apontam que existe uma redução na ocorrência CT

entre os usuários de SPAs após a realização de tratamento para o uso SPAs [62,67], sugerindo que os riscos para envolvimento em CT possam ser reduzidos nessa população após certas intervenções.

1.3.1 Impacto psicomotor do uso de SPAs no trânsito

Cada classe de SPAs afeta o desempenho na direção de veículos de forma distinta. A maioria dos efeitos pode ser dividida em efeitos agudos e efeitos crônicos. Os efeitos agudos estão relacionados com o uso único de uma substância, enquanto que os efeitos crônicos estão relacionados com o uso de uma substância por um longo período de tempo [23]. A maioria dos efeitos das SPAs vai variar de acordo com o tipo de substância, via de administração, dose administrada e variações individuais dos sujeitos, como questões de tolerância e vulnerabilidades [46].

Uma ampla variedade de SPAs possui potencial de alterar a capacidade psicomotora e, consequentemente, interferir na habilidade de conduzir automóveis. Entre elas, incluem-se:

- Substâncias ilícitas (ex: cocaínicos, canabinóides);
- Medicações prescritas (ex: benzodiazepínicos, opióides);
- *Club drugs* e *designer drugs* (drogas sintéticas).

De maneira geral, os principais efeitos observados após o consumo de SPAs envolvem o estado de alerta (ex: sedação, estimulação); visão (ex: visão turva, visão sensível ao brilho); performance (ex: alteração da coordenação e habilidades motoras); condições psico-sociais (ex: mudanças de comportamento; tomada de decisão prejudicada; aumento de comportamentos de

risco) e cognição (ex: mudanças no processamento de informações) [24]. O impacto individual de cada SPA está sendo amplamente investigado na literatura através de diferentes delineamentos metodológicos que incluem, por exemplo, estudos epidemiológicos [68–70], estudos de administração controlada [71–74] e estudos com simuladores de trânsito [75–78]. Entretanto, os resultados ainda são bastante divergentes, principalmente no que se refere a substâncias estimulantes, onde alguns estudos relatam uma melhora na performance após o consumo enquanto outros relatam uma piora [26,28,79,80]. A **Tabela 2** apresenta de forma resumida o impacto psicomotor das principais SPAs encontradas em condutores que poderiam influenciar a capacidade de direção de automóveis.

Tabela 2 Impacto do uso de substâncias psicoativas no funcionamento cerebral e funções psicomotoras que podem influenciar a habilidade de condução de um automóvel.

		Prejuízos psicomotores						
Tipo de substância	**Classe da substância**	**Sonolência**	**Funções cognitivas**	**Funções motoras**	**Humor**	**Controle lateral do veículo**	**Tempo de reação**	**Equilíbrio**
SPAs ilícitas	Canabinóides	✓	✓	✓	✓	✓	✓	✓
	Cocaínicos	-	✓	✓	✓	-	-	-
	Anfetamínicos	-	✓	✓	✓	-	✓	✓
	MDMA[a]	-	✓	-	✓	-	-	✓
	Alucinógenos	-	✓	✓	✓	-	✓	✓
Medicações Prescritas	Benzodiazepínicos	✓	✓	✓	-	✓	-	✓
	Opióides	✓	✓	✓	✓	✓	-	✓
Novas SPAs/ *designer drugs*	Canabinóides sintéticos	✓	✓	✓	✓	✓	✓	✓
	Cationas sintéticas	-	✓	✓	✓	-	-	-

✓ O consumo da substância tem como consequência esse prejuízo psicomotor;

– O consumo da substância não implica (ou não se tem informações) nesse prejuízo psicomotor;

[a] metilenodioximetanfetamina. **Fonte:** adaptado de OMS, 2016 [81]

Recentemente, Elvik realizou uma meta-análise de estudos epidemiológicos a fim de estimar o risco de envolvimento em CT associados ao uso de SPAs [21], e os principais resultados desse estudo estão apresentados resumidamente na **Tabela 3**. De forma geral, ele observou que dentre onze substâncias avaliadas, todas possuem certa associação com o risco de CT. Entretanto, observa-se que o risco final, mesmo quando significativo, é geralmente inferior a 100%. Além disso, devido ao desenho dos estudos incluídos, não se pode atribuir o efeito de causalidade do uso de SPAs em relação às colisões.

Além do efeito observado pelo uso de uma única SPA, alguns estudos passaram a investigar também o efeito da combinação de diferentes substâncias e seu impacto nas habilidades psicomotoras relacionadas à capacidade de direção [76,82]. Isso se deve principalmente ao fato da grande prevalência de motoristas abordados em rodovias ou então envolvidos em CT que tiveram amostras positivas para mais de uma substância, seja álcool e outras SPAs, seja uma combinação de diferentes SPAs [47,83–85]. De acordo com evidências recentes, o risco de se envolver ou de ser gravemente ferido em uma CT é maior quando existe a combinação de múltiplas substâncias do que quando existe o consumo de uma substância apenas. Entretanto, o risco de colisões e de lesões em motoristas sob o efeito álcool segue até o momento sendo maior do que sob o efeito de qualquer SPA utilizada separadamente [69,86–88].

Tabela 3 Sumário das estimativas de risco de colisões de trânsito associadas com o uso de substâncias psicoativas

Substância	**Severidade da colisão**	**Melhor estimativa de risco ajustada para viés de publicação**	**Intervalo de confiança (95%)**
Compostos Anfetamínicos	Fatal	**5,17**	**2,56 - 10,42**
	Lesão	**6,19**	**3,46 - 11,06**
	Dano material	**8,67**	**3,23 - 23,32**
Analgésicos	Lesão	1,02	0,89 - 1,16
Antiasmáticos	Lesão	**1,31**	**1,07 - 1,59**
Antidepressivos	Lesão	**1,35**	**1,11 - 1,65**

Anti-histamínicos	Dano material	1,28	0,90 - 1,80
Benzodiazepínicos	Lesão	**1,12**	**1,02 - 1,22**
	Fatal	**2,30**	**1,59 - 3,32**
Canabinóides	Lesão	**1,17**	**1,08 - 1,28**
	Dano material	**1,35**	**1,04 - 1,76**
	Fatal	1,26	0,88 - 1,81
	Lesão	1,10	0,88 - 1,39
Cocaínicos	Dano material	**1,26**	**1,10 - 1,44**
	Fatal	**2,96**	**1,18 - 7,38**
	Lesão	1,66	0,91 - 3,02
Opióides	Dano material	1,44	0,93 - 2,23
	Fatal	**1,68**	**1,01 - 2,81**
	Lesão	**1,91**	**1,48 - 2,45**
Penicilina	Dano material	**4,76**	**2,10 - 10,80**
	Lesão	1,12	0,91 - 1,39
Zopiclona	Fatal	2,60	0,89 - 7,56
	Lesão	1,42	0,87 - 2,31
	Dano material	**4,00**	**1,31 - 2,21**

Fonte: adaptado de Elvik, 2013 [21]

1.3.2 Uso de cocaínicos e seu impacto no trânsito

A cocaína é uma substância psicoestimulante consumida e abusada por aproximadamente 17 milhões de pessoas no mundo todo [89]. No Brasil, estima-se que aproximadamente 2,6 milhões de pessoas (o que representa quase 2% da população) façam uso regular de cocaínicos [90]. Desta forma, a grande prevalência do consumo dessa substância na população geral, principalmente nos países sul-americanos, repercutiu na grande prevalência do uso da mesma por motoristas e demais usuários das vias. Entretanto, mesmo com o aumento do número de casos de CT com motoristas positivos para cocaínicos [46,47], poucos estudos investigaram os efeitos da associação do uso de cocaínicos com a condução de veículos.

Estudos com administração controlada de cocaínicos sugerem que a administração destes em pequenas doses (50 – 300 mg) não causa prejuízo na capacidade de direção, podendo

inclusive ocasionar o aumento da atenção e diminuir o tempo de resposta a estímulos [91,92]. Entretanto, esses resultados devem ser interpretados com cautela, uma vez que a maioria dos estudos de administração é realizado com usuários crônicos - que já possuem certo grau de tolerância para os efeitos da substância, e com doses bem menores do que as normalmente utilizadas. Um estudo que investigou a associação do uso de cocaínicos com o envolvimento em CT, por outro lado, evidenciou que motoristas com uso recente de cocaínicos se envolveram 12,2 (IC95% 7,2 – 20,6) vezes mais em CT do que aqueles que não fizerem uso de nenhuma outra SPA [93]. Da mesma forma, considerando a fatalidade das CT, Elvik encontrou que motoristas positivos para cocaínicos tiverem 2,96 vezes mais chances de se envolver em colisões com vítimas fatais [21].

Até presente momento, acredita-se que o principal risco do uso de cocaínicos associado a direção seja o fato dos motoristas se tornarem mais imprudentes devido a sensação subjetiva de poder e pelo efeito rebote gerado após a diminuição das concentrações da substância no organismo, que está relacionado a uma diminuição dos funções cerebrais [26,94]. Além disso, alguns estudos também apontam que o uso de estimulantes estão relacionados ao descumprimento das leis de trânsito (ex: não respeitar o semáforo e dirigir em velocidades acima do permirtido) e maior falta de atenção [95]. Além disso, o uso crônico de cocaínicos está associado a dificuldades de processamento de tarefas cognitivas que requerem atenção, percepção espacial, memória, flexibilidade cognitiva, controle de velocidade, capacidade de abstração e funcionamento executivo, além de um aumento significativo de comportamentos impulsivos [79,96–99]. Stoduto e colaboradores, estudando uma amostra de motoristas no Canadá, observaram que a prevalência de CT foi igual a 18,9% entre os indivíduos que reportaram o uso frequente de cocaínicos no último ano, comparado a apenas 7,4% entre indivíduos que não

reportaram o uso de cocaínicos. Da mesma forma, um estudo realizado na Espanha mostrou que o uso semanal de cocaína estava associado a um maior histórico de envolvimento em CT (OR 2,8; IC95% 1,1 – 7,1).

Embora o nível do prejuízo psicomotor e as consequências relativas do uso de cocaínicos por motoristas ainda não estejam bem definidos, acredita-se que, de maneira geral, o risco de CT esteja aumentado após o consumo dessa classe de substâncias [46]. Entretanto, muito avanço ainda deve ser feito a fim de se elucidar o impacto psicofarmacológico do uso dos cocaínicos na capacidade de condução de veículos, bem como para conhecer as diferenças entre as diferentes formas de apresentação dessa classe de substâncias (cocaína em pó, crack, merla, oxi) e os efeitos combinados do uso de cocaínicos com outras classes de substâncias.

1.4 Detecção de substâncias psicoativas através de matrizes biológicas

Diversas matrizes biológicas podem ser utilizadas dentro do campo da toxicologia forense com a finalidade de detecção de SPAs - tais como o sangue, o suor, a urina, o FO, o humor vítreo, mecônio, unha e cabelo, dentre outras [100–103]. O sangue é considerado a matriz de preferência para detecção de SPAs para fins médico-forenses, principalmente devido ao fato de que a detecção da presença de uma determinada SPA no sangue é a evidência mais direta do uso desta pelo indivíduo, e também pelo fato de que a análise no sangue permite uma melhor inferência quanto aos efeitos farmacológicos das SPAs [101,104]. Entretanto, de forma geral, a escolha da matriz biológica é feita principalmente de acordo com a finalidade do teste (ex: investigação do histórico do uso, investigação de consumo recente) e a viabilidade da coleta [101].

Devido à grande praticidade de coleta, matrizes alternativas como a urina e o FO são geralmente elegidas como matrizes de escolha quando se trata de testes de triagem para detecção *in loco* [101,105]. Logo, devido à grande utilização dessas duas matrizes na fiscalização de trânsito [101,106,107], as vantagens e desvantagens da detecção de SPAs em ambas serão discutidas a seguir.

1.4.1 Urina

A urina é a matriz biológica mais utilizada para a detecção de SPAs, principalmente devido ao fato de que ela pode ser facilmente obtida em grandes volumes através de métodos de coleta não invasivos e também porque a maioria das SPAs é eliminada através desse biofluido [100,108]. Entretanto, uma das principais desvantagens da utilização da urina é que a coleta requer banheiro no local da testagem. Além disso, por ser facilmente adulterada, é recomendado que a coleta de urina seja sempre assistida por um profissional, o que pode resultar em constrangimento tanto para o sujeito quanto para o coletador [100,104,109]. No caso da fiscalização de trânsito, entretanto, alguns autores sugerem que não existe a necessidade de coleta assistida, uma vez que os condutores abordados de forma randômica não estariam preparados para realizar o tamponamento ou a adulteração da amostra [109].

No geral, SPAs e seus metabólitos possuem uma janela de detecção média (de 1 a 3 dias) na urina, que pode variar bastante dependendo da substância utilizada, da via de administração, do metabolismo do sujeito, da frequência do uso e da técnica de detecção aplicada [104,110]. SPAs administradas de forma fumada ou injetada são excretadas através da urina quase imediatamente após a administração. Em casos de uso frequente ou crônico, o acúmulo de metabólitos no

organismo pode fazer com que a substância possa ser detectada por um maior período de tempo, com estudos relatando casos de detecção semanas após a administração de canabinóides e cocaínicos em populações de usuários crônicos [111–113]. Para a maioria das SPAs, a urina vai conter maiores concentrações da droga inalterada durante as primeiras seis horas após o consumo; depois desse período, existe uma maior concentração de metabólitos [100,104].

É importante ressaltar que devido a essa janela de detecção intermediária, a detecção de SPAs na urina não reflete necessariamente na alteração da capacidade psicomotora [109,114]. Logo, o uso da urina como matriz biológica na detecção de SPAs é mais recomendado quando o objetivo do teste é verificar o uso passado ou o monitoramento do uso de SPAs e medicamentos na prática clínica [115,116] do que na fiscalização de trânsito, cujo objetivo seria identificar motoristas dirigindo sob o efeito de SPAs [109].

1.4.2 Fluido oral

O FO é uma matriz biológica líquida e incolor, composta pela combinação de saliva, fluido crevicular gengival, transudato da mucosa oral, fragmentos celulares, bactérias e resíduos de alimentos. A saliva, por sua vez, é um fluido incolor e viscoso, formado pelas secreções de três pares de glândulas principais - as submandibulares, as parótidas e as sublinguais, além de outras glândulas menores, apresentando pH na faixa de 5,8 a 7,4. A saliva, e consequentemente o FO, possui baixo teor de proteína (0,3%), e o seu volume de produção pode variar muito ao longo do dia, sofrendo influências de diversos fatores, como por exemplo questões emocionais, fome, saúde geral e estimulação mecânica [117].

As glândulas salivares recebem alto aporte sanguíneo das artérias carótidas e uma fina camada de células epiteliais separa os ductos salivares da circulação sistêmica. Portanto, a barreira existente entre a saliva e o sangue é constituída apenas pela parede capilar, membrana basal e membrana das células epiteliais glandulares [118]. Desta forma, a passagem de substâncias do sangue para o FO pode acontecer através de mecanismos de difusão ou de utrafiltração; entretanto, a maioria das drogas de abuso utiliza o mecanismo de difusão devido às suas baixas massas moleculares (de 100 a 500 Dalton). Todavia, cabe salientar que o transporte através de difusão passiva só ocorre com moléculas não-ionizadas, lipossolúveis e não ligadas a proteínas plasmáticas, as quais conseguem atravessar livremente as membranas a favor de um gradiente de concentração [102,119]. Logo, a relação da concentração plasma:FO de drogas e metabólitos depende do pKa das matrizes, do nível de ligação proteica da substância e da lipossolubilidade da droga. Assim, substâncias básicas, como os opióides, os CA e os cocaínicos, acabam sofrendo ionização no FO devido ao pH mais ácido (~ 6,7) e ficando retidos na cavidade bucal [114]. De forma geral, devido à facilidade de transporte entre sangue e FO, a maioria das drogas pode ser detectada em FO rapidamente após a administração ou absorção pela corrente sanguínea.

Durante os últimos anos, o FO tem sido considerado como uma matriz alternativa para a detecção de substâncias psicoativas, principalmente na área forense. Entre as principais vantagens da utilização do FO para fins médico-legais está o fato de que essa matriz pode ser coletada *in loco*, de forma simples e não invasiva, dificultado as possibilidades de adulteração e o possível constrangimento por parte do profissional e do indivíduo doador [120]. Além disso, a utilização do FO como amostra biológica clínica apresenta um baixo risco ocupacional para os profissionais de saúde durante sua coleta e processamento. Por outro lado, essa matriz biológica também apresenta desvantagens, como contaminação oral em caso de certas formas de

administração (ex: oral, intranasal e fumada), pequeno volume de amostra e pequena concentração de SPAs e metabólitos, o que faz com que a sensibilidade analítica para a utilização dessa matriz na detecção de SPAs tenha que ser alta [102,121,122]. Além disso, a estabilidade dos analitos em amostras de FO pode ser afetada de diversas maneiras, incluindo a forma e o dispositivo de coleta e a temperatura e tempo de armazenamento – portanto, coletas em ambiente de fiscalização devem ser rigidamente controladas [123,124].

Assim como para outras matrizes biológicas, uma ampla variabilidade interindividual é observada entre a dose da droga administrada e as concentrações encontradas no FO. De maneira geral, a maioria das SPAs pode ser detectada de 5 a 48 horas após o consumo, em concentrações pequenas, na faixa dos nanogramas por mililitro [125]. Nesse sentido, outra vantagem da utilização do FO sobre a urina na fiscalização no trânsito é que se espera que a correlação positiva entre a presença da substância ou metabólito com os sinais de intoxicação seja melhor no FO do que na urina [102,122]. A **Tabela 4** sumariza as vantagens e desvantagens comparadas entre urina e FO como matrizes de escolha para detecção de SPA.

Tabela 4 Vantagens e desvantagens do uso de urina e fluido oral como matrizes de escolha para a detecção de substâncias psicoativas.

Urina	**Fluido Oral**
Coleta de grandes volumes (aproximadamente 50 mL);	Coleta em volume limitado (aproximadamente 1 mL); certas substâncias causam xerostomia;
Necessidade de coleta assistida, necessidade de banheiro para a realização da coleta;	Não interfere em questões de privacidade;
Potencial para adulteração/substituição significativo;	Baixo potencial para adulteração;
Detecção predominante de metabólitos;	Detecção predominante de drogas inalteradas;
Detecção informa uso no passado.	Detecção informa uso recente.

