CLINICAL & FORENSIC

Toxicology News

ISSN 2374-9679

September 2018

An AACC/CAP Educational Newsletter for Toxicology Laboratories

Newer-Generation Antipsychotics

Therapeutic Drug Monitoring Can Provide Benefits to Patients

By Bridgit O. Crews, PhD

Antipsychotics have been in use for more than 60 years to treat acute psychosis, schizophrenia, and bipolar mania. This class of drugs includes both older, first-generation antipsychotics and newer-generation antipsychotics (NGAs). NGAs can be divided into second-generation (SGAs) and third-generation antipsychotics and include some 20 compounds, such as clozapine, olanzapine, risperidone, quetiapine, and aripiprazole.

Over the past 20 years, NGAs have largely replaced first-generation antipsychotics for management of schizophrenia and bipolar mania and are increasingly prescribed for other, off-label uses due to their lower propensity to cause adverse and debilitating neurologic side effects. This increase has occurred despite concerns regarding their high cost, safety, efficacy, and lack of evidence to support the off-label uses (1). In 2018, quetiapine, aripiprazole, and risperidone all appeared among the top 200 most-prescribed drugs in the U.S., together accounting for more than 20 million prescriptions (2). The 2015 Medical Expenditure Panel Survey ranked aripiprazole as the eighth-highest drug for total expenditures, at roughly $5 billion (3).

Recently updated consensus guidelines for therapeutic drug monitoring (TDM) in neuropsychopharmacology strongly recommend TDM for several commonly prescribed antipsychotics and recommend TDM for special indications or specific problem-solving for almost every antipsychotic (4). This article presents an overview of the most commonly prescribed NGAs and the evidence supporting TDM for them.

Source of Therapeutic Effects

Antipsychotics achieve their therapeutic effects by blocking receptors for the neurotransmitter dopamine. The first-generation drugs primarily antagonize dopamine 2 receptors, but also interact to a lesser degree with other receptors. These other interactions often produce what are referred to as "extra-pyramidal side effects," which include muscle rigidity, tremors, restlessness, and slowness of movement (5).

SGAs, on the other hand, are not only antagonists of dopamine, but of serotonin as well. In addition to blocking dopamine 2 receptors, they have an even higher affinity for 5-HT_{2A} receptors (members of the serotonin receptor family). As a result, patients prescribed SGAs generally experience a much lower incidence of debilitating extra-pyramidal side effects.

Clozapine, the original SGA, demonstrated not only a lower incidence of extra-pyramidal side effects than first-generation drugs, but also improved therapeutic efficacy in a substantial proportion of patients. This success led to clozapine becoming a gold standard for treating patients who do not respond to other treatments or who are especially suicidal or violent. Efforts to further reduce side effects resulted in the development of many more SGAs, including risperidone, olanzapine, and quetiapine.

Aripiprazole, created in the late 1990s, is categorized as a third-generation antipsychotic because it is actually a partial dopamine 2 receptor *agonist*.

NGAs currently comprise nearly the entire global antipsychotics market. Although NGAs lead to fewer debilitating neurological side effects, patients commonly experience unwanted metabolic effects, including weight gain, type 2 diabetes, and lipid dysregulation (5). Because these drugs tend to have a relatively narrow therapeutic index between the minimum effective concentration and the mini-

Continued on page 2

Inside...

Newer-Generation Antipsychotics

Continued from page 1

mum toxic concentration, TDM has an important role in keeping blood concentrations within the therapeutic ranges.

Clinical Need

Clinicians often rely on their experience, the patient's history of response to antipsychotics, and dose equivalencies to determine appropriate dosing (6). Guidelines for schizophrenia treatment suggest managing the dose according to a patient's tolerance and clinical status. Factors that complicate dosing include substantial interindividual variation in absorption and metabolism, drug–drug interactions, and potential for patient nonadherence. Plasma concentrations can be particularly helpful in determining doses for patients who do not respond or exhibit low tolerance.

Although there is little evidence to support routine TDM for all NGAs, for several of them clear evidence supports its utility for optimizing therapy. For some especially vulnerable patient populations—such as pediatric patients, elderly patients, and patients with intellectual disabilities—TDM can be particularly important to optimize response and minimize long-term adverse effects. TDM can also be useful to confirm patient adherence and rule out "pseudo-resistance," when patients do not respond because they are not taking the drug as prescribed. Clinical studies report high (74%) rates of self-discontinuation of therapy, likely due to unwanted metabolic side effects such as weight gain (7). In the case of symptom recurrence, TDM may help differentiate nonadherence from a fluctuating clinical disease course or even drug toxicity.