Fonte: adaptado de Drummer 2005 [126]

1.5 Uso de dispositivos de triagem para fiscalização no trânsito

O desenvolvimento e a aplicação de técnicas que permitam a detecção de SPAs nas vias através da análise de matrizes biológicas alternativas são elementos importantes na prevenção e fiscalização do uso de SPAs por condutores [101]. De maneira geral, a detecção de SPAs em fluidos biológicos para fins forenses envolve duas etapas: 1) testes de triagem e 2) testes confirmatórios [100]. Testes de triagem são geralmente realizados através de técnicas de imunoensaio que, dependendo do teste, possuem anticorpos designados para a detecção de uma droga específica, um metabólito ou uma classe de substâncias [105,116,127]. Esses ensaios podem ser divididos em dois tipos principais: testes *in loco* (também chamados de testes instantâneos ou testes rápidos) e testes laboratoriais [101,128].

Os testes de triagem instantâneos possuem diversas vantagens que facilitam a sua aplicação na fiscalização do trânsito, principalmente o fato deles fornecerem os resultados de forma rápida (aproximadamente dez minutos) e no próprio local de abordagem [103]. Atualmente, uma ampla variedade de dispositivos de trigem de SPAs através de fluidos biológicos está disponível no mercado internacional e, em menor número, no Brasil [103]. De forma geral, esses dispositivos são de fácil manipulação, podendo ser aplicados por profissionais treinados para a aplicação [103,126]. Apesar das grandes vantagens do uso desses dispositivos, principalmente no que se refere à praticidade do uso, algumas desvantagens, como as limitações analíticas, surgem como fatores limitantes do uso dessa tecnologia [103,126]. Nesse sentido, diversos estudos foram realizados a fim de investigar a confiabilidade de dispositivos de triagem de SPAs, observando-se uma a alta variabilidade nos resultados – seja entre estudos diferentes avaliando o mesmo dispositivo, seja entre dispositivos diferentes em um mesmo estudo [129–132].

Visando a avaliação da aplicabilidade destes dispositivos na fiscalização do trânsito, dois importantes estudos multicêntricos foram realizados: O Projeto ROSITA (*Roadside Testing Assessment*), que foi realizado em duas fases, e o Projeto DRUID (*Driving under the Influence of Drugs, Alcohol and Medicines*). O projeto ROSITA-1 ocorreu entre 1999 e 2000 em oito países europeus, e teve como principal objetivo a avaliação de dispositivos de detecção de SPAs em FO e em urina na prática de agentes de fiscalização de trânsito. A partir dessa primeira fase, houve a necessidade manifestada pelos agentes de trânsito de melhor investigar os dispositivos de FO, uma vez que essa matriz foi vista como a mais adequada para o contexto de fiscalização. Dessa forma, entre 2003 e 2005, o ROSITA-2 avaliou a utilização de nove dispositivos de triagem em FO na prática dos agentes de trânsito. Como resultados da segunda fase, viu-se que nenhum dos nove dispositivos testados apresentou confiabilidade suficiente[1] para ser aplicado no trânsito [131].

O aumento do levantamento de dados realizados ao longo dos anos 2000 por diferentes estudos, somado ao alto índice de mortalidade evidenciado nas rodovias europeias (cerca de 50 mil mortes no ano de 2000), fez com que a União Europeia tomasse uma série de medidas a fim de reduzir as CT em 50% até o ano de 2011. Nesse contexto, foi elaborado e executado o Projeto DRUID, que ocorreu entre os anos de 2006 e 2009 e contou com a colaboração de 18 países, reunindo os maiores especialistas da área de trânsito. Um dos principais objetivos desse projeto foi obter informações sobre o impacto das SPAs na segurança viária e produzir recomendações para os formuladores de políticas de segurança. Durante o estudo, oito dispositivos de FO foram testados, dentre os quais apenas três obtiveram avaliação geral final aceitável[2] [133].

[1] Os critérios estabelecidos pelo Projeto ROSITA são apresentar valores de sensibilidade e especificidade superiores a 90% e acurácia superior a 95%.

[2] Para o Projeto DRUID, consideraram-se aceitáveis para a utilização de detecção de SPAs os dispositivos que obtiveram valores de sensibilidade, especificidade e acurácia superiores a 80%.

Desde a divulgação dos resultados destes dois projetos, diversos fabricantes relataram mudanças nos dispositivos a fim de obter melhorias práticas e analíticas. Entretanto, estudos atuais seguem reportando limitações metodológicas referentes a esses instrumentos, como alto número de resultados falso-positivos (FP) e alta prevalência de reatividade cruzada entre diferentes substâncias [129,134–136]. Assim, a aplicação de técnicas confirmatórias, principalmente em amostras positivas, ainda é essencial dentro da toxicologia forense.

O primeiro país a implementar o uso de dispositivos de triagem para SPAs na fiscalização de trânsito foi a Austrália, especificamente o estado de Victória, em 2004 [107]. Atualmente, todos os estados australianos seguem uma legislação de tolerância zero[3] para matanfetaminas, MDMA e canabinóides (SPAs com o uso mais prevalente na população), sendo que algumas outras localidades também realizam a fiscalização para outras substâncias. A testagem dos motoristas é realizada de forma randômica - ou seja, a autoridade policial possui poder legal de parar motoristas de maneira aleatória, sem a necessidade de ter ocorrido infração de trânsito [13,31,137]. A fiscalização para SPAs ocorre basicamente em cinco etapas [81]:

1) Abordagem do veículo;
2) Testagem do FO, com o motorista dentro do veículo, utilizando dispositivos de triagem com leitura visual dos resultados. Se o resultado for positivo, realiza-se o passo 3; se negativo, o motorista é liberado;
3) Testagem se uma segunda amostra de FO, fora do veículo, e agora com o uso de um dispositivo com leitura automática. Se o resultado for positivo, realiza-se o passo 4; se negativo, o motorista é liberado;

[3] Na Austrália, cada um dos seis estados é responsável pelas políticas de segurança no trânsito, legislação e fiscalização dentro de suas jurisdições.

4) Coleta de uma terceira amostra de FO para a realização da análise confirmatória, feita em laboratório através de técnicas mais sensíveis e específicas;
5) Se o resultado da análise confirmatória for positivo, realiza-se a tomada das medidas legais necessárias, observando-se as peculiaridades do caso (ex: motorista recidivante).

A Noruega possui legislação sobre dirigir sob o efeito de SPAs desde 1959; todavia, apenas recentemente a polícia foi autorizada a realizar a testagem randômica de SPAs em condutores abordados nas rodovias. Assim como na Austrália, os agentes de fiscalização de trânsito tem a autorização legal de testar qualquer motorista na via, independente dele apresentar sinais de intoxicação [13]. Além da Austrália e da Noruega, outros países como a Alemanha, a Dinamarca e a Bélgica também já aprovaram o uso de dispositivos de triagem nas práticas de fiscalização de trânsito. Nos Estados Unidos, a maioria dos estados já implementou leis que consideram crime dirigir sob a influência de SPAs que não o álcool. Entretanto, a testagem para SPAs só é permitida após o reconhecimento de sinais e sintomas por profissionais treinados (*drug recongnition expert*) através de testes específicos [13].

Pode observar-se, portanto, que o enquadramento jurídico e administrativo quanto ao fato de dirigir sob o efeito de SPAs varia muito de acordo com as particularidades sociais, legais, econômicas e históricas de cada país. De forma geral, três tipos abordagens são encontradas: leis de tolerância zero, leis de prejuízo psicomotor e *per se laws* (**Tabela 5**). Atualmente, 159 países possuem leis nacionais proibindo em algum nível a combinação de SPAs e direção; entretanto, a maioria dos países não define quais as substâncias consideradas nem qual seria o limite de detecção implementado. Assim, as leis acabam sendo muito vagas para serem efetivas e acabam não sendo fiscalizadas e respeitadas [7,81].

No Brasil, a legislação vigente de trânsito considera crime o ato de dirigir sob influência de álcool (em qualquer concentração por litro de sangue) ou SPAs que causem dependência. Contudo, apesar da previsão legal, atualmente só é possível a avaliação *in loco* (isto é, nas barreiras de fiscalização) do teor estimado de etanol, através de etilômetros (ou bafômetros, como são popularmente conhecidos). Assim, não existe atualmente no Brasil nenhum instrumento ou dispositivo homologado pelo Conselho Nacional de Trânsito (CONTRAN) para a detecção de outras SPAs além do álcool para ser utilizado em abordagens de fiscalização.

Tabela 5 Principais tipos de legislações no que se refere a detecção de SPAs por condutores

Tipo de lei	Características	Exemplos de países
Tolerância zero	Proibido conduzir um veículo com qualquer quantidade de SPAs no corpo	Austrália Espanha
Dirigir sob o efeito	Proibido conduzir um veículo quando a habilidade de dirigir está prejudicada devido ao uso de alguma SPA	Brasil (?) Luxemburgo
Per se law	Proibido conduzir um veículo acima de quantidades específicas de SPAs, independente de estado alterado perceptível ou não	Reino Unido Noruega

Fonte: desenvolvido pela autora.

No que se refere ao controle e prevenção do uso de SPAs por condutores, políticas de fiscalização são comprovadamente efetivas para reduzir os índices de colisões e lesões no trânsito [138–141]. Nesse sentido, países com leis mais rigorosas e com um modelo de fiscalização de trânsito mais intenso parecem observar uma menor prevalência de CT e um efeito de dissuasão mais positivo entre a população [142]. Nesse sentido, o Brasil ainda precisa evoluir muito no que se refere a legislação e fiscalização de trânsito quanto ao uso de álcool e outras

SPAs por motoristas [143–145]. Dentre os poucos estudos realizados visando a avaliação da efetividade da maior restrição quanto aos níveis de álcool permitidos em motoristas ao longo da história do Brasil, por exemplo, viu-se que houve uma tendência na diminuição nos números de CT em certas localidades, principalmente onde a fiscalização é mais frequente [146–148]. Por outro lado, alguns estudos reportam que as mudanças na lei não refletiram na diminuição das mortes no trânsito [149] e que muitos motoristas, apesar de serem a favor de leis mais restritivas, não tiveram mudanças de comportamento quando a beber e dirigir [150]. Nesse sentido, autores apontam que diversos outros fatores, tais como fiscalização intensiva e randômica, coleta de dados e avaliação da efetividade dos programas e ações de forma sistemática e em nível nacional necessitam ser implementadas para que exista as mudanças e melhorias que vão além da simples proibição do uso de SPAs por condutores [145,151–153].

De forma geral, o Brasil está evidenciando um aumento do debate quanto ao uso de álcool e direção; entretanto, questões referentes ao uso de SPAs associadas ao trânsito continuam sendo abordadas em pequena escala [143,151]. Ainda, as políticas e legislações brasileiras não levam em consideração as evidências científicas dentro dessa temática, o que aumenta a distância entre as leis e a efetividade prática das mesmas [151,154]. Logo, o desenvolvimento do conhecimento quanto a realidade brasileira no que se refere ao uso de SPAs por condutores, bem como a aproximação da legislação às práticas científicas, é de extrema relevância social em vista de proporcionar condições mais efetivas na melhora da segurança no trânsito no país.

2 OBJETIVOS

2.1 Objetivo Geral

O objetivo geral da presente tese foi investigar fatores de risco para CT envolvendo o uso de SPAs e avaliar a confiabilidade de dispositivos de triagem para SPAs que possam ser implementados na fiscalização de condutores brasileiros.

2.2 Objetivos Específicos

- Estimar a prevalência de dirigir sob o efeito de SPAs em usuários de crack;
- Estimar a prevalência de histórico de envolvimento em CT em usuários de crack;
- Investigar se questões psiquiátricas e padrões de uso de SPAs estão relacionadas ao histórico de envolvimento em CT em usuários de crack;
- Avaliar a confiabilidade de dispositivos de testagem móvel disponíveis no mercado quanto a detecção de SPAs na urina;
- Avaliar a confiabilidade de dispositivos de testagem móvel disponíveis no mercado quanto a detecção de SPAs no FO;
- Avaliar a confiabilidade de dispositivos de triagem no que diz respeito a detecção de cocaínicos.

3 ARTIGOS

3.1 Artigo 1

Prevalence of driving under the influence of psychoactive substances and road traffic crashes among Brazilian crack-using drivers.

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Prevalence of driving under the influence of psychoactive substances and road traffic crashes among Brazilian crack-using drivers

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ABRSTRACT

Background: Substance use disorders are associated with the increased risk of driving under the influence (DUI), but little is known about crack-cocaine and its relationship with road traffic crashes (RTC). **Method**: A multicenter sample of 765 crack-cocaine users was recruited in six Brazilian capitals in order to estimate the prevalence of DUI and RTC involvement. Legal, psychiatric, and drug-use aspects related with traffic safety were evaluated using the Addiction Severity Index - 6th version (ASI-6) and the Mini International Neuropsychiatric Interview. **Results:** Seventy-six (28.3%) current drivers reported accident involvement following crack-cocaine use. Among drivers (n=269), 45.7% and 30.5% reported DUIs in the past 6 months and 30 days, respectively. Drivers reporting DUI's in the past month (n=82) had higher scores in the "psychiatric", "legal", and "family problems" subscales from the ASI-6, and lower scores in the "family social support" subscale in comparison to those without a history of DUIs (n=187). An overall high prevalence of psychiatric comorbidity and substance consumption was observed. Participants with 5+ years of crack-cocaine use were more likely to have been in a RTC (RR=1.52, 95%IC: 1.02-2.75), independently of marijuana use, binge drinking and psychiatric comorbidities. **Conclusion:** The high prevalence of RTC and DUI involvement among crack-using drivers supports the idea that they are at a high risk group regarding traffic safety. Years of crack consumption seem to be associated with RTC involvement. Also, the presence of psychiatric comorbidities, poly-drug use, and cognitive impairment usually associated with crack addiction could yield additional risk of accidents.

Keywords: Crack-cocaine; Road traffic crashes; Driving under the influence; Drug Abuse; Psychiatric comorbidities.

INTRODUCTION

According to the World Health Organization, more than 1.2 million people annually die on the road (World Health Organization, 2015). It is well established that the use of alcohol before driving increases the risk of road traffic crashes (RTC), and therefore, the effect of alcohol-related impairment in driving abilities is broadly discussed in literature (Compton and Berning, 2015; Hingson and Winter, 2003; Martin et al., 2013). On the other hand, data on the impact of psychoactive substances (PAS) other than alcohol in driving skills is still lacking, even with an increasing prevalence of drug-positive individuals involved in RTCs (Derakhshanfar et al., 2012; Pérez et al., 2009). Studies have shown that stimulant substance use impact driving performance and have been associated with reckless driving or reduced driving ability (MacDonald et al., 2008). Also, stimulant substance use has also being linked to fatal crashes related to failing to obey traffic laws, yielding at traffic signals, driving at faster speeds, and lack of attention (Romano and Voas, 2011).

Cocaine is one of the most widely consumed PASs, with approximately 17 million users worldwide (United Nations Office on Drugs and Crime, 2015), 2.6 million of which are located in Brazil (Laranjeira, 2014). The presence of cocaine in biological samples obtained from drivers has been commonly reported, with its prevalence varying according to region, population, and data collection procedure (Faller et al., 2012; Penning et al., 2010; Walsh et al., 2004). The Integrated Project DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) found a mean prevalence of 0.42 percent for cocaine positive drivers in Europe. However, when evaluating drivers under the suspicion of committing a DUI, other independent studies revealed higher rates of cocaine positive drivers, such as 1 percent in Denmark (Simonsen et al., 2012),

3.4% in Ireland (Fitzpatrick et al., 2006) and 3.5% in Spain (Gómez-Talegón and Alvarez, 2006). One study comparing PAS use in random motor vehicle drivers in Brazil and Norway found no differences in stimulant consumption between the countries, with a prevalence for cocaine of 0.5 and 0.2 percent, respectively (Gjerde et al., 2014).

The level of driving impairment caused by cocaine is still unclear (Kelly et al., 2004). Due to the psychostimulant effect of cocaine, drivers may initially experience increased alertness and feel less tired. However, the increased risk for RTC following cocaine consumption could happen because drivers may become reckless due to a subjective sensation of power, and may be subjected to a rebound effect that slows down brain functions (Penning et al., 2010). An extensive review on the epidemiology of drug driving described by Gjerde and colleagues concluded that there is an increased risk for motor vehicle crashes following cocaine use (Gjerde et al., 2015). Concern for the fatality rate of such crashes, a meta-analysis revealed an odds-ratio of 2.96 for fatal injuries following cocaine consumption (Elvik, 2013).

Adverse health outcomes such as mental disorders, road-traffic accidents, and violence seem to be increased in subjects with substance use disorders (SUDs), especially in alcohol, opioid, cocaine, and amphetamine users (Degenhardt and Hall, 2012). In this sense, previous studies have shown that individuals with SUDs are more involved in RTCs than the general population, and have an increased risk of driving under the influence of psychoactive substances (DUI) (Macdonald et al., 2003; Sloan et al., 2014; Stoduto et al., 2012). The reported prevalence of RTC involvement among individuals with SUDs ranged from 12.6 to 45.3 percent (Alvarez et al., 2010, 2007). However, the causal relationship between this association is uncertain due to the fact that some confounding variables, such as the presence of associated psychiatric comorbidities and poly-drug use, are not always controlled and the quantification of risk is poor

(Degenhardt and Hall, 2012). One study investigating a sample of cocaine users showed that cocaine users are significantly more likely to report collision involvement than non-users (Stoduto et al., 2012). Specifically, the most negative effects of cocaine on driving performance are more present among heavy and chronic users (Kelly et al., 2004).

Crack-cocaine (a smoked presentation of cocaine) is more harmful than powder cocaine, and its chronic use leads to severe neuropsychological and cognitive dysfunctions (Di Sclafani et al., 2002; Hoff et al., 1996; Narvaez et al., 2012). Although there aren't any studies that evaluate the relationship between RTCs (along with other traffic safety issues) and crack-cocaine abuse, previous studies have shown that crack-cocaine users have higher rates of occupational, family, and legal problems than users of other substances (Kessler et al., 2012). Moreover, chronic cocaine users show high levels of impulsivity, attentional bias, and worse executive performance and inhibitory control when compared to healthy controls (Madoz-Gúrpide et al., 2011; Potvin et al., 2014; Spronk et al., 2013). Therefore, we believe crack-cocaine users may be a risk population for DUIs and RTCs. In view of the lack of information regarding psychoactive substance use and driving among crack-cocaine users, we aimed at estimating the prevalence of DUIs and RTCs in a sample of Brazilian crack-cocaine users who were seeking treatment at public facilities. We also investigated whether psychiatric comorbidities and patterns of PAS use are associated with a history of RTC involvement.

METHODS

Study design and sampling

This is a secondary data analysis of a cross-sectional multicenter study in which we evaluated 768 crack-cocaine users from six Brazilian capitals: Porto Alegre (n=342), Salvador (n=60), São Paulo (n=65), Rio de Janeiro (n=108), Vitória (n=71) and Brasilia (n=119). Porto Alegre included two recruitment centers, which allowed a greater number of participants from there. Subjects were recruited from inpatient and outpatient treatment centers between April 2011 and November 2012. Inclusion criteria asked that participants be 18 years of age or older and sought treatment in inpatient or outpatient settings. The participants also had to meet the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th version, revised text criteria) criteria for cocaine dependence, as well as reported use and preference to crack-cocaine.

Data collection was obtained through interviews of users in the recruitment treatment centers. These interviews were conducted after a week of abstinence for users in inpatient centers and within the first week after users joined services for outpatients. Individuals who did not complete this initial evaluation, as well as those who had some emotional or physical impairment that could limit data collection, were excluded. Data collection involved six regional coordinators and 24 interviewers in different states. The interviewers were trained and supervised under the responsibility of the regional coordinators from the six research centers, with technical assistance and supervision of professionals from our Center (the main study site).

The recruitment of research volunteers proved to be extremely difficult and took a large amount of time because a) crack-cocaine users do not seek public outpatient treatment with frequency and b) they don't usually adhere to treatment. Also, Brazilian regulations regarding research prevented investigators from paying for the subjects' participation. Therefore, the compensation of basic food donations was given for the participants' time and effort.

Instruments and measures

In order to assess the level of substance use and the socio-demographic characteristics of the sample, we used the validated Brazilian Portuguese version of the Addiction Severity Index, 6th version (ASI-6) (Kessler et al., 2012). Psychiatric comorbidities were evaluated through the Mini International Neuropsychiatric Interview, also validated for Brazilian Portuguese (Amorim, 2000). In order to access the damage and impairment specifically caused by crack-cocaine use, a questionnaire developed by our group on the profile of crack-cocaine use was applied. The assessment of data regarding individual's driving profile and PAS consumption is shown in Table 1.

Table 1 Instruments and measures

Variable	Assessment question (question number)	Instrument
Driving Status	Do you use or have an automobile? (E7)	ASI-6
Driver License	Do you have a valid driver's license? (E6)	ASI-6
Driving Under the Influence	How many days in the past 6 months (L32A) and in the past 30 days (L32B) did you drive under the influence of alcohol or others drugs?	ASI-6
Arrested for Impaired Driving	During your lifetime, how many times have you been arrested for driving while under the intoxication of alcohol (L13A)? And in the past 6 months (L13B)?	ASI-6
Motor vehicle accident caused under the influence of Crack-Cocaine	Have you ever been involved in a car or motorcycle accident as a consequence of your crack-cocaine use? (25.1)	Crack-Cocaine use profile
Drug use in the last 30 days	Drug section	ASI-6
...Alcohol	How many days in the last 30 days did you drink an alcoholic beverage of any kind? (D13)	ASI-6
...Binge Drinking	How many days in the last 30 days did you drink more than 5 alcoholic drinks (men)/4 alcoholic drinks (women) in one day? (D13)	ASI-6
...Marijuana	How many days in the last 30 days did you smoke marijuana? (D13)	ASI-6
...Crack-Cocaine	How many days in the last 30 days did you use crack-cocaine? (D13)	ASI-6

Data analysis

Patients included in this study were divided into three groups: 1) non-drivers (n=496); 2) subjects who drive, but did not report driving under the influence in the last 30 days (n=187), and 3) subjects who reported driving under the influence at least one day in the previous 30 days (n=82). This data depended on self-reporting that regarded sober driving and driving under the influence of psychoactive substances in the past 30 days. Three individuals did not answer the DUI question, and were therefore excluded from the study, yielding a sample of 765 participants. Drug use in the last month was categorized into "no consumption" (people who did not consume the PAS in the last month) and "consumption" (people who used the PAS at least once in the last month). Categorical variables were compared using the Chi-Square test, followed by an adjusted residuals analysis for crossovers bigger than 2x2. ASI-6 subscale scores and other quantitative variables with normal distribution were compared using ANOVA, followed by the post-hoc Tukey test. A Poisson Regression model was adjusted in order to evaluate the variables associated with RTCs among drivers with and without history of RTC involvement.

RESULTS

Sociodemographic characteristics of the sample

The sociodemographic characteristics of the sample were very homogeneous within the recruitment places. Therefore, they were grouped together in one sample, independent of the recruitment site. The sample comprised mainly of young adults (mean age of 31 years), men (84.8%), Caucasians (40.5%), with less than 8 years of schooling (43.8%), and without any

income in the last month (45%). In regards to the profile of drivers, a smaller prevalence of women and a higher prevalence of individuals with more than five years of schooling and higher gross income among drivers was found (Table 2).

Driving status, legal aspects, road traffic crashes history and ASI-6 subscales

Seventy-six participants who drive (28.3%) and sixty-nine participants who do not drive (13.9%) reported accident involvement following crack-cocaine use. Among drivers, 45.7% and 30.5% reported DUIs in the past 6 months and 30 days, respectively. Among non-drivers and drivers, 13.5% and 58.7% had a valid driver's license, and 7.1% of the sample reported having been arrested for impaired driving. We also observed that 21.9% of the individuals without a DUI in the last month had reported a DUI in the last 6 months (Table 2).

Drug use pattern and ASI-6 subscales

When it came to drug consumption, we found a higher prevalence of use of drugs other than crack-cocaine. For example, nearly half of the sample admitted to binge drinking (42.6%) and/or use marijuana (43.3%) in the past month. In this instance, the group of individuals who drove under the influence in the past month had a positive association with marijuana use and binge drinking (Table 2). The comparison of the ASI-6 subscales between the three groups showed differences in the "psychiatric," "legal," "employment," and "family" categories. Overall, the DUI group presented higher scores in the "psychiatric," "legal," and "family

problem support" scales, and lower scores in the "family social support" domain. Furthermore, the individuals who drove had higher "employment" subscales scores in comparison with non-drivers.

Table 2 Sociodemographic data, legal aspects related to driving, drug consumption characteristics and ASI-6 subscales scores among crack-cocaine users who do not drive, drivers who did not drive under the influence, and drivers who drove under the influence.

Variables	Non drivers (n=496)	Individuals who did not drive under the influence (n=187)	Individuals who drove under the influence (n=82)	*p*
Age[1]	32.1±8.7	30.6±8.0	31.1±8.3	0.101
Gender[2]				**<0.001**
...Male	402 (81.0)$^{-}$	170 (90.9)$^{+}$	77 (93.9)$^{+}$	
...Female	92 (18.6)$^{+}$	17 (9.1)$^{-}$	114 (6.1)$^{-}$	
Race[2]				**0.001**
...Non-Caucasians	157 (31.7)$^{+}$	39 (20.9)$^{-}$	17 (20.7)	
...Caucasians	175 (35.3)$^{-}$	94 (50.3)$^{+}$	41 (50.0)	
...Mixed races and others	164 (33.1)	54 (28.9)	24 (29.3)	
Education[2]				**<0.001**
...8 years or less	249 (50.2)$^{+}$	65 (34.8)$^{-}$	22 (26.8)$^{-}$	
...More than 8 years	247 (49.8)$^{-}$	122 (65.2)$^{+}$	60 (73.2)$^{+}$	
Received some income[2]	246 (49.6)$^{-}$	117 (62.6)$^{+}$	58 (70.7)$^{+}$	**<0.001**
Income received (R$)[1]	930±1370[a]	1494±1565[b]	1582±1417[b]	**<0.001**
Valid driver license[2]	67 (13.5)$^{-}$	106 (56.7)$^{+}$	52 (63.4)$^{+}$	**<0.001**
DUI in the last 6 months	48 (9.7)$^{-}$	41 (21.9)	82 (100)$^{+}$	**<0.001**
Arrested for impaired driving[2]				
...Life	-	6 (3.2)	13 (15.9)	**<0.001**
..Last six months	-	2 (1.1)	5 (6.1)	-
Motor vehicle accident following crack-cocaine use[2]	69 (13.9)$^{-}$	50 (26.7)$^{+}$	26 (31.7)$^{+}$	**<0.001**
Drug use[2]				
...Alcohol	271 (54.6)	104 (55.6)	53 (64.6)	0.239
...Alcohol in binge	199 (40.1)	82 (43.9)	45 (54.9)$^{+}$	0.04
...Marijuana	210 (42.3)	73 (39.0)	48 (58.5)$^{+}$	0.009
ASI-6 subscales[1]				
...Drugs	72.42±9.76	72.61±9.69	71.67±9.86	0.761
...Family	53.45±8.8	53.44±8.4	54.12±8.94	0.804
...Alcohol	49.53±9.45	49.33±8.11	50.21±9.42	0.766
...Psychiatric	50.38±8.08[b]	48.09±8.96[a]	51.62±8.12[b]	**0.001**

...Medical	50.27±9.14	48.58±9	49.44±9.16	0.091
...Legal	50.06±6.44[a]	51.44±7.31[a]	55.06±8.73[b]	**<0.001**
...Employment	38.59±5.16[b]	35.51±7.37[a]	34.29±7.58[a]	**<0.001**
...Family Social Support	48.39±9.68[b]	46.53±9.6[b]	43.32±10.48[a]	**<0.001**
...Family Problem Support	54.17±9.38[b]	54.96±9.15[b]	59.89±8.14[a]	**<0.001**

[1] Mean±standart-deviation. ANOVA, different letters (a and b) represent significant difference between groups by the post-hoc Tukey test. [2] Absolute frequencies (%). Chi-Square test. Positive^{+} and negative^{-} association by adjusted residual > |2|.

Psychiatric characteristics, drug use pattern, and its association with road traffic crashes in crack-cocaine drivers

The prevalence of psychiatric comorbidities and the drug-use pattern of current crack-cocaine drivers with and without a history of RTCs (following crack-cocaine consumption) are shown in Figure 1. Among drivers, the most prevalent psychiatric comorbidities and conditions were suicide risk (56.5%), depression (43.1%), alcohol use disorder (39%), antisocial personality disorder (39%), and anxiety disorder (26.1%). Considering these psychiatric comorbidities and drug-use patterns, the only variable associated with RTC involvement in the bivariate analysis was the use of crack-cocaine of five years or more (p=0.014) (Figure 1). Furthermore, the multivariable Poisson regression shows that crack-cocaine users with crack consumption of more than five years (even when controlled for antisocial personality disorder, DUI, marijuana use and binge drinking) were more likely to be involved in an RTC (RR: 1.52 IC95%: 1.02 – 2.27) (Figure 2).

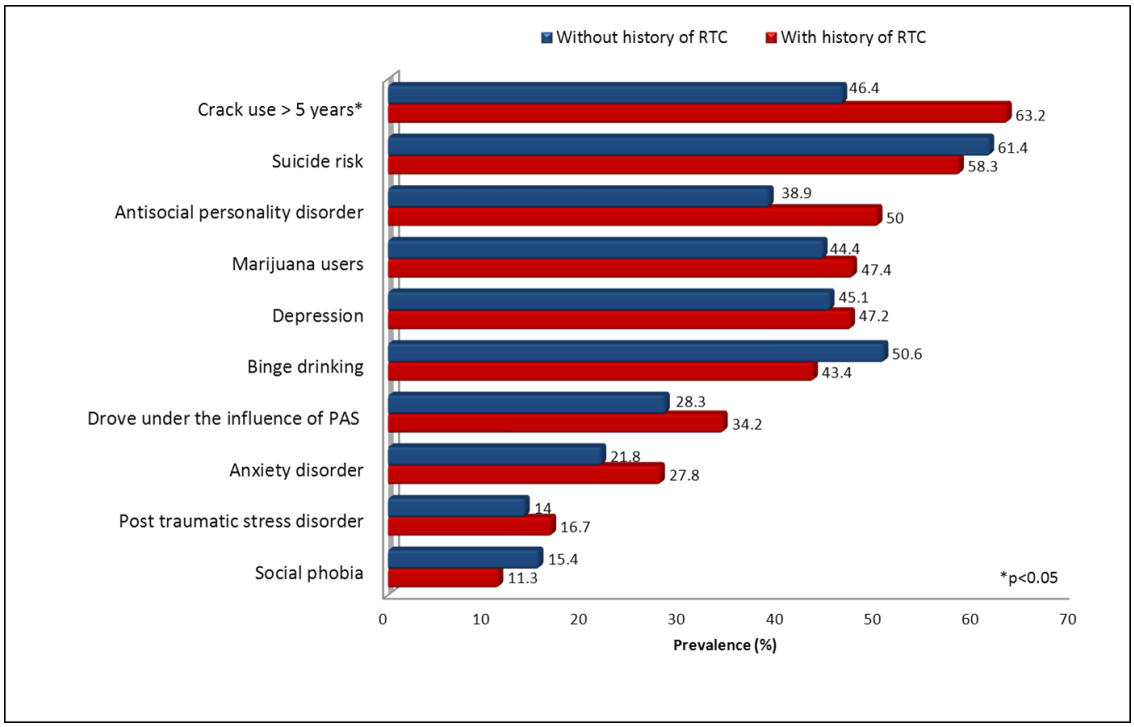

Figure 1 Prevalence of drug use and psychiatric comorbidities in crack-cocaine drivers with and without histories of road traffic crashes following crack-cocaine consumption.

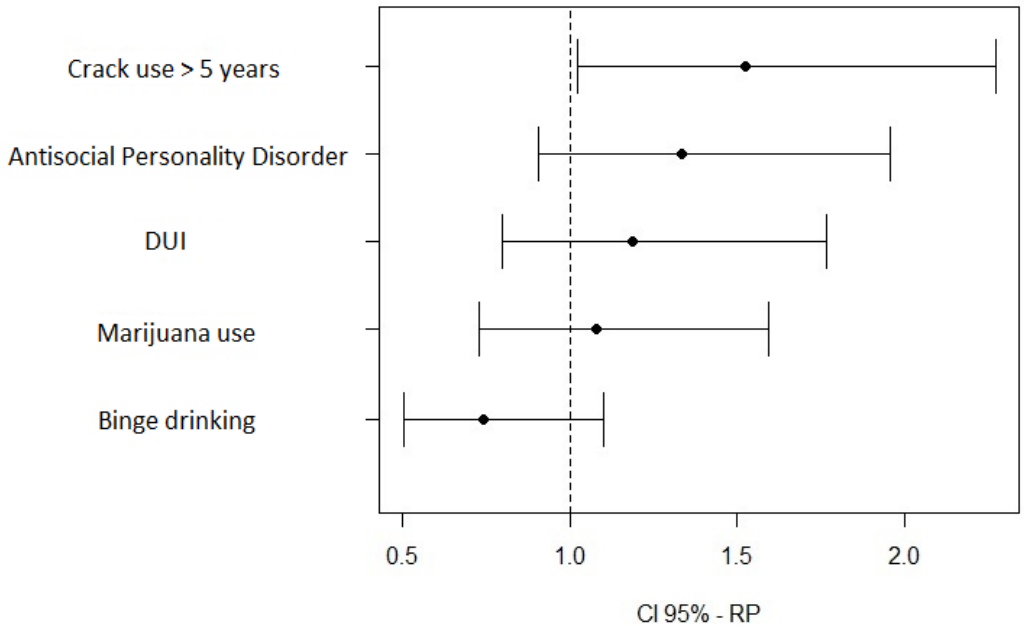

Figure 2 Association of drug use, antisocial personality disorder, and driving under the influence of psychoactive substances with road traffic crashes involvement.

DISCUSSION

To the best of our knowledge, this is the first study which analyzed road traffic crashes involvement, DUI prevalence and legal and psychiatric aspects in a sample of crack-cocaine users. In the present study, we found a high prevalence of individuals who reported impaired driving and an involvement in road traffic crashes following crack-cocaine consumption. Furthermore, we found that subjects reporting DUIs in the past month had more psychiatric, legal, and social problems in the ASI-6 when compared with subjects reporting no DUIs. Even with the high prevalence of consumption of other drugs and psychiatric comorbidities, years of crack-cocaine consumption was the only aspect associated with RTCs among current drivers.

The sociodemographic characteristics of our sample are in line with Brazilian national data. This data shows that crack-cocaine users are mostly young adult males with poor education levels and low income (Bastos and Bertoni, 2014). In our sample, drivers and non-drivers presented different income statuses and employment scores. Therefore, the low prevalence of drivers among our sample is probably due to the low socio-economic status evidenced within this population. Also, our results show a higher prevalence of women and non-Caucasians among non-drivers, which suggests a possible gender and sociodemographic disparity among driving status and motor vehicle assessment in Brazil. Due to this fact and the evidence shown in our results, we might suggest that traffic accident involvement in the Brazilian crack-cocaine population is minimized by the lack of car ownership among this group – if all crack-cocaine users had access to motor vehicles, we would probably see higher rates of RTC due to the severe dependence, comorbidities, and impairment observed among this population.

Prior studies have shown that drug users are involved in more traffic accidents than the general population. When evaluating a sample of drug-dependent patients under treatment, Alvarez et al. found an RTC prevalence of 11.3 percent in the previous year and 45.3 percent in lifetime, with 13.2 percent of the subjects reporting DUIs in previous year (Alvarez et al., 2010). High prevalence of traffic accidents and DUIs were also found in samples of injection drug users (Darke et al., 2004) and alcohol-, heroin-, methadone-, stimulant-, and cannabis-dependents (Albery et al., 2000; Macdonald et al., 2004). These studies also revealed a high prevalence of drug users who drove without a valid driver´s license, showing similar results to ours. Although risk perception was not investigated by the present study, a hypothesis of the large involvement of drug users in RTCs relies on the fact that this population usually perceive drugged driving to be less dangerous than the general population (Darke et al., 2004; Kelly et al., 2004; Matthews et al., 2014).