NGA Metabolism

Drug–drug interactions, renal or hepatic impairment, and genetic variation in drug metabolizing enzymes can also lead to interindividual variation in active drug concentrations for a given dose. Table 1 lists the major cytochrome P450 (CYP) enzymes involved in metabolism of the most commonly prescribed NGAs (8).

CYP3A4, CYP2D6, and CYP1A2 are the major enzymes involved in NGA metabolism. Polymorphic variability in CYP2D6 results in a wide range of drug-metabolizing phenotypes, from ultra-rapid metabolizers to those with poor or no metabolism. Several antidepressants that are commonly prescribed as adjunct therapies, including fluoxetine, paroxetine, and bupropion, potently inhibit CYP2D6.

Several factors can also cause inhibition and induction of CYP1A2 and CYP3A4. Fluvoxamine, verapamil, and ciprofloxin strongly inhibit CYP1A2, whereas omeprazole, cigarette smoking, and certain foods induce it. Some antimicrobials (e.g., erythromycin) and certain protease inhibitors (e.g., ritonavir) strongly inhibit CYP3A4. Antiepileptics, including carbamazepine, phenobarbital, and phenytoin, strongly induce CYP3A4. For certain NGAs, evidence supports the use of dose adjustment and TDM for patients co-prescribed inducers or inhibitors (8).

For several NGAs, plasma concentrations appear to add value over dose alone for achieving a good clinical response and minimizing side effects. As with most drugs, the timing of the blood draw relative to drug ingestion may impact the accuracy and reliability of TDM. The recommended time interval for most NGAs is 12 or 24 hours after the last dose, depending on the drug's average elimination half-life (4). The following sections summarize the recommendations and evidence for TDM of some of the most commonly prescribed NGAs (4,8,9,10).

Amisulpride

Amisulpride mainly undergoes renal clearance with minor hepatic metabolism to inactive metabolites. The renal involvement makes amisulpride a potential drug of choice for patients with liver impairment, although patients with decreased renal function, older adults, and women may experience increased plasma concentrations. Plasma amisulpride levels correlate with both nonresponse and incidence of extra-pyramidal symptoms. In most patients, dose predicts plasma levels, but diet, drug–drug interactions, and the exceptions listed above all affect this relationship. A plasma concentration between 200–320 ng/mL appears to result in the best and safest response. One study estimated a benefit for amisulpride TDM for one of every seven patients tested (11).

Aripiprazole

CYP2D6 and CYP3A4 metabolize aripiprazole. The active metabolite, 7-dehydroaripiprazole, circulates at levels around 40% of parent aripiprazole, although aripiprazole produces the main therapeutic effects. In general, the dose correlates well with plasma concentrations and clinical effectiveness, with the potential exception being ultra-rapid metabolizers. Aripiprazole monitoring may be useful to confirm adherence and investigate suspected genotypic differences, but thus far evidence does not support an extensive role for TDM in optimizing aripiprazole levels.

Clozapine

CYP1A2 primarily metabolizes clozapine to form norclozapine. CYP3A4 also metabolizes clozapine to form clozapine-*N*-oxide. Glucuronidation also plays a role in clozapine metabolism. Norclozapine has no known therapeutic effects but may lead to unwanted side effects. Age, sex, race, drug–

Table 1. Pharmacokinetic Properties of Common Newer-Generation Antipsychotics

Drug	Common trade name	Primary metabolizing enzymes (7)	Therapeutic range in ng/mL and (calculated therapeutic index) (4,7)	Proposed alert levels (ng/mL) (4)
Amisulpride	Solian	Minimal metabolism	100–320 (3.2)	640
Aripiprazole	Abilify	CYP2D6, CYP3A4	100–350 (3.5)	1,000
Clozapine	Clozaril	CYP1A2	350–600 (1.7)	1,000
Olanzapine	Zyprexa	CYP1A2, UGT1A4, CYP2D6	20–80 (4)	100
Paliperidone	Invega	Minimal metabolism	20–60 (3)	120
Quetiapine	Seroquel	CYP3A4	100–500 (5)	1,000
Risperidone	Risperdal	CYP2D6, CYP3A4	20–60*(3)	120*
Sertindole	Serdolect	CYP2D6, CYP3A4	50–100 (2)	200
Ziprasidone	Geodon	Aldehyde oxidase, CYP3A4	50–200 (4)	400

* Equates to sum concentration of risperidone plus 7-hydroxyrisperidone.

drug interactions, and even inflammation can alter clozapine levels. Elevated clozapine levels tend to increase the incidence of obsessive-compulsive symptoms, delirium, confusion, and seizures (12). Plasma levels above 1,000 ng/mL are significantly correlated to seizures. Cigarette smoking induces CYP1A2, effectively decreasing clozapine levels. Cessation of smoking has led to threefold increases in plasma concentrations of clozapine (13). CYP1A2 inhibitors such as fluvoxamine increase clozapine concentrations, and CYP3A4 inducers such as carbamazepine may decrease active drug levels.