The high prevalence of psychiatric comorbidities found in crack-cocaine users could add a greater risk for RTCs in this population. One of the first studies evaluating oral fluid samples of drivers in Brazil reported that drivers who tested positive for drugs and/or alcohol had a higher prevalence of psychiatric disorders, including drug abuse/dependence, when compared to those with negative samples (Faller et al., 2012). In the same way, international studies also found a high prevalence of mental disorders among DUI offenders (Freeman et al., 2011; Karjalainen et al., 2013) and re-offenders (Lapham et al., 2006). This is partly similar to our data showing that crack-cocaine users reporting DUI showed higher scores in the psychiatric problem domain of the ASI-6. It is known that several psychiatric comorbidities, including attention deficit disorder (Aduen et al., 2015), dementia (Barco et al., 2015), schizophrenia (Segmiller et al., 2015), and bipolar disorder (Fletcher et al., 2013), can increase the occurrence of traffic offences and traffic

crashes. Furthermore, symptoms that are frequently associated with crack-cocaine addiction, such as depression, anxiety, insomnia, and social dysfunction, are also associated with poor driving behavior (Brand et al., 2015). In our sample, we found a high prevalence of these comorbidities (especially depression and suicide risk) among users with a history of RTCs, but such variables were not associated with having a greater risk for accident involvement in an independent way.

The fact that crack-cocaine users are usually multidrug users (Bastos and Bertoni, 2014; Narvaez et al., 2012) also raises concern regarding impaired driving. We found that our sample comprised of a great amount of polydrug users and that the DUI group had a higher prevalence of marijuana consumption and binge drinking. The combination of cocaine and alcohol generates cocaethylene, a potentially more toxic metabolite (Farooq et al., 2009). Cocaethylene can lead to an increased heart rate, blood pressure, and myocardial oxygen consumption (Farré et al., 1997). All of these symptoms have been associated with changes in attention, executive function, and verbal memory (Woicik et al., 2009). Moreover, the concomitant use of alcohol and crack is widely observed and results in the exacerbation of effects and enhancement of toxicity (Farooq et al., 2009). A recent study showed that the effects of alcohol and cocaine (whether consumed alone or simultaneously) significantly increased the risk of injury and aggressive incidents. However, the simultaneous use of alcohol and cocaine did not lead to significantly greater rates of injury than the use of either substance alone (Zhao et al., 2015). Many authors evaluated the influence of marijuana use in driving impairment (Desrosiers et al., 2015; Hartman and Huestis, 2013), but there is lack of evidence regarding the physiological and psychomotor impairment caused by the co-administration of marijuana and cocaine. One qualitative study of the use of cannabis among crack-cocaine users found that the combination of such substances reduced

crack's undesirable effects, improving sleep and appetite while reducing craving for crack-cocaine (Gonçalves and Nappo, 2015). Based on the fact that alcohol-drug and drug-drug combinations significantly increased the risk of RTCs and consecutive severe injuries (Hels et al., 2013; Li et al., 2013), the frequent concomitant use of crack-cocaine and other PASs is a particular cause of concern regarding accident prevention in crack-cocaine users.

The neurocognitive impairment caused by the chronic use of crack-cocaine could make it difficult to carry out complex tasks such as driving a vehicle. Currently, the consequences of neurocognitive effects triggered by cocaine use are still dubious; however, there seems to be a consensus on its effects in several specific mental functions such as attention, learning and memory, executive functions, and reaction time (Mittenberg and Motta, 1993; Vonmoos et al., 2014). In addition, executive dysfunctions (including the deterioration in problem solving skills, cognitive inflexibility and diminished inhibition) are being reported among substance-dependent samples (Barry and Petry, 2008; Verdejo-García et al., 2006), especially among crack-cocaine users (Narvaez et al., 2012). This may be due to dysfunctions caused by the chronic use of cocaine in the orbitofrontal cortex and in the anterior cingulate gyrus - areas related with mediation of attention and executive functions, respectively (Jovanovski et al., 2005). Also, changes in the frontal lobe can result in maladaptive behaviors, such as an increased need for immediate gratification, minimization, poor decision making, and denial of negative consequences (Bechara, 2005). These maladaptive behaviors could generate risky driving behaviors, even when the drug users are not intoxicated. Moreover, the association of crack-cocaine with other drugs, such as marijuana and alcohol, reinforces a reduced plasticity to respond to environmental eventualities and the persistence to adopt inadequate responses. There would also be a greater difficulty in searching for effective approaches to circumvent negative

consequences (Cunha et al., 2004; Di Sclafani et al., 2002; Narvaez et al., 2012). Given that such adaptive and critical thinking skills are involved in driving a vehicle, the use of other PAS by crack-cocaine users can further aggravate safety issues regarding impaired driving. In our study, crack-cocaine users who had used crack-cocaine for more than five years were more likely to have been in an RTC, independent of marijuana use, binge drinking and DUI, which is in accordance with previous studies (Stoduto et al., 2012). These results indicate that the use of crack-cocaine for long periods could be the principal factor related with RTCs in crack-cocaine users. These results are possibly due to a great cognitive impairment or a more severe addiction associated with individuals of longer crack-cocaine use.

Crack-cocaine users are also more likely to show personality features and attitudes that are related to risky driving than other drug users. Among personality characteristics, impulsivity and sensation-seeking have been widely reported in DUI offenders, who were also more likely to show antisocial attitudes in comparison to drivers without criminal records (Jornet-Gibert et al., 2013; Pawłowska and Rzeszutko, 2015). In the same fashion, higher levels of impulsivity and sensation-seeking characteristics have been found in drug abusers, including the samples of cocaine users (Mahoney et al., 2015). Furthermore, crack-cocaine users have a higher prevalence of antisocial personality disorder, even when compared to alcohol and other drug abusers (Kessler et al., 2012). We found no differences in traffic accident involvement among users with or without antisocial personality disorder (APD), although half of the individuals who reported RTC were diagnosed with APD. It is known that the chronic use of stimulants can exacerbate impulsive traits (Ersche et al., 2010). Therefore, evidence suggests that the development of substance abuse disorders would further amplify risk-taking tendencies (Ryb et al., 2005).

One of the limitations of this study was that the sample only comprised of users who were seeking treatment; this does not represent the general population of crack-cocaine users. Taking into consideration that our results are from a secondary analysis of a study whose main aim was different from the one we presented here, it is not possible to better evaluate neurocognitive aspects and personality features that could be associated with greater risk-taking dispositions in driving performance. Also, because of the self-reported methodology and potential memory bias, it is possible that our data is underestimated. Furthermore, we didn't compare our sample of crack-cocaine users with other groups. For example, we didn't study people who used different PSAs nor did we study sober/non-using groups. The comparison between the different groups would've been important to know, as it would've helped us understand the particularities between crack-cocaine users and safe driving behaviors. On the other hand, the strength of our study comes from the fact that we used a multicenter sample, which expands these results to more than one region of the country.

Finally, treatment interventions were associated with a decrease of the average number of collisions of alcohol and cocaine-dependent patients (Gómez-Talegón and Alvarez, 2006; Macdonald et al., 2004). This highlights the need for RTC prevention programs for drug users and suggests that psychoeducation and motivational interventions against DUI should be developed and addressed during the treatment of crack-cocaine users. Besides a Breathalyzer, there aren't any other objective modes of measurement to evaluate someone to see if they are driving while intoxicated in Brazil. This is an important fact that should be considered, as there are worries concerning the monitoring of DUI for drugs besides alcohol. These worries are expressed through a form that must be filled out by police as a way to register impaired psychomotor ability. In practice, this means that most of the conducted DUI arrests in Brazil are

due to alcohol intoxication, limiting data and evidence about the prevalence of drugged driving positive individuals. Therefore, we reinforce the need to include the use of mobile screening tests for PASs along with the use of Breathalyzers in Brazilian roadblocks. Also, the referral of drug and alcohol positive drivers to health recovery programs is of extreme relevance in order to evaluate the need of drug-specific treatment interventions, once it has been reported that many of the DUI offenders have a serious addiction and might not be responsive to traditional criminal deterrents administered alone (Sloan et al., 2014).

CONCLUSIONS

In conclusion, crack-cocaine users have low socioeconomic status, which probably limits motor vehicle assessment. However, from the moment that a crack-cocaine user has access to driving a motor vehicle, he/she will be likely involved in a road traffic accident due to the high prevalence of psychiatric comorbidities, severe development of drug dependence, loss of inhibitory control, and cognitive impairment caused by crack-cocaine consumption. As shown here, the high prevalence of RTC and DUI involvement among crack users who drive supports the idea that these populations are in the "high-risk" population that affects traffic safety. Moreover, years of crack consumption seem to be associated with RTC involvement, independently of marijuana consumption or binge drinking. A hypothesis for this is that individuals with longer crack-cocaine use developed a more severe dependence to crack-cocaine. This increased dependence causes greater cognitive impairment and therefore, allows for a higher risk of an RTC occurrence. Taking into consideration the scarce information about drug driving impairment and crack-cocaine consumption, these results could point out the importance

of establishing several associations between these two factors, resulting in the development of accident prevention strategies tailored towards crack-cocaine users.

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3.2 Artigo 2

Reliability of point-of-collection testing devices for drugs of abuse in urine and oral fluid: a systematic review.

Juliana Nichterwitz Scherer, Taís Regina Fiorentin, Bruna Tassi Borille, Graciela Pasa, Tanara Rosangela Vieira, Renata Pereira Limberger and Flavio Pechansky.

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A partir dos dados e resultados encontrados nesse estudo, os autores estão coletando informações adicionais para a tentativa de elaboração de uma meta-análise, que está como perspectiva futura do doutorado.

Reliability of point-of-collection testing devices for drugs of abuse in urine and oral fluid: a systematic review

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ABSTRACT

Point-of-collection testing (POCT) devices for drugs of abuse are used to screen for the presence of psychoactive substances (PAS) in different types of settings and environments. However, these quick and advantageous tools have disadvantages, including low reliability measures in comparison to chromatographic assays. We conducted a systematic review of the PubMed, EMBASE, SIGLE and PROQUEST databases focusing on the reliability of measurements of PAS found in urine and oral fluid using POCT devices. We observed high variability in reliability measures of oral fluid and urine POCT devices for the five most important drug classes (cocaine, amphetamine compounds, benzodiazepines, cannabinoids and opioids) tested. Therefore, we discuss the strengths and limitations of POCT techniques in order to guide physicians, policymakers and other professionals who also conduct such tests. The use of POCT devices often involves legal and moral aspects of the subjects tested, which demands critical evaluation of these devices before they are implemented in different settings.

Keywords: point-of-collection testing devices; psychoactive substances; drug screening; forensic toxicology; drug testing.

INTRODUCTION

According to the Drug World Report, substance abuse is a significant problem worldwide, with 1 out of 20 people between the ages of 15 and 64 years having used an illicit drug in 2014 [1]. The widespread use of psychoactive substances (PAS) leads to the need for drug testing in several settings and environments, such as emergency departments, drug treatment clinics, the workplace, and traffic enforcement [2-4]. Forensic toxicology is a science which encompasses a number of related disciplines aiming to assist in the detection and interpretation of drugs and poisons, including PAS, for medico-legal purposes [5]. The analytical techniques used for such purposes can be divided into two main categories: 1) screening methods and 2) confirmatory methods [5]. However, even with the rising development of new technologies, the search for accurate techniques for drug detection by forensic toxicologists is still a challenge [6-8].

Point-of-collection testing (POCT) devices are advantageous tools for drug screening, mainly because they present results quickly and *in loco*. Although blood is considered the golden standard matrix for toxicological analysis for legal matters, most POCT devices utilize urine or oral fluid as the matrix of choice, since these can be collected through less invasive procedures [5,9]. The main advantages and disadvantages of these alternative specimens were evaluated by several investigators and experts and are well described elsewhere [3.10,11]. There are several POCT devices commercially available, most of them promising to have similar sensitivity and specificity when compared with the golden standard methodologies used by forensic laboratories - usually chromatographic assays [9, 12].

Aiming at the analytical evaluation of POCT devices and their applicability in traffic enforcement, two important multicenter projects were conducted: the ROSITA (Roadside Testing Assessment) project [13], and the DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) Integrated Project [14]. The second phase of ROSITA (2003-2005) evaluated nine POCT devices, and concluded that no device was reliable enough in order to be recommended for roadside screening of drivers [15]. A few years later, the DRUID project (2006-2011) evaluated eight oral fluid screening devices, and concluded that just three of them presented measures higher than 80% for sensitivity, specificity, and accuracy in their overall evaluation [16]. Therefore, despite their high practicality, recent data still suggests that the reliability of such devices is still limited [17, 18].

It is important to consider that the use of POCT devices often involves legal and moral aspects of the subjects tested. The confident implementation of these devices in any setting is of utmost importance. Therefore, a critical evaluation of their reliability and functionality is needed. This brings us to the focus of this paper: to investigate the reported reliability of oral fluid and urine POCT devices in the detection of PAS. We considered their sensibilities, specificities and accuracy performance measures through a systematic review of the literature.

METHODS

A comprehensive systematic review was conducted in accordance to the PRISMA guidelines [19]. The online databases of PubMed (MEDLINE), EMBASE, SIGLE (System for Information on Grey Literature in Europe) and PROQUEST (Dissertations and Thesis International Database) were searched for eligible articles written in English. The search strategy

combined multiple sets of search terms such as “point-of-collection devices”, “psychoactive substances”, “drug screening”, and “drug detection”, among others. Two independent investigators (JNS and TRF) conducted this search from April 2015 to July 2015.

The following inclusion criteria were established: 1) original research papers published from the year 2000 onwards; 2) papers evaluating one or more point-of-collection drug screening devices using a validated chromatographic assay as the confirmatory method; 3) analysis of oral fluid or urine as the biological matrix for drug screening detection; 4) studies including at least one of the following classes of drugs of abuse: cocaine (COC), amphetamine compounds (AMP), benzodiazepines (BZD), cannabinoids (CNB) and opioids (OPI). Review papers or paper that did not identify reliability parameters (sensibility, specificity or accuracy) in their results were excluded from this study. The search did not find studies in SIGLE and PROQUEST databases. A study flowchart can be seen in **Figure 1**.

Our search strategy generated 123 articles, and the two independent reviewers (JNS and TRF) assessed the titles and abstracts of all the articles for relevance. This screening identified 87 potentially relevant articles. The full text of these articles was retrieved and accepted through the consensus of the participating parties, yielding a sample of 44 papers. Corresponding authors were contacted when full text articles were not available. Reference lists in the included articles were double-checked so as not to miss further relevant articles. The main part of each study was dual-extracted following a pre-specified protocol.

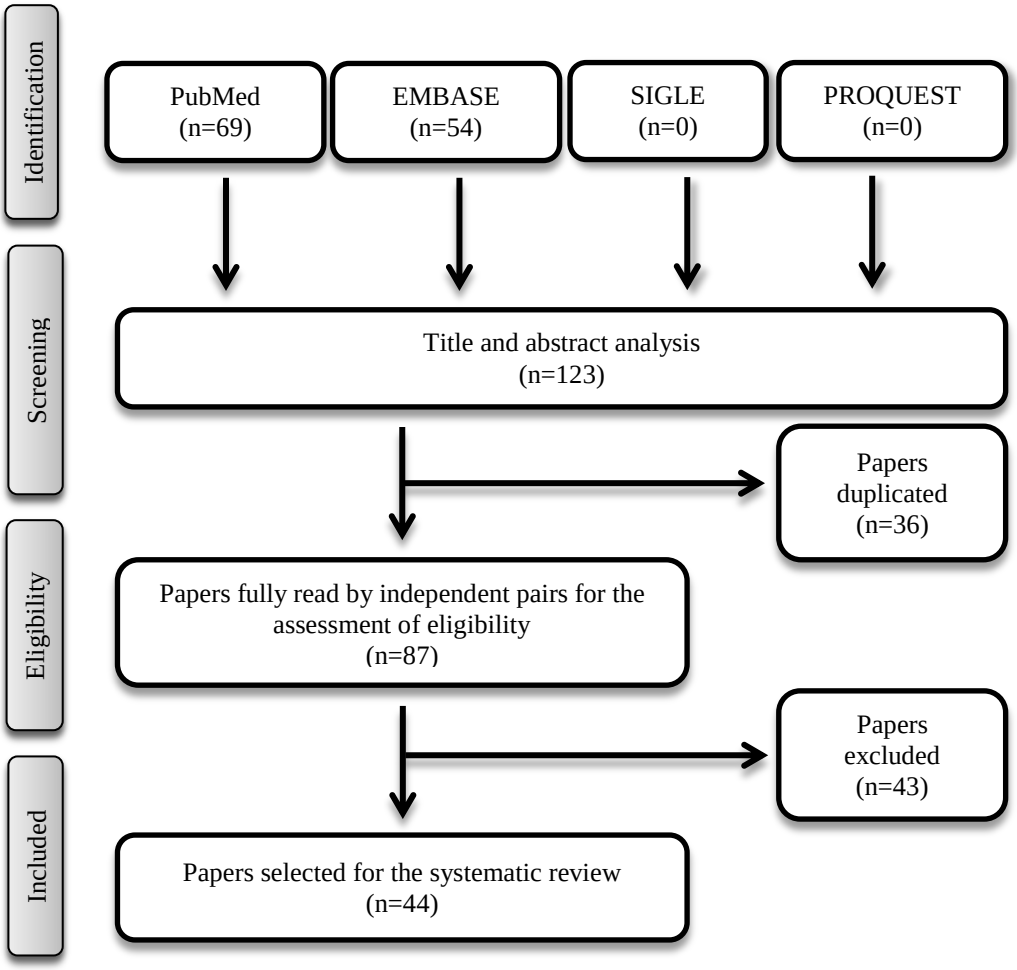

Figure 1 Flowchart of the search process

RESULTS

Description of the studies

The specifications of the 44 studies included in this review are summarized in **Table 1.** Of the 44 studies, 19 (43.2%) were conducted in traffic enforcement settings, 13 (29.5%) with

drug users, 9 (20.4%) in laboratories and 1 (2.3%) in hospitals. Two studies (2.6%) did not specify their sample selection, referring to them as “volunteers”.

Considering the matrix of choice, 13 (29.5%) studies evaluated urine screening devices only, 28 (63.6%) evaluated oral fluid devices only, and 3 (6.8%) evaluated devices with both matrices. A total of 27 urine POCT devices were evaluated by different studies, with the Triage™ (Biosite Diagnostics, USA; n=7) and the Syva Rapid Test™ (Dade Behring Inc., USA; n=5) being the most evaluated urine POCT devices. On the other hand, a total of 19 oral fluid POCT devices were evaluated, with the Drugwipe™ (Securetec, Germany; n=16) and the Draëger DrugTest™ (Draëger Safety AG & CO., Germany; n=13) being the most evaluated devices.

Considering the classes of drugs investigated, 40 (90.9%) studies analyzed CNB (14 in urine; 29 in oral fluid), 31 (70.4%) analyzed COC (14 in urine; 20 in oral fluid), 33 (75%) analyzed AMP (14 in urine; 22 in oral fluid), 16 (36.4%) analyzed BZD (11 in urine; 7 in oral fluid), and 32 (72.7%) analyzed OPI (16 in urine; 19 in oral fluid).

Table 1 Specifications of the studies included in the present review

Author, year	Study setting	PAS tested	Screening device	Biological matrix	Reference
Peace *et al*., 2000	Clinical	CNB, COC, AMP, BZD, OPI	Triage™	Urine	[30]
			QuickScreen Pro-Multi Drug Screening Tests™		
			Syva Rapid Test™		
			Rapid Drug Screen™		
Leino *et al*., 2001	Traffic enforcement, drivers	CNB, COC, AMP, BZD, OPI	Dip Drug Scan 6 test™	Urine	[31]
			OnTrak Testcup™		
			RapiTest Multidrug™		
			Status DS™		
			Surescreen Drug Multi-test™		
			Syva Rapid Test		
			Triage ™		
			Syva Rapid Cup ™		
Gronholm & Lisluunde, 2001	Traffic enforcement, drivers	CNB, COC, AMP, BDZ, OPI	Syva Rapid Cup™	Urine	[35]
			Syva Rapid Test™		
			Surescreen Drug Multi-test™		
			Triage™		
			Dip Drug Scan 6 test ™		
			RapiTest Multidrug™		
			Status DS™		
			OnTrak Testcup™		
			RapiScan™	Oral fluid	
			Drugwipe™		
Kadehjian, 2001	Laboratory	CNB, COC, AMP,	Syva Rapid Test ™	Urine	[29]

		OPI	Syva Rapid Cup™		
			Roche Testcup™		
			Triage™		
			Casco-Nerl microLINE™		
			Syva ETS analyzer™		
Barrett *et al*., 2001	Non specified	CNB, COC, AMP, OPI	ORALscreen™	Oral fluid	[42]
Crouch *et al*., 2002	Traffic enforcement, drivers	CNB, COC, AMP, OPI	AccuSign™	Urine	[43]
			Rapid Drug Screen™		
			OnTrak Testcup™		
			OnTrak Teststik™		
			Triage™		
Walsh *et al*., 2003	Laboratory	CNB, COC, AMP, OPI	OralLab™	Oral fluid	[44]
			RapiScan™		
			Drugwipe™		
			SalivaScreen ™		
Phillips *et al*., 2003	Laboratory	CNB, COC, AMP, BZD, OPI	Signify ER Drug Screen Test™	Urine	[45]
			Triage™		
Kacinko *et al*., 2004	Laboratory	OPI	RapiScan™	Oral fluid	[46]
Biermann *et al*., 2004	Traffic enforcement, drivers	CNB, COC, AMP, OPI, Metadna	Toxiquick™	Oral fluid	[47]
Crouch *et al*., 2005	Laboratory	CNB, COC, AMP, OPI	Oratect™	Oral fluid	[48]
			Uplink™		
			Drugwipe™		
Toennes *et al*., 2005	Traffic enforcement, drivers	CNB, COC, AMP, OPI	Draëger DrugTest™	Oral fluid	[49]
			Mahsan-Kombi/DOA4-test™	Urine	
Laloup *et al*., 2006	Traffic	CNB	Draëger DrugTest™	Oral fluid	[50]

	enforcement, drivers				
Moody *et al*., 2006	Clinical, drug users	CNB, COC, AMP, BDZ, OPI	Instant-View Test Cards™	Urine	[51]
			OnTrak TesTcup™		
Haller *et al*., 2006	Clinical, drug users	OPI	Monitect Oxycodone™	Urine	[52]
Walsh *et al*., 2007	Laboratory	CNB, COC, AMP, BZD, OPI	OralSTAT™	Oral fluid	[53]
			OralLab™		
			Oratect™		
			RapiScan™		
			SmartClip™		
			Impact™		
			Uplink™		
			Drugwipe™		
			OraLine™		
			SalivaScreen™		
Drummer *et al*., 2007	Traffic enforcement, drivers	CNB, AMP	Drugwipe™	Oral fluid	[54]
			RapiScan™		
Leino & Loo, 2007	Non specified	OPI	QuikPac II OneStep Buprenorphine cassette™	Urine	[55]
			QuikStrip OneStep Buprenorphine strip tests™		
Wilson *et al*., 2007	Clinical, drug users	AMP	RapiScan™	Oral fluid	[56]
Concheiro *et al*., 2007	Traffic enforcement, drivers	CNB, COC, AMP, BDZ, OPI	OralLab™	Oral fluid	[57]
			Draëger DrugTest™		
Crouch *et al*., 2008	Traffic enforcement, drivers	CNB, COC, AMP, OPI	OralSTAT™	Oral fluid	[15]
			OralLab™		
			Oratect™		

			RapiScan™		
			SmartClip™		
			Impact™		
			Uplink™		
			Drugwipe™		
			OraLine IV™		
			SalivaScreen™		
Kintz et al, 2009	Clinical, drug users	CNB	DDSV™	Oral fluid	[58]
Bagøien *et al*., 2009	Emergency rooms	CNB, COC, AMP, BDZ, OPI	AccuSign™	Urine	[59]
Röhrich *et al*., 2010	Traffic enforcement	CNB, AMP	RapidSTAT™	Oral fluid	[60]
Wille *et al.*, 2010	Traffic enforcement	CNB, COC, AMP	RapidSTAT™	Oral fluid	
			Drugwipe™		
			Draëger DrugTest™		
Pehrsson *et al*., 2011	Traffic enforcement	CNB, COC, AMP, BZD, OPI	Drugwipe™	Oral fluid	[36]
			RapidSTAT™		
Blencowe *et al*., 2011	Traffic enforcement	CNB, COC, AMP, BZD, OPI	BIOSENS Dynamic™	Oral fluid	[16]
			DDS 806™		
			Drugwipe ™		
			Draëger DrugTest™		
			OralLab™		
			OrAlert		
			Oratect™		
			RapidSTAT™		
Pehrsson *et al*., 2011	Traffic enforcement	CNB, COC, AMP, OPI	Drugwipe™	Oral fluid	[61]
Basilicata *et al*.,	Laboratory	CNB, COC, AMP,	DDS-UR™	Oral fluid	[62]

2011		OPI			
Greene *et al*., 2011	Laboratory	CNB, COC, AMP, BDZ, OPI	Integrated E-Z Split Key Cup II™	Urine	[63]
Stano-Rossi *et al*., 2012	Traffic enforcement	CNB, COC, AMP, OPI	DDS™	Oral fluid	[38]
			RapidSTAT™		
			Drugwipe™		
			Draëger DrugTest™		
Desrosiers *et al*., 2012	Clinical, drug users	CNB	Draëger DrugTest™	Oral fluid	[64]
Vanstechelman *et al*., 2012	Clinical, drug users	CNB, COC, AMP, OPI	Draëger DrugTest™	Oral fluid	[33]
			DDS™		
			RapidSTAT™		
			OrAlert™		
Attema-de Jonge *et al*., 2012	Clinical, drug users	CNB, COC, AMP, BDZ, OPI	TesTcard 9™	Urine	[32]
			Syva Rapid Test™		
			Triage™		
Bosker *et al*., 2012	Clinical, drug users	CNB	Draëger DrugTest™	Oral fluid	[65]
			Drugwipe™		
Lin *et al*., 2013	Laboratory	CNB, COC, AMP, BDZ, OPI	NexScreen™	Urine	[66]
			DrugCheck Waive RT™		
Moore *et al*., 2013	Traffic enforcement, drivers	CNB, COC, AMP, OPI	DDS2™	Oral fluid	[67]
Wille *et al.*, 2013	Clinical, drug users	CNB	Drugwipe™	Oral fluid	[68]
Arroyo *et al*., 2014	Traffic enforcement	CNB, COC	DDS 801™	Oral fluid	[69]
Beck *et al*., 2014	Clinical, drug users	CNB, COC, AMP, BDZ, OPI	Concateno multicomponent Dip and Read test device™	Urine	[70]
Desrosiers *et al*., 2014	Clinical, drug users	CNB	StatSure Saliva Sample™	Oral fluid	[71]
			Oral-Eze™		

			Draëger DrugTest™		
Logan *et al*., 2014	Traffic enforcement	CNB, COC, AMP, BZD, OPI	Draëger DrugTest™	Oral fluid	[72]
			Drugwipe™		
Molnar *et al*., 2014	Clinical, drug users	CNB	Drugwipe™	Oral fluid	[73]
			DDS™		
Musshoff *et al*., 2014	Traffic enforcement	CNB, COC, AMP, BZD, OPI	Draëger DrugTest™	Oral fluid	[37]
			RapidSTAT™		
			Drugwipe™		
			DrugScreen™	Urine	

Legend: CNB = cannabinoids; COC = cocaine; AMP = amphetamines; BDZ = benzodiazepines; OPI = opioids.

Reliability evaluation of POCT devices in urine and oral fluid

The overall variability of the reliability measures of urine POCT devices for COC, AMP, BZD, OPI and CNB detection is presented in **Table 2,** and the measures for oral fluid POCT devices are presented in **Table 3**.

Overall, urine POCT devices presented sensibilities ranging from 19% (AMP) to 100% (all classes of PAS), specificities ranging from 34% (OPI) to 100% (all classes of PAS), accuracy ranging from 50% (CNB) to 100% (OPI), positive predictive value (PPV) ranging from 41% (AMP) to 100% (COC, AMP, OPI and BZD), and negative predictive value (NPV) ranging from 34.3% (CNB) to 100% (COC, AMP, OPI and BZD). Of the five classes of PAS, the CNB group had a greater variability in accuracy measures among the different studies and devices (50 - 99.2%).

With regard to oral fluid POCT devices, sensibilities ranged from 10% (OPI) to 100% (all classes of PAS), specificities ranged from 9% (CNB) to 100% (all classes of

PAS), accuracy ranged from 55% (CNB) to 100% (COC, AMP, OPI and BZD), PPV ranged from 4.8% (AMP) to 100% (all classes of PAS), and NPV ranged from 25% (CNB) to 100% (all classes of PAS). Similar to the urine POCT devices results, CNB was the PAS class with greater variability in the accuracy measures of oral fluid POCT devices (55 - 99%).

Urine POCT devices showed lower variability in sensibility results for all classes of substances in comparison with oral fluid devices. Besides for OPI detection, urine devices also showed lower variability in specificities parameters than oral fluid devices. Urine devices presented higher variability in accuracy measures for AMP and OPI than oral fluid devices, while oral fluid devices showed higher variability for COC, BDZ and CNB than urine devices.

Table 2 Variability in Cutoff, Sensibility, Specificity, Accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) Measures for Point-of-Collection Devices for Drug Screening in Urine

Substance	**Cutoff (ng/mL)**	**Sensibility (%)**	**Specificity (%)**	**Accuracy (%)**	**PPV (%)**	**NPV (%)**
Cocaine	30 -300	48 – 100	47 – 100	65 – 97.6	71.4 - 100	49 – 100
Amphetamines	250 - 1000	19 – 100	43 – 100	58 – 99.1	41 - 100	65 – 100
Benzodiazepines	100 - 300	72.6 – 100	95 – 100	86.3 – 97.8	85.6 - 100	76.8 – 100
Opioids	5 – 2000	32 – 100	34 – 100	64 - 100	57 – 100	62 – 100
Cannabinoids	14 – 150	35 – 100	39 – 100	50 - 99.2	51.4 - 99	34.3 - 99.2

Table 3 Variability in Cutoff, Sensibility, Specificity, Accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) Measures for Point-of-Collection Devices for Drug Screening in Oral Fluid

Substance	**Cutoff (ng/mL)**	**Sensibility (%)**	**Specificity (%)**	**Accuracy (%)**	**PPV (%)**	**NPV (%)**
Cocaine	5 – 200	11.1 – 100	40 – 100	63 - 100	22 - 100	77.3 - 100
Amphetamines	25 – 300	16.7 - 100	33 – 100	73 - 100	4.8 - 100	51 - 100
Benzodiazepines	5 – 300	33 – 100	87.5 – 100	77 – 100	91 - 100	80 - 100
Opioids	10 – 300	10 – 100	76.5 – 100	63 - 100	8.3 – 100	69.2 - 100
Cannabinoids	5 – 200	23.1 – 100	9 – 100	55 - 99	46 - 100	25 - 100

DISCUSSION

For the major five drug classes tested around the world [20, 21], the present review found high variability in reliability measures among studies evaluating oral fluid and urine POCT devices. These results are very concerning, since the use of such devices usually involves legal and moral aspects of the subjects tested, and usually implies immediate consequences (e.g. driver imprisonment, work suspension, social constriction). Therefore, even when recommended, the use of such devices should be carefully conducted and their results should be critically evaluated before such devices being confidently implemented in different settings.

General considerations concerning POCT devices

It is important to consider that POCT devices have limitations with regard to their analytical methods. Most POCT devices for drug-of-abuse testing are immunoassays, which consist of the use of agglutination reactions, chromogenic antibodies, chromogenic drug conjugates, fluorescent antibody conjugates, or fluorescent drug conjugates [9]. Depending on the assay, antibodies are designed to detect a specific drug, a metabolite, or a class of compounds, but an undesirable cross-reactivity with other molecules could be frequently implied [5, 9, 12]. For example, drugs and drug metabolites with significant structural similarities to the target analyte may cross-react with target analyte-specific antibodies, producing false positive results. More generally, cross-reactivity is the degree to which any substrate other than the target substrate interacts with an antibody. Information on cross-reactivities for the individual or

different substances in a drug class is usually stated in the manufactures' instructions that come with the diagnostic kits.

In general, screening methods provide a qualitative determination as to presence (positive results) or absence (negative result) of drugs in a sample and are used to eliminate negative samples to the investigation. In this sense, positive results reflect a concentration above the calibrated cutoff, while negative results reflect concentrations below the cutoff, and do not exclude the presence of a drug or its metabolite [9, 12]. The cutoffs for screening tests are established by each manufacturer supplying the immunoassay kits. According to the Walsh Guidelines for Research on Drugged Driving, the cutoff concentrations should be at least as low as the lower end of the therapeutic range [20]. For recreational drugs without therapeutic use, the Walsh Guidelines suggest the use of a low analytical cutoff concentrations that are likely to detect drugs 24h after use of a typical dose [20].

POCT devices usually did not achieve excellent parameters for both sensibility and specificity as the same time, and they often present false positive results. In this sense, the use of confirmatory analysis is imperative in the forensic toxicology scenario. Confirmatory analyses are essential to ensure a high degree of reliability in order to qualify and quantify the amount of the substance present in the sample. The detection or initial identification of drugs (screening analysis) should be confirmed by a second, more specific technique than the first. Therefore, the use of mass spectrometry is currently recommended [22]. Liquid chromatography and gas chromatography coupled to mass spectrometry (LC-MS or LC-MS/MS and GC-MS or GC-MS/MS) are the techniques mostly used for this purpose [22].

The matrix that will be used in the toxicological test should be chosen according to its purpose. Because of its lower detection window and acceptable correlation with plasma drug

levels, oral fluid has been used in contexts where acute intoxication needs to be investigated, such as traffic enforcement and emergency hospitals [23]. On the other hand, the use of urine is recommended when the purpose of the test is to verify PAS use or abuse such as in drug treatment programs, because drugs and metabolites can be detected in urine after longer periods of time [3, 21]. Also, it is important to consider that urine contain higher concentrations of drugs and its metabolites than oral fluid does. This is probably the reason why urine POCT devices showed better reliability measures in the majority of the reliability measures evaluated when compared with oral fluid POCT devices.

Specific considerations concerning the drug group tested

Cocaine (COC)

COC is a psychostimulant substance that can be administrated by several routes, such as by intravenous injection, smoking and inhalation. Because of its basic properties, COC is likely to be found in oral fluid, especially after the first hours of administration [24-26]. Also, there are often higher concentrations in the oral fluid after smoked administration due to local absorption in the mucous membranes of the buccal cavity [27]. In urine, COC can be detected for 3-7 days after the last use, depending on the frequency of use (e.g, chronic users) [21, 28]. COC major metabolite, benzoylecgonine, is usually use as the target drug in both urine and oral fluid screening tests for COC, mainly because this metabolite has a greater window of detection compared with the parent drug. On the other hand, COC detection in oral fluid could be hindered in cases of acute use, once the pattern drug is more prevalent in comparison with benzoylecgonine in the first two hours after administration [24, 26].

In the present review, the worse sensibility result (48%) for COC detection in urine was found in the Triage™ evaluation by Kadehjian et al. [29]. However, in other studies, this same device showed better results, such as 100% in Peace et al. [30] and in Leino et al. [31], and 96% in Jonge et al. [32]. Considering oral fluid screening, the DDS™ (Cozart, U.K.) evaluation by Vanstechelman et al. presented the worse sensitivity result (11.1%) [33]. Overall, the most prevalent oral fluid POCT devices evaluated in the literature performed well for cocaine detection, with mean sensibility, specificity and accuracy for Drugwipe™ being 90% (±12.4%), 94.4% (±20.3%) and 93.1% (±11.8%), and for Draëger DrugTest™ being 82.4% (±18.5%), 99.1% (±15,5%) and 96.2% (±13.6%), respectively.

Amphetamines (AMP)

AMP compounds have gained great popularity as a drug of abuse, especially because of its euphoria and energy effects. This class of drugs includes amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and numerous other "designer" AMP. Usually, screening tests for this PAS use amphetamine or amphetamine/d-methamphetamine as the target drug. Also, in some cases, immunoassays are directed against MDMA molecule. Because of structural similarities or common metabolic pathways, some over-the-corner medications and dietary aids could cross-react with the target drug antibodies, resulting in false positive results [28]. More than that, a recent reviewed showed that most of the oral fluid POCT devices are unable to detect some amphetamine-type stimulants, such as methylphenidate, fenproporex, or diethylpropion [34]. In the present review, the AMP were the drug group which presented the lowest sensibility and PPV measures in urine detection and the lowest PPV measure in oral fluid detection, perhaps due to these limitations in the analytical methods.

In urine detection, the Triage™ evaluation by Kadehjian et al. [29] showed the lowest sensibility measure (19%) for AMP, but other studies found good results for this same device, such as 91.8% [35], 98% [31] and 100% [32]. In oral fluid, the lowest sensibility result (16.7%) was found in the RapidSTAT evaluation by Vanstechelman et al. [33]. Blencowe et al. [16] also found a low sensibility result (54%) when analyzing this device, but other studies showed better results, such as 72% [36] and 90% [37, 38]. Considering all studies, the Drugwipe™ achieved mean sensibility of 87% (±22%), specificity of 95% (±26.1%) and accuracy of 93% (±8.4), whereas the Draëger DrugTest™ achieved 67% (±19.5%), 98.8% (±12.3%) and 96,1% (±10.7%), respectively.

Benzodiazepines (BDZ)

BDZ are a class of substances with widely medical use. The BZE are generally lipophilic drugs with low solubility in water and exhibit good absorption from the gastrointestinal tract, first-pass metabolism, and high plasma–protein binding (70–99%) [24]. BZE excretion is predominantly through phase II metabolites (glucuronide conjugates) [39]. Considering OF detection, the correlation of BZE concentration between OF and blood are low because of high protein binding and weak acid polarity [40]. According to previous studies, this drug group is the most complicated group for screening tests. Most commercially available POCT devices are detected against diazepam, nordiazepam, or oxazepam. Although the majority of benzodiazepines are metabolized in one of those compounds, clonazepam, lorazepam, and alprazolam are not metabolized in one of those, and, therefore, the detection of these substances could be hindered, resulting in a false negative result [28]. Also, cross-reactivity with mirtazapine and citalopram has been reported [35].

Our results showed that BDZ were the drug class less evaluated among the studies. More than that, a significant part of these studies found a very low number of positive samples, and therefore their results should be interpreted with caution. Taking this in consideration, the overall accuracy for BZD detection in urine was well accepted. The worse sensibility measure for oral fluid detection of BDZ was reported by Musshoff et al. [37] regarding the Draëger DrugTest™ (33%). Blencowe el al. [16] also found a low sensibility results for BDZ detection regarding the Draëger DrugTest™ evaluation. For the Drugwipe™, results were a bit higher, with mean accuracy of 98.8 (±0.7). Again, sensibility parameters were usually not available due to the lack of positive samples.

Opioids (OPI)

OPI are a broad class of depressant substances with medical relevance – especially for analgesia purposes, but OPI are also frequently abused. Considering the broad range of OPI compounds, their considerable variety in molecular structure, in addition to the fact that these substances can be administrated by several routes, the immunoassay testing of these compounds are very problematic. Therefore, its bioavailability in biological matrices can vary widely. Morphine is the most common target drug used by screening devices, but there are also some devices available that use as target molecules buprenorphine, methadone, and oxycodone [28]. In this sense, the sensibility of OPI detection will depend on the target drug; POCT devices directed against morphine will present intermediate/low sensibility for other substances [28].

The OPI group presented the worse specificity result in urine and the worse sensibility in oral fluid. Considering urine detection, the Syva Rapid Cup™ evaluation by Kadehjian et al. [29] showed the lowest specificity measure (32%). However, this device showed specificities of

93.6% and 91% in others studies [31, 35]. For oral fluid, the worse sensibility measure was found by Pehrsson et al. [36] when evaluating the Drugwipe™. Taking consideration all studies, the Drugwipe™ showed mean sensibility of 60% (±33.4%), specificity of 98.8% (±33.4) and accuracy of 96.7% (±12.2%). For the Draëger DrugTest™, the mean measures were 62% (±31.2%), 97% (±4.3%) and 95.4% (±3.8%), respectively.

Cannabinoids (CNB)

The *Cannabis sativa* (cannabis) plant contains a unique class of compounds named CNB, in which the Δ9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid. Cannabis is the most widely produced and consumed illicit drug worldwide and although the main form of its use is smoked, it can also be ingested with food or inhaled. Since THC is highly lipophilic, following absorption, initially it is quickly distributed into tissues that are highly perfused, such as the lung, heart, brain, and liver, accumulates in adipose and only minor amounts of THC and metabolites diffuse from the plasma into oral fluid. The major metabolite 11-nor-9-carboxy-Δ9-THC (THC-COOH) is excreted within 5-day (80–90%), which more than 65% is excreted in the feces, and 20-35% being glucuronidated and eliminated in the urine [28, 41].

An important point that needs to be consider regarding CNB detection is related to the long excretion half-life of THC-COOH in the body. Whereas the presence of THC-COOH in urine could either be due to recent use or due to an accumulation after long-term usage, de detection of THC in oral fluid could be regarded as evidence of recent CNB use [28, 41]. In most cases, POCT devices use THC or THC-COOH as the target drug for the detection of CNB.

Here we found that CNB were the most evaluated drug group among the studies. Also, CNB presented the higher variability in accuracy measures for both urine and oral fluid devices.

The Syva Rapid Test™ evaluation by Kadehjian et al [29] presented the worse reported sensibility result for CNB detection in urine (35%), with other studies showing better results, such as 96% in Leino et al [31] and 97.8% in Gronholm et al. [35]. Considering oral fluid detection, the worse sensibility result was found by Vanstechelman et al. [33] when evaluating the OrAlert™ device. For both Drugwipe™ and Draëger DrugTest™, the mean sensibility found considering by the studies included in the present review was low (46.6±16.5% and 67±16.3%, respectively).

Limitations of the studies reviewed

Studies analyzed in this review presented a number of limitations. Because of the lack of parameters (such as number of true positives, true negatives, false positives and false negatives in the majority of the papers reviewed, it was not possible to conduct a meta-analysis of the data. Also, in the studies evaluating samples of drivers, the small number of positive cases limits the analysis for sensibility. By the same token, several studies only did a confirmatory analysis in case of positive results in screening tests, which underestimated the number of false negatives.

Conclusions

POCT devices could be considered a rapid and accurate way to screen for drugs of abuse. However, when evaluating or choosing a POCT device, certain features should be considered, such as clinical utility, reliability of device manufacturer, specimen type, test menu, methodology, analytical performance, result interpretation, and cost. In this sense, physicians,

policy makers, and other professionals who perform such tests have the obligation to identify the strengths and limitations of POCT techniques in order to critically evaluate the results of a drug-screening test.

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3.3 Artigo 3

Oral fluid testing for cocaine: analytical evaluation of two point-of-collection drug screening devices

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*Os dois autores tiveram a mesma contribuição para o trabalho

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Oral fluid testing for cocaine: analytical evaluation of two point-of-collection drug screening devices.

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ABSTRACT

The use of point-of-collection testing (POCT) devices for drugs of abuse in oral fluid is an advantageous tool that has been used for different purposes - particularly traffic enforcement. However, even with the widespread report of cocaine consumption, the reliability of POCT devices has been reported in different magnitudes. This study evaluated the reliability of two POCT devices for the detection of cocaine in oral fluid samples of 110 cocaine users: 1) the DDS2™ (cutoff = 30 ng/mL) and 2) the Multi-Drugs Multi-Line – Twist Screen Test Device™ (MDML) (cutoff = 20ng/mL). Results of the screening tests were compared with a Liquid Chromatography-Mass Spectrometry (LC-MS) assay. Sensitivity, specificity, and accuracy of DDS2™ were 100%, 77.77%, and 80% when compared with LC-MS with a cutoff of 30 ng/mL, and 88.89%, 89.15% and 89.09% with a cutoff of 10 ng/mL. The MDML™ device achieved sensitivity, specificity and accuracy of 100%, 65.6% and 70.9% when compared with LC/MS with a cutoff of 20 ng/mL, and 92.6%, 71.1% and 76.6% with a cutoff of 10 ng/mL. When compared with a 10 ng/mL cutoff, the DDS2™ achieved reliability parameters higher than 80%. On the other hand, the MDML™ device did not achieve the minimal recommendation of 80% for all parameters at the same time. Taking into consideration the reliability results showed here, the authors believe that the use of these POCT devices seems to be suitable for cocaine detection in forensic tests only if all positive specimens are further confirmed by a validated method.

Keywords: cocaine, point-of-collection testing, oral fluid, drug screening

INTRODUCTION

Point-of-collection testing (POCT) devices for drugs of abuse are recent technologies used to detect the presence of psychoactive substances (PAS) in body fluids in a simple and quick manner (1-3). Usually, the use of POCT devices brings several advantages, such as fast and in loco detection, non-invasive collection procedures and easy handling, which propelled the popularity of this kind of device in several settings, such as hospitals, treatment centers, traffic enforcement environments and research centers, among others (1, 4-6).

The use of oral fluid (OF) in forensic toxicology has also gained strength in the last few years, and a great number of the POCT devices commercially available use OF as the matrix of choice for detecting PAS (7-9). The main advantages of using OF in screening procedures are that this matrix is easily available and can be collected without the inTUSPion of privacy (8-9). With regard to cocaine, previous studies had shown a good correlation between its levels detected in OF and plasma, suggesting that OF could be used to investigate acute cocaine intoxication (10-12). However, as recently highlighted by Ellefsen and colleages, the reliability measures of POCT devices for cocaine detection in OF reported on the literature vary widely between different studies (11).

The DDS2™ mobile test system is a handheld OF testing device that has reached the market recently. As far as the authors know, there is just one field study that conducted an initial evaluation of this device. In this study, fifty screening tests were performed with voluntary drivers – of those, five samples were screened and confirmed positive for cannabinoids and one for methamphetamine. The methamphetamine sample was also confirmed positive for amphetamines, yielding one false negative screening result (13). In the same fashion, the Multi-

Drugs Multi-Line – Twist Screen Test Device™ (MDML) (formerly marketed as OrAlert™ by Innovacon Inc.), also a POCT device that detects PAS through OF, has been evaluated in one study so far, which found a sensitivity for cocaine equal to 50% (14).

In forensic analysis, it is important that screening devices achieve good measures of reliability, especially in sensitivity of detection. Moreover, the use of POCT devices for law and traffic enforcement is frequent, and a false result could imply several legal and administrative consequences. Therefore, since cocaine is one of the most used PAS in Brazil and in the world (15-16), the aim of this study was to evaluate the reliability of the DDS2™ and the MDML™ mobile test systems for the detection of cocaine in OF, based on the devices' cutoff limits, as well as compare their results to the cutoff established by Walsh and colleagues (17).

METHODS

Sample selection and ethics

A total of 110 cocaine or crack-cocaine users seeking treatment in public and private facilities were recruited by convenience sampling from August to November 2015 at inpatient and outpatient services specialized in drug addiction in the city of Porto Alegre, Brazil. Inclusion criteria included being a substance user seeking treatment for drug abuse; being at least 18 years old; and providing written informed consent. Individuals were excluded if they were considered clinically and intellectually unable to participate (e.g. psychosis, dementia, mental retardation). Data collection was obtained through interviews conducted within the first twenty-four hours after patients joined treatment, and involved two coordinators and two interviewers, who were

trained and supervised weekly under the responsibility of the principal investigators (JNS and TRF).

Ethical approval for the study was obtained from the Institutional Review Board of Hospital de Clínicas and Hospital Mãe de Deus, both located in Porto Alegre. A written consent was obtained from all participants.

Instruments, screening tests and procedures

Data regarding substance use and sociodemographic characteristics of the sample were assessed through the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (18) and through a sociodemographic questionnaire, respectively. After the initial interview, all subjects were tested with the two drug screening devices.

The MDML™ (Alere Inc., Massachusets, USA) consists of an OF collector and a detection element. Results are indicated with red lines and need to be visually interpreted. Red lines indicate a negative result for the substance in question. Red control lines indicate a successful test. The classes of drugs tested with this device are amphetamines, methamphetamines, cocaine, opiates, cannabinoids and phencyclidine. This device also stores part of the OF collected to be sent to the laboratory for confirmation, and therefore, its use eliminates the need of a second sample collection for confirmatory analysis. Its cocaine detection cutoff is 20 ng/mL.

The DDS2™ mobile test system (Alere Inc., Abingdon, United Kingdom) comprises a collector swab, a disposable test cartridge, a handheld instrument to interpret results and a printer for permanent recording of test results. This device tests a panel of six classes of drugs, including

cannabinoids, cocaine, opiates, methamphetamine, amphetamines and benzodiazepines. OF collection is made with a collector pad which is swabbed around the gums, tongue and inside cheeks until the sample presence indicator turns completely blue. The cocaine detection cutoff is 30 ng/mL.

Once MDML™ collection required higher volume of OF (~ 1 mL), and that this device also stores the OF used for confirmatory analysis, it was performed before DDS2™, which needs lower volume of OF (~ 0.6 mL). The two collections were performed in sequence, with no interval between them. The interview, the sample collection, and the result interpretation of the devices were performed by two research assistants, supervised daily by one of the main investigators (JNS and TRF). The two research assistants, as well as the main investigators, received online training with the manufacturers in order to use the devices with the best practice. In cases of uncertain about the screening results interpretation, the main investigators were consulted, aiming at reducing misinterpretation. The confirmatory samples collected with the MDML™ device were transported under refrigeration to the laboratory, where it was aliquoted and stored at -80 ± 2 ^{o}C until confirmatory analysis.

Confirmatory analysis

Confirmatory analyses were made on a Agilent 1260 infinity LC system equipped with G1311B quaternary pump, G1329B autosampler, G1314F UV/VIS detector and G1316A thermostatizer coupled to an Agilent 6120B series mass detector (Agilent Technologies, Palo Alto, CA, USA). The column used in the analyses was a Phenomenex Kinetex HILIC (150 mm × 4.6 mm, particle size of 2.6 μm) (Torrence, CA, USA) maintained at 30 °C. Chemstation

software (v. B.04.03) was used for data analysis. Parameters were set to optimize the quantification ion and analysis was performed in single ion monitoring (SIM) mode. Ionization was achieved using electrospray in the positive ionization mode (ESI+). An Eppendorf centrifuge, model 5430R (Hamburg, Germany) was used to prepare the samples. MS confirmations were performed for all samples, including positives and negatives presumptively identified by the screening test. Each confirmation test was performed on a standard volume of 100 µL of OF. The samples were processed by buffer dilution followed by centrifugation and filtration (0.22µm). The limit of detection and the limit of quantification were 1.7 ng/mL and 4.25 ng/mL, respectively for both parent drug (COC) and benzoylecgonine (BZE).

Data analysis

Both POCT devices tested use BZE as a target drug with cutoff levels at 30 ng/mL for DDS2™ and 20 ng/mL for MDML™. Therefore, the reliability parameters of each POCT device were first calculated comparing the devices screening results to the LC-MS confirmatory analysis results considering BZE as the target drug at the device' screening cutoff and at the cutoff of 10 ng/mL established by Walsh and colleagues in the Guidelines for Research on Drugged Driving (17). We also present the results comparing the same cutoffs (30 ng/mL for DDS2™, 20 ng/mL for MDML™ and 10 ng/mL) using COC alone and COC together with BZE (COC together with BZE = either COC or BZE present above the cutoff) as the target drugs. True positive (TP) samples screened and confirmed positive; true negative (TN) samples were negative in both assays. False positive (FP) samples screened positive, but the target drug was not present at the specified confirmation cutoffs; false negative (FN) samples screened negative

but confirmed positive for the target drug. Performance parameters were calculated as: sensitivity = 100x(TP/TP + FN); specificity = 100x(TN/TN + FP); and accuracy = 100x(TP + TN/Total results).

RESULTS

Sociodemographic characteristics of the sample and pattern of cocaine use

The sociodemographic characteristics of the sample are detailed in **Table 1**. In summary, the sample was comprised mostly by men (94.5%), caucasians (47.3%), with a mean age of 33 years old. Also, the respondents were mostly low-educated (62.7% with less than eight years of schooling) and unemployed (58%). A total of seven participants declared they were abstinent of cocaine for at least three months. Considering the current users, more than 50% reported daily cocaine use, and 60% reported crack-cocaine as the preferred form of cocaine use.

Table 1 Sociodemographic data and drug use patterns

Variable	Number of subjects (%)
Age[a]	33.7 ± 9.4
Gender	
…Male	104 (94.5)
…Female	6 (5.5)
Race	
…Caucasians	52 (47.3)
…Black	25 (22.7)
…Mixed races	33 (30)
Education	
…Elementary school	69 (62.7)
…High school	34 (30.9)
…Superior school	7 (6.4)
Gross income	
... Without income	31 (28.2)
…< 2 minimum wages[b]	54 (49.1)

…2-5 minimum wages[b]	25 (22.7)
Frequency of cocaine use*	
…Daily	59 (53.6)
…Weekly	26 (23.6)
… Monthly	18 (16.4)
… Abstinent	7 (6.4)
Cocaine administration	
…Snorted	29 (26.4)
…Smoked (crack)	70 (63.6)
…Both	2 (1.8)

[a]Mean ± Standard deviation

[b]One minimum wage in Brazil (R$: 880.00) is equivalent to 251.4 U.S. Dollars

*In the last three months

Reliability of DDS2™ detection of cocaine

The DDS2™ reliability measures of cocaine detection are shown in **Table 2**. Sensitivity, specificity, and accuracy when compared with the LC-MS with a cutoff of 30 ng/mL were 100%, 77.77%, and 80%. Comparing DDS2™ results with the 10 ng/mL cutoff established by Walsh and colleagues in the Guidelines for Research on Drugged Driving (17), we found a sensitivity of 88.89%, specificity of 89.15% and accuracy of 89.09%. When analyzing the results taking into consideration COC or COC together with BZE as the target drug, we could observe a decrease in sensitivity parameters, and a tendency of lower number of FP results.

In **Figure 1** it is presented the distribution of COC and BZE concentrations in OF considering DDS-2^{TM} reliability measures for BZE detection with the cutoff of 30 ng/mL and 10 ng/mL. Considering the 30 ng/mL cutoff, the mean concentrations (±standard deviation) of COC and BZE were: 7.3 (±15.0) ng/mL and 1.6 (±3.6) ng/mL in TN cases; 85.6 (±136.1) ng/mL and 151.2 (±175.5) ng/mL in TP cases; and 43.9 (±63.4) ng/mL and 11.8 (±9.5) ng/mL in FP cases, respectively.

Table 2 Results of the DDS2™ evaluation for cocaine detection according to the test cutoff and the cutoff established by Walsh and colleagues for BZE, COC and BZE/COC together.

	For BZE according to DDS2™ cutoff (30 ng/mL)	For BZE according to Walsh cutoff (10 ng/mL)	For COC according to DDS2™ cutoff (30 ng/mL)	For COC according to Walsh cutoff (10 ng/mL)	For COC and BZE according to DDS2™ cutoff (30 ng/mL)	For COC and BZE according to Walsh cutoff (10 ng/mL)
N of tests	110	110	110	110	110	110
TN	77	74	71	57	71	55
FN	0	3	6	20	6	22
TP	11	24	17	25	22	30
FP	22	9	16	8	11	3
Sensitivity	100	88.89	73.91	55.55	78.57	57.69
Specificity	77.77	89.15	81.61	87.69	86.58	94.83
PPV	33.33	72.73	51.51	75.76	66.66	90.90
NPV	100	96.10	92.21	74.03	92.21	71.43
Accuracy	80	89.09	80	74.54	84.54	77.27

TN = True negatives; FN = False negatives; TP = True positives; FP = False positives; PPV = Positive predictive value; NPV = Negative predictive value.

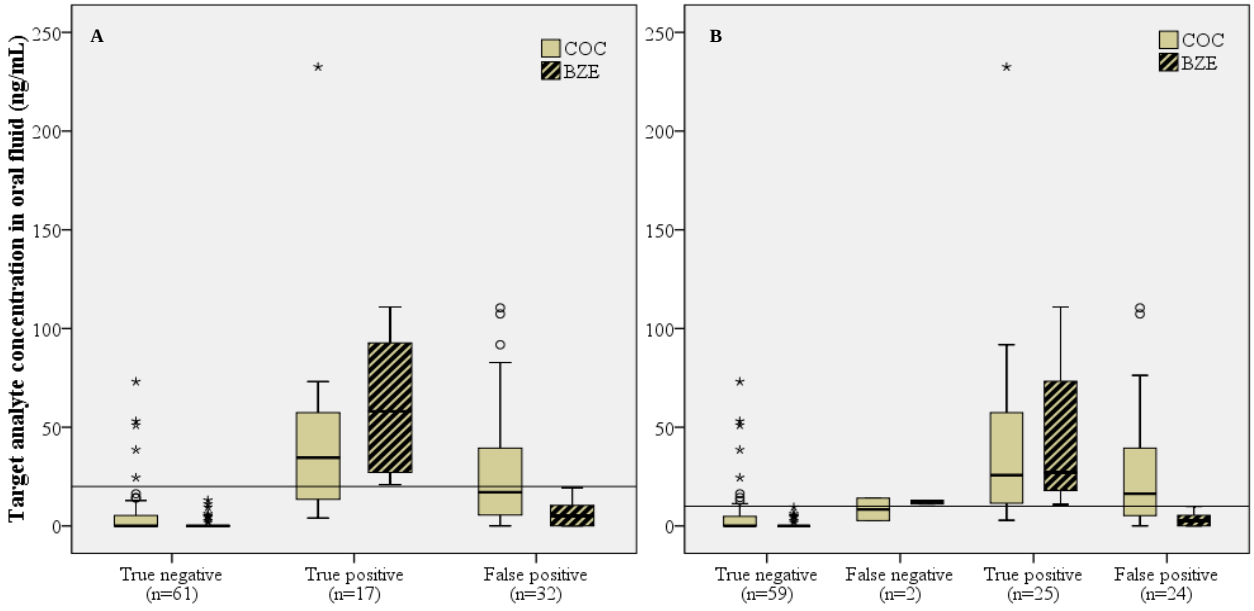

Figure 1 Pattern cocaine (COC) and benzoylecgonine (BZE) concentrations in oral fluid considering DDS-2™ reliability measures for BZE detection with the cut-off of 30 ng/mL (figure 1a) and 10 ng/mL (figure 1b).

Reliability of MDML™ detection of cocaine

The MDML™ reliability measures of cocaine detection are shown in **Table 3**. Sensitivity, specificity, and accuracy when compared with the LC-MS with a cutoff of 20 ng/mL were 100%, 65.59%, and 70.9%. When comparing MDML™ results with the 10 ng/mL cutoff, we found a sensitivity of 92.59%, specificity of 71.08% and accuracy of 76.36%. Similarly with the DDS2™ results, when analyzing COC or COC together with BZE, we found a decrease in sensitivity parameters, as well as tendency of lower number of FP results.

In **Figure 2** it is presented the distribution of COC and BZE concentrations in OF considering MDML™ reliability measures for BZE detection with the cutoff of 20 ng/mL and 10 ng/mL. Considering the 20 ng/mL cutoff, the mean concentrations (±standard deviation) of COC and BZE were: 5.4 (±13.4) ng/mL and 0.9 (±2.6) ng/mL in TN cases; 80.7 (±124.7) ng/mL and 106.6 (±152.0) ng/mL in TP cases; and 24.6 (±32.0) ng/mL and 5.8 (±6.2) ng/mL in FP cases, respectively.

Table 3 Results of the MDML™ evaluation for cocaine detection according to the test cutoff and the cutoff established by Walsh and colleagues for BZE, COC and BZE/COC together.

	For BZE according to MDML™ cutoff (20 ng/mL)	For BZE according to Walsh cutoff (10 ng/mL)	For COC according to MDML™ cutoff (20 ng/mL)	For COC according to Walsh cutoff (10 ng/mL)	For COC and BZE according to MDML™ cutoff (20 ng/mL)	For COC and BZE according to Walsh cutoff (10 ng/mL)
N of tests	110	110	110	110	110	110
TN	61	59	56	49	56	48
FN	0	2	5	12	5	13
TP	17	25	23	33	32	39
FP	32	24	26	16	17	10
Sensitivity	100	92.59	82.14	73.33	86.49	75
Specificity	65.59	71.08	68.29	75.38	76.71	82.76
PPV	34.69	51.02	46.94	67.35	65.31	79.59
NPV	100	96.72	91.80	80.33	91.80	78.69
Accuracy	70.90	76.36	71.82	74.54	80	79.09

TN = True negatives; FN = False negatives; TP = True positives; FP = False positives; PPV = Positive predictive value; NPV = Negative predictive value.

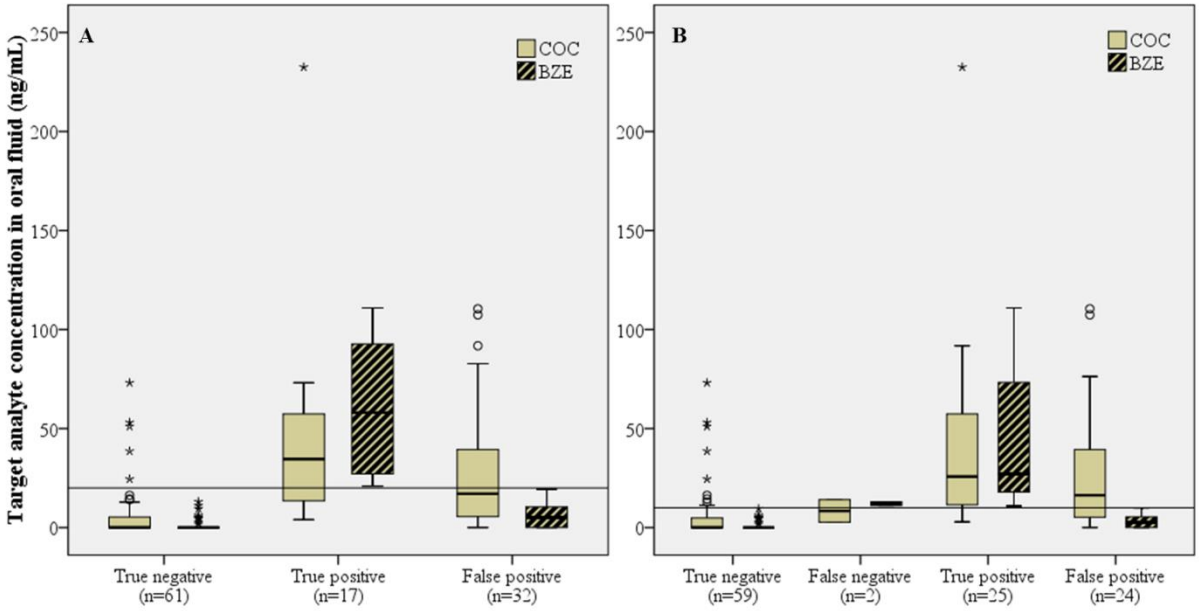

Figure 2 Pattern cocaine (COC) and benzoylecgonine (BZE) concentrations in oral fluid considering MDML™ reliability measures for BZE detection with the cut-off of 20 ng/mL (figure 2a) and 10 ng/mL (figure 2b).

DISCUSSION

To our knowledge, these are the first data identifying cocaine detection rates for the DDS2™ and MDML™ mobile test systems, with performance characteristics obtained with different confirmation cutoffs, in a sample with high prevalence of cocaine-positive subjects. When considering the devices main target molecule (BZE), DDS2™ achieved good parameters of reliability (>80% according to DRUID project) at the cutoff of 10 ng/mL set by Walsh and colleagues in the Guidelines for Research on Drugged Driving (17). The MDML™ device did not achieve the minimum parameters of reliability neither at 20 ng/mL nor at 10 ng/mL cutoffs. When considering the analysis for COC, alone or together with BZE, we found worse sensitivity parameters for both devices.

In forensic toxicology, it is recommended that POCT devices for drugs of abuse achieve good sensitivity, in order to separate negative samples from potentially positive samples (1,19). The sensitivity of POCT devices for OF detection of cocaine found in the literature seems to vary widely among different studies. Other OF POCT devices, such as the Drug Test 5000™ and the Drugwipe 5+™, have been evaluated in several studies, and their reliability measures concerning cocaine detection seem to diverge according to the study design and population, confirmatory analysis procedures and number of positive cases. Logan et al. (20) evaluated both Drug Test 5000™ and Drugwipe 5+™ on a roadside study and found sensitivity of 88.9% and 90%, respectively. Other two studies which also evaluated both devices using samples of drivers at the roadside found sensibilities of 76% and 97% for Drug Test 5000™ and 100% and 90% for Drugwipe 5+™ (21, 22). On the other hand, when some devices were evaluated using OF samples from drug users, where there is a higher prevalence of positive samples, they achieved

worse sensitivity parameters, such as 50% for Drug Test 5000™ and 11.1% for Cozart DDS™ (14).

In the present study, we found sensitivities ranging from 75-100% for DDS2™ and from 55.55-100% for MDML™, depending on the target drug and the cutoff limit established. When FN results were assessed based on the BZE immunoassay screening cutoff, they were quite rare (resulting in high sensitivity parameters), but the prevalence of FP was quite significant (resulting in lower specificity parameters). The authors believe that one of the reasons for the high number of FP can be the presence of other substances that were not evaluated in the present method. Also, the cross-reaction with COC in cases of acute exposure can contribute for FP results when considering just BZE as the target drug, since BZE detection can present cross-reactivity with COC in POCT devices (6). As can be seen in the Tables 2 and 3, the number of FP when just COC is used as a target drug, or either when COC together with BZE are used as target drugs is lower than the number of FP using only BZE as target drug. Also, it was found that, when considering BZE as the target drug, the FP cases presented high levels of COC, which indicates that the devices can also detect high concentrations of COC, indicating it as positive results. Therefore, the results of such devices should be carefully evaluated; especially in cases were false results could lead to strict penalties and legal problems. More than that, confirmation of positive results through a validated method of confirmatory analysis becomes a requisite following these screening procedures in order to qualify and quantify the metabolites presented in the sample (19, 23, 24).

The evaluation of the reliability parameters found here should also take into consideration the target drug used for analysis. Several pharmacokinetic studies have shown there is a higher

concentration of COC in OF in comparison with BZE in the first hours after COC use (10, 11, 25, 26). On the other hand, after approximately 2h, BZE starts to be the most predominant metabolite found in OF (8, 10). Considering that both POCT devices use BZE and not the pattern drug (COC) as the target drug, OF analysis could be hindered in situations of acute exposure, which can result in FN results. On the other hand, the present study shows that the samples with high concentrations of COC had positive results in both devices, even with the absence of BZE, probably due to cross-reactivity. Moreover, some pharmacokinetics studies have shown that BZE can be detected in OF for approximately 1–2 days after cocaine administration (10, 11, 27). Therefore, it is important to consider that a positive can imply cocaine use, but cannot imply psychomotor impairment.

The fact that these POCT devices are based on immunoassay methods generates some analytical limitations, such as possible cross-reactivity with other molecules, which increase the importance of confirmatory analysis (2, 19, 28). Therefore, there is need for more studies to evaluate such parameter for both devices, since we were unable to analyze them. The analytical technique used for confirmatory analysis can be considered other limitation of the study since it was used a single LC-MS method. Techniques such as a triple quadrupole mass spectrometer are more often used for this purpose nowadays, but the use of single equipment is still a valuable choice for confirmatory analysis due to its robustness, especially in cases when there is no other alternative available, as can occur in development countries (29-33). Also, testing the two devices in sequence can result in the possibility of stimulation, and hence decreasing drug concentration in the second sample collection. However, one strength of our study was the fact that we analyzed the devices ‘‘in real world’’ scenarios, with a high prevalence of drug positive

samples. More than that, the authors did the confirmatory analyses of all samples, independently of the screening result, in order to improve the validity of our data.

Overall, DDS2™ showed better reliability measures than the MDML™ device. More than that, the fact that the MDML™ results need to be visually interpreted by the presence or absence of the red lines add a critical limitation for this device. Based on our results, the authors can conclude that the DDS2™, considering the cutoff of10 ng/mL, could be used with at least 80% of confidence for BZE detection. Nevertheless, because of the high number of false positive samples found in this study, the authors strongly recommend the use of confirmatory analysis in cases of positive results screening with both devices evaluated here.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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4 CONCLUSÕES E CONSIDERAÇÕES FINAIS

O uso de SPAs além do álcool por motoristas é identificado como um problema mundial emergente. Até o presente momento, as principais prioridades de ação levantadas pela OMS e outros órgãos internacionais quanto a esse tema englobam: a) investigar a prevalência do uso de SPAs por motoristas e o número de CT ocasionadas sob o efeito de substâncias; b) desenvolver e estabelecer leis e limites de detecção para a testagem de SPAs em motoristas; c) investigar populações de risco e métodos de prevenção de reincidência; d) desenvolver e avaliar tecnologias que auxiliem no controle de dirigir sob o efeito de SPAs; e e) integrar as políticas de trânsito com as políticas de drogas orientadas para a saúde pública [29,81]. Logo, a prevenção do uso de SPAs por condutores, especialmente na população de usuários frequentes de SPAs – que possuem altas taxas de recidivismo, é um grande desafio dentro das políticas públicas. Nesse contexto, os resultados apresentados pela presente tese envolveram dois dos diversos fatores que precisam ser reconhecidos e evidenciados a fim de buscarmos melhores práticas de prevenção e fiscalização dentro da segurança no trânsito: a investigação de uma população de risco e seus fatores associados e a avaliação de tecnologias que possam ser implementadas nos ambientes de fiscalização.

Apesar de o crack ser uma SPA cujo uso é amplamente difundido em diversos países [89,155], e do reconhecimento do fato de que usuários de SPAs possuem uma maior prevalência de envolvimento em CT [28,62,156], nenhum estudo até então havia investigado questões referentes a segurança no trânsito nessa população. Nossos resultados evidenciaram que a amostra de usuários de crack apresentou alta prevalência de histórico de dirigir sob o efeito de SPAs, bem

como alta prevalência de CT sob efeito de crack. Além disso, quando investigamos se as comorbidades psiquiátricas e o padrão do uso de múltiplas SPAs estariam associados à prevalência de colisões, encontramos que apenas o uso de crack por mais de cinco anos estava relacionado a este desfecho. Logo, apesar do baixo nível socioeconômico e menor acesso a veículos, usuários de crack se mostraram uma população de risco para segurança de trânsito envolvendo álcool e outras SPAs. Nesse sentido, seria importante que abordagens de psicoeducação e intervenções motivacionais sobre segurança no trânsito também fossem desenvolvidas durante o tratamento de usuários de crack. Mais do que isso, o tratamento do próprio TUSP, bem como o tratamento concomitante das comorbidades psiquiátricas associadas, são extremamente importantes para a redução dos riscos associados a CT.

Apesar da legislação vigente do código de trânsito brasileiro proibir a condução de veículos sob o efeito de SPAs, ainda não existe nenhum equipamento aprovado pelo CONTRAN que possibilite a detecção de SPAs além do álcool nas abordagens de fiscalização de trânsito. Logo, no Brasil, ao contrário de outros países como a Noruega e a Austrália, ainda não há a utilização de um dispositivo de triagem comprovadamente eficaz e regulamentado para a detecção de SPAs além do álcool. Entretanto, por se tratar de um teste que envolve aspectos legais e morais dos sujeitos envolvidos, existe a necessidade de utilização de tecnologias de alta confiabilidade, porém simultaneamente práticas, rápidas e de fácil manipulação. Nesse sentido, é de extrema importância que exista uma avaliação crítica desses dispositivos antes que eles sejam recomendados e implementados com confiança dentro da fiscalização de trânsito.

Quando investigamos os artigos disponíveis na literatura que avaliaram a confiabilidade de dispositivos de triagem que poderiam ser implementados na fiscalização de trânsito, observamos que, apesar de existir uma ampla variedade de testes, os resultados encontrados

apresentam grande variabilidade no que diz respeito a sensibilidade, especificidade e acurácia. Nesse sentido, uma série de fatores pode influenciar na análise de SPAs em fluidos biológicos e, portanto, acarretar oscilações de performance na avaliação desse dispositivos, como por exemplo a presença de reatividade cruzada com certas moléculas [157,158], interpretação equivocada dos resultados [159], variações nos métodos de coleta e armazenamento da amostra [131], questões analíticas do método confirmatório e especificidades locais das classes de substâncias [101,106,122]. Além disso, como comentado por George e Braithwaite, a maioria dos dispositivos de triagem é fabricada visando o mercado americano e europeu e, portanto, os dispositivos possuem o menu de testagem de acordo com as SPAs utilizadas nessas regiões [159]. Nesse sentido, Souza e colaboradores verificaram que dispositivos de triagem geralmente não detectam certos CA com uso prevalente no Brasil, como o metilfenidato, o fenproporex e o dietilpropion [160]. Isso reforça a importância de testar essas tecnologias dentro de um contexto local, através de estudos com metodologias consistentes e robustas, antes que elas sejam implementadas.

A cocaína em suas diferentes formas de apresentação é uma das classes de SPAs ilícitas mais consumidas no Brasil [90]. Assim, é importante que dispositivos de triagem sejam testados no contexto nacional para que se avalie a confiabilidade dos mesmos quanto a detecção dos tipos de cocaínicos consumidos no país. A análise do dispositivo DDS2™, que até então não havia sido avaliado para a detecção de cocaínicos, revelou que esse dispositivo apresenta sensibilidade, especificidade e acurácia superiores a 80% para a detecção de benzoilecgonina (BZE) com o cutoff de 10 ng/mL (cutoff recomendado pelo guia de Walsh e colaboradores [161]). Já o dispositivo Multi-Drugs Multi-Line – Twist Screen Test Device™ (MDML) não atingiu esses parâmetros de forma concomitante para nenhuma das análises realizadas. Além disso, em ambos os dispositivos foi encontrado um grande número de resultados FP quando analisado o BZE

como molécula alvo. Entretanto, viu-se também que as amostras FP possuíam concentração de cocaína inalterada (COC) significativa, indo de acordo com dados que concluem que a molécula de COC tem reatividade cruzada com os anticorpos para BZE. Logo, é possível que, mesmo tendo BZE como molécula alvo, esses dispositivos também detectem altas concentrações de COC, o que é interessante na perspectiva da fiscalização de trânsito.

As peculiaridades dos dispositivos de triagem levantadas por esses resultados forçam a hipótese de que mais estudos são necessários a fim de avaliarmos a confiabilidade desses dispositivos para aplicação em um contexto nacional. Além disso, é importante que toxicologistas, agentes de fiscalização e operadores de políticas públicas tenham entendimento sobre as vantagens e limitações das técnicas para que se possa ter uma avaliação crítica dos resultados. Mais do que isso, é extremamente importante avaliar que o processo de testagem *in loco* é dependente de analises confirmatórias e, portanto, necessita de um complexo processo de encadeamento que inclui: a coleta de amostra para o teste confirmatório, armazenamento da mesma, transporte da amostra confirmatória para um laboratório, padronização das técnicas de análise confirmatória, realização da análise, devolução do resultado e, em certo casos, julgamento posterior dos casos por juízes. Logo, a implementação do uso de dispositivos de triagem leva em consideração um processo amplo e complexo, que deve considerar fatores que vão muito além confiabilidade dos dispositivos.

Em conclusão, para que a implementação de intervenções tenha sucesso, como a implementação da testagem de SPAs através de dispositivos de triagem, é necessário que seja orientada por informações baseadas em evidências, dentro do contexto local, o que requer reconhecer e compreender o problema relacionado ao uso de SPAs e seu impacto no trânsito. Para tanto, é importante o maior conhecimento da prevalência do uso de SPAs por motoristas

brasileiros, o entendimento das percepções de risco de CT associadas a conduzir sob o efeito de SPAs dentro da população, a investigação das características dos motoristas de risco e o impacto local do uso SPAs no trânsito. Mais do que isso, é preciso que a legislação aborde claramente os níveis máximos de SPAs permitidos nos fluidos biológicos e que as penalidades relativas a essas infrações sejam rigorosas e efetivas [162,163]. Ainda, é fundamental que as intervenções de fiscalização estejam atreladas a intervenções de saúde e de educação, tenham forte respaldo político e sejam amplamente divulgadas.

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ANEXO 1 – Projetos em andamento e perspectivas futuras

Como visto anteriormente, o uso de dispositivos de triagem para a detecção de SPAs já é uma prática utilizada por agentes de fiscalização de trânsito em diversos países (vide seção 1.5 - Uso de dispositivos de triagem para fiscalização no trânsito). Nesse sentido, através de legislações e ações baseadas em evidências científicas, os países desenvolvidos adotaram práticas de fiscalização quanto a detecção de SPAs adaptadas aos contextos locais, incluindo a escolha dos dispositivos mais adequados e das classes de substâncias/limites de detecção a serem detectados.

Na presente tese, a confiabilidade de diferentes dispositivos de triagem foi avalidada através de uma revisão sistemática, e dois dispositivos foram avaliados analiticamente para a confiabilidade de detecção de cocaínicos em amostras de FO de usuários de SPAs. Em paralelo ao desenvolvimento desses estudos, foi desenvolvido um terceiro estudo para complementar os estudos anteriores e para avaliar a aplicabilidade *in loco* desses dispositivos através da testagem em ambientes reais de fiscalização de trânsito. De uma forma ampla, o objetivo principal deste terceiro estudo foi avaliar tecnologias de detecção de SPAs para serem implementadas na fiscalização de condutores brasileiros, levando em consideração as necessidades e limitações do contexto local.

A logística desse estudo foi realizada em três fases, cujos objetivos específicos foram os seguintes:

- Fase 1 - descrição crítica das tecnologias disponíveis e utilizadas pelas polícias em diversos países para detecção de SPAs em condutores, no que se refere a aplicabilidade, aos benefícios esperados e aos custos de implementação;
- Fase 2 - apresentar e discutir com profissionais e gestores públicos na área de trânsito as tecnologias de detecção de SPAs possíveis de serem implementadas no Brasil;
- Fase 3 – implementar, através de estudos pilotos com as polícias brasileiras, a utilização da(s) tecnologia(s) mais adequadas ao contexto nacional.

Até o presente momento, as fases 1 e 2 já foram concluídas, e os resultados das mesmas encontram-se na **Tabela 6** a seguir.

Tabela 6 Resultados e produtos decorrentes das fases 1 e 2 do "Projeto Tecnologias de *Screening* de SPAs no Trânsito – Avaliação de Tecnologias para Detecção de Substâncias Psicoativas em Condutores Brasileiros"

Atividade	**Perídio de execução**	**Status**	**Resultados/Produtos**
Fase 1			
Revisão da literatura	Março a Julho de 2015	Concluído	- Artigo 2 da presente tese; - Artigo de revisão sobre custo-benefício do uso de dispositivos de detecção de SPAs no trânsito (em fase de elaboração).
Visitas a instituições de pesquisa e de fiscalização em diversos países	Abril, Junho, Julho, Outubro de 2015	Concluído	Foram realizadas 3 visitas técnicas de pesquisadores vinculados ao projeto a congressos científicos e centros de referência para debater com profissionais da área as melhores estratégias de fiscalização e análise toxicológica para detecção de SPAs a serem implementadas no contexto brasileiro.

Fase 2			
Realização de Workshops	Novembro de 2015	Concluído	2 Workshops foram realizados: - 10/novembro/2015 - em Porto Alegre no Centro Colaborador em Álcool e Drogas e Drogas HCPA/SENAD; - 17/novembro/2015 - em Brasília - na Pré-Conferência da 2a Conferência Global de Alto Nível em Segurança no Trânsito

No que diz respeito à implementação do estudo piloto da fase 3, as coletas de dados já foram realizadas e os resultados estão em processo de análise. Entretanto, os resultados preliminares mostraram que, dentre os 3,321 motoristas abordados nas barreiras de fiscalização durante os dias de coletas de dados, 309 possuíram os critérios de inclusão[4] para entrar no estudo, e 178 (57,6%) aceitaram participar do mesmo. Entre os 178 participanetes, 106 (59.2%) aceitaram realizar o teste do etilômetro, com 34 (32,1%) indivíduos apresentando etilometria positiva, e 164 (92%) realizaram o teste de triagem para SPAs, com 33 (20%) indivíduos apresentando resultados positivos para pelo menos uma SPAs que não o álcool[5]. Nesse sentido, os cocaínicos (n= 14; 42,4%) e os canabinóides (n= 9; 27,3%) foram as classes de substâncias mais detectadas entre os motoristas que apresentaram testes positivos. Mais do que isso, considerando os motoristas que obtiveram resultado positivo para pelo menos uma das SPAs, 24% também apresentou resultado positivo para álcool e 48% recusaram a realização do etilômetro.

[4] Por questões éticas, somente foram convidados a participar do estudo indivíduos maiores de 18 anos que apresentasse alguma situação que o impedisse que retornasse à via conduzindo um veículo (ex: etilometria positiva; recusar fazer etilometria, estar sem documentos...).

[5] Dados referentes aos resultados dos testes de *screening* – não foram realizadas as análises confirmatórias para essas amostras até o presente momento.

Assim, mesmo tendo apenas os dados preliminares deste estudo, já fica evidenciado o grande prevalência do uso de álcool e outras SPAs por motoristas. Somados, os achados desses estudos reforçam a relevânda dos resultados da presente tese e justificam a continuação de estudos que avaliem o uso de SPAs por condutores, bem como a avaliação de medidas de fiscalização que possam ser efetivas dentro do contexto brasileiro. Assim, as perspectivas futuras da aluna incluem a finalização da análise dos dados do estudo piloto (conforme o plano de publicação abaixo), o desenvolvimento da meta-análise a partir dos resultados obtidos no artigo 2 e, em longo prazo, o desenvolvimento de novos projetos que continuem buscando o entendimento dos fatores de risco associados ao uso de SPAs e condução de veículos, bem como a investigação de métodos e ações eficazes de prevenção e fiscalização dentro do contexto nacional.

Tabela 7 Plano de publicação para os artigos do "Projeto Tecnologias de *Screening* de SPAs no Trânsito – Avaliação de Tecnologias para Detecção de Substâncias Psicoativas em Condutores Brasileiros"

Título do artigo	**Revista a ser submetido**	**Autores**	**Data prevista para submissão**
Effectiveness and cost evaluation of enforcement policies for drug drivers: a systematic review	Pharmaco Economics (FI:3,57)	Sousa, T.; Pasa, G.;Scherer, J.; Fiorentin, T.; Pechansky, F.	Junho/2017
Drug use among Brazilian drivers using oral fluid screening devices as part of traffic checkpoints: a pilot study	Accident; analysis and prevention (FI: 2,07)	Sousa, T.; Scherer, J.; Silvestrin, R.; Roglio, V.; Brolese, G.; Pasa, G.; Schuch, J.; Limberger, R.; Pechansky, F.	Agosto/2017
Perception of coercion: evaluating drivers in roadside surveys	Traffic injury prevention (FI: 0,8)	Silvestrin, R.; Sousa, T.; Scherer, J.; Roglio, V.; Pechansky, F.	Junho/2017

Lack of correlation between BAC levels and clinical signs evaluated by traffic agents: the importance of using breathalyzer in roadblocks.	Accident; analysis and prevention (FI: 2,07)	Scherer, J.; Sousa, T.; Schuch, J.; Roglio, V.; Silvestrin. R.; Limberger, R.; Pechansky, F.	Maio/2017
Performance and analytical evaluation of four oral fluid drug screening devices: results from a Brazilian roadside study	Journal of Analytical Toxicology (FI: 2,3).	Scherer. J; Sousa, T.; Fiorentin. T; Gonzalez, M.; Santos, M.; Zamboni, A.; Limberger, R.; Pechansky, F.	Agosto/2017

ANEXO 2 – Carta de aceite artigo 3

Gmail

Juliana Scherer <julianascherer@gmail.com>

Journal of Analytical Toxicology - Decision on Manuscript ID JAT-16-2243.R1

Journal of Analytical Toxicology <onbehalfof+bruce-goldberger+ufl.edu@manuscriptcentral.com>
Responder a: bruce-goldberger@ufl.edu
Para: julianascherer@gmail.com

22 de janeiro de 2017
15:25

22-Jan-2017

Dear Ms. Scherer:

It is a pleasure to accept your manuscript titled "Oral fluid testing for cocaine: analytical evaluation of two point-of-collection drug screening devices." in its current form for publication in the Journal of Analytical Toxicology.

Thank you for your contribution. On behalf of the Editors of the Journal of Analytical Toxicology, we look forward to your continued contributions to the Journal.

Sincerely,

Bruce A. Goldberger, Ph.D.
Professor, University of Florida
Editor-in-Chief, Journal of Analytical Toxicology

ANEXO 3 – Artigos publicados durante o período do Doutorado

1) *High levels of brain-derived neurotrophic factor are associated with treatment adherence among crack-cocaine users*
   Autores: Juliana N. Scherer, Silvia Schuch, Felipe Ornell, Anne O. Sordi, Giovana Bristot, Bianca Pfaffenseller, Flavio Kacpczinski, Felix H.P. Kessler, Fabio Fumagalli, Flavio Pechansky, Lisia von Diemen.
   Revista: Neuroscience Letters, 2016.

2) *Saúde e cárcere: estruturação da atenção básica à saúde no Sistema prisional do Rio Grande do Sul*
   Autores: Felipe Ornell, Renata Maria Datta Panichi, Juliana Nichterwitz Scherer, Sonia Lucinda Modena, Vanessa Dal Cin, Adriana Mokwa Zaninif, Silvia Chwartzmann Halpern.
   Revista: Sistema Penal e Violência, 2016.

3) *Confirmatory factor analysis (CFA) of the Crack Use Relapse Scale (CURS)*
   Autores: Rosimere Pedroso, Luciana Zanatello, Luciano Guimarães, Márcia Pettenon, Veralice Gonçalves, Juliana N. Scherer, Felix H.P. Kessler, Flavio Pechansky.
   Revista: Archives of Clinical Psychiatry, 2016.

4) *NBOMe: a new dangerous drug similar to LSD*
   Autores: Lysa Remy, Nino Marchi, Juliana N. Scherer, Tais Fiorentin, Renata Limberger, Flavio Pechansky, Felix H.P. Kessler.
   Revista: Revista Brasileira de Psiquiatria, 2015.

ANEXO 4 – Artigos submetidos durante o período do Doutorado

1) *Crack-cocaine users show less family cohesion when compared to alcohol users*
   Autores: Nino Cesar Marchi, Juliana Nichterwitz Scherer, Mayra Pacheco Pachado, Luciano Santos Pinto Guimarães, Gerson Siegmund, Melina Nogueira de Castro, Silvia Halpern, Daniela Benzano, Maria Lucia Formigoni, Marcelo Cruz, Flavio Pechansky e Felix Henrique Paim Kessler.
   Revista: Revista Brasileira de Psiquiatria, 2016.

2) *Infrational Act and the inter-relationship with psychic trauma and drug abuse*
   Autores: Magda Maria Rodrigues Ferreira Valadares, Laís Rodrigues Valadares, Felipe Ornell, Vinícius Serafini Roglio, Juliana Nichterwitz Scherer, Felix Henrique Paim Kessler, Silvia Chwartzmann Halpern.
   Revista: Trends in Psychology/Temas em Psicologia, 2016.

3) *Hepatitis C: clinical and biological features related to different forms of cocaine use*
   Autores: Silvia Schuch, Juliana Nichterwitz Scherer, Felix Henrique Paim Kessler, Anne Sordi, Flavio Pechansky e Lisia von Diemen.
   Revista: Trends in Psychiatry and Psychotherapy, 2016.

4) *Simultaneous determination of cocaine/crack biomarkers in human oral fluid, urine and plasma by LC-MS method and its application in drug users*
   Autores: Taís Regina Fiorentin, Felipe Bianchini D'avila, Eloisa Comiran, Amanda Zamboni, Juliana Nichterwitz Scherer, Tanara Rosângela Vieira Sousa, Flavio Pechansky, Paulo Eduardo Mayorga Borges, Pedro Eduardo Fröehlich, Renata Pereira Limberger.
   Revista: Journal of Analytical Toxicology, 2016.

5) *Childhood trauma effects on BDNF, TBARS and NPY during crack-cocaine withdrawal*
   Autores: Anne O. Sordi, Simone Hauck, Lisia von Diemen, Felix Henrique Paim Kessler, Silvia Schuch, Juliana Nichterwitz Scherer, Flávio Kapczinski, Bianca Pfaffenseller, Carolina Gubert, BiancaWollenhaupt de Aguiar, Renata Limberger, Giovanni Abrahão Salum, Flavio Pechansky.
   Revista: Neuroscience Letters, 2016.

6) *Comparison of cocaine/crack biomarkers concentrations in oral fluid, urine and plasma simultaneously collected from drug users*
   Autores: Taís Regina Fiorentin* , Juliana Nichterwitz Scherer*, Marcelo Caetano Alexandre Marcelo, Tanara Rosângela Vieira Sousa, Flavio Pechansky, Marcos Flôres Ferrão, Renata Pereira Limberger. *As duas autoras contribuíram igualmente para o artigo.
   Revista: Therapeutic Drug Monitoring, 2016.

7) *Anxiety and depression symptoms in sexual minority ecstasy and LSD drug users*

Autores: Lysa Remy, Juliana Nichterwitz Scherer, Luciano Guimarães, Hilary L. Surratt, Steven P. Kurtz, Flavio Pechansky , Felix Kessler.
Revista: Trends in Psychiatry and Psychotherapy, 2016.

8) *Psychiatric disorders in aesthetic medicine: The importance of recognition of signs and symptoms*
Autores: Juliana Nichterwitz Scherer, Felipe Ornell, Joana C. M. Narvaez, Rafael Ceita Nunes.
Revista: Revista Brasileira de Cirurgia Plástica, 2017.

9) *Markers for severity of problems in interpersonal relationships of crack-cocaine users: interplay of frequency of substance use and comorbidities*
Autores: Mayra Pachado, Juliana Scherer, Luciano Guimarães, Flavio Pechansky, Felix Kessler, Rosa Almeida.
Revista: Substance Use and Misuse, 2017.

10) *Histórico de situação de rua como marcador de vulnerabilidades entre usuários de crack em seis capitais brasileiras*
Autores: Silvia Halpern, Juliana Scherer, Felipe Ornell, Carla Dalbosco, Sibele Faller, Vinícius Roglio, Felix Kessler, Flavio Pechansky, Lisia von Diemen.
Revista: Cadernos de Saúde Pública, 2017.

ANEXO 5 – Prêmios recebidos durante o período do Doutorado

1) 2016: Melhor trabalho na categoria América Latina – 21ª Conferência em Álcool Drogas e Trânsito (T2016), realizada pelo International Counsil in Alcohol, Drugs and Traffic Safety (ICADTS), pela apresentação do trabalho "*Oral fluid testing for cocaine: analytical evaluation of the DDS2 mobile test system*". (Primeira autora)

2) 2016: Melhor trabalho na categoria Iniciação Científica – XXVIII Jornada Sul-Rio-Grandense de Psiquiatria Dinâmica: Transformações da Psicoterapia, realizada pelo Centro de Estudos Luis Guedes (CELG), pela apresentação do trabalho *"Associação entre Trauma Precoce e Idade do Primeiro Uso de Substâncias Psicoativas"*. (Co-orientadora)

3) 2016: Trabalho destaque na XXVIII Semana de Iniciação Científica da UFRGS, pela apresentação do trabalho: *"Prevalência de envolvimento em atividades ilegais entre usuários de álcool e crack internados em unidade especializada"*. (Co-orientadora)