Most studies find a greater probability for patient response at clozapine levels above 350 ng/mL. Adherence monitoring may also be useful for clozapine. Overall, guidelines strongly recommend using TDM with clozapine (4). Clozapine's history of causing life-threatening agranulocytosis necessitates neutrophil monitoring for all patients prior to and during clozapine therapy.

Olanzapine

CYP1A2, CYP3A4, and UDP-glucuronosyltransferase 1A4 inactivate a large percentage of oral olanzapine in first-pass metabolism. Some studies report substantial variation in plasma concentrations among individuals for a given dose. Drug–drug interactions and smoking potentially further modulate this relationship. Long-acting injectable olanzapine does not correlate with oral daily dosages, and guidelines recommend TDM for dose adjustments and formulary changes. Plasma concentrations of 20–40 ng/mL tend to produce the maximum benefit, with concentrations above 80 ng/mL leading to increased adverse effects. TDM may provide useful information in patients who do not respond to therapy. Overall, the guidelines strongly recommend using TDM for olanzapine (4).

Risperidone and Paliperidone

CYP2D6 metabolizes risperidone through 9-hydroxylation to form the active metabolite 9-hydroxyrisperidone. The drug's effects depend on both risperidone and 9-hydroxyripseridone concentrations, so monitoring should include both. 9-Hydroxyrisperidone primarily undergoes renal clearance with potential for accumulation in specific populations. Elevated plasma levels correlate with extra-pyramidal side effects in some studies but not others. Paliperidone is the drug version of 9-hydroxyrisperidone. Long-acting formulations include paliperidone, which can be dosed as few as four times per year, as well as depot forms for risperidone.

Guidelines recommend using TDM when switching from oral formulations to long-acting forms because intramuscular administration leads to unpredictable interindividual variation in plasma concentrations. Monitoring may also be useful to confirm adherence, but the evidence is limited.

Quetiapine

CYP3A4 and CYP2D6 extensively metabolize quetiapine to primarily inactive metabolites. Only the minor metabolites 7-hydroxyquetiapine and norquetiapine are known to be active. Renal and hepatic impairment may decrease clearance and elderly patients may be more susceptible to elevated plasma levels. Strong CYP3A4 inducers may decrease the drug's effectiveness. Limited studies support a direct relationship between plasma levels and efficacy but suggest a threshold plasma concentration exists. The therapeutic range of 100–500 ng/mL suggested by recent guidelines reflects data from a limited number of studies. Future studies may elucidate additional benefits of quetiapine TDM.

Ziprasidone

Aldehyde oxidase, CYP3A4, and possibly CYP1A2 metabolize ziprasidone. Several ziprasidone metabolites circulate, and limited knowledge exists regarding their contribution to clinical effects. CYP3A4 metabolism makes drug–drug interactions potentially relevant. Reports on the correlation between dose and plasma concentrations are mixed. Guidelines recommend TDM in specific cases to confirm adherence and to evaluate plasma levels for given doses.

Current TDM Methods

Currently, a major challenge for TDM of antipsychotics is a scarcity of monitoring methods. Other hurdles include the need for time-sensitive specimen collection and cost. Most methods are laboratory-

developed tests using liquid chromatography-tandem mass spectrometry (LC-MS/MS) or high-performance liquid chromatography. LC-MS/MS testing requires substantial capital investment and the specialized capacity to develop, validate, maintain, and troubleshoot the assays. Certified reference standards for analytes, metabolites, and their stable-labeled forms are commercially available for many of the most commonly prescribed medications. For laboratories that have LC-MS/MS capability, published multiplex methods demonstrate adequate sensitivity using a one-step protein precipitation sample preparation and relatively fast chromatography (14).

Until recently, no automated assays were available for measuring NGA concentrations. However, Saladax Biomedical recently began marketing assay kits for clozapine, quetiapine, aripiprazole, risperidone, olanzapine, and paliperidone for use on general chemistry platforms. Several of these kits have received CE Mark for sale in Europe, and the risperidone assay is currently under review by the U.S. Food and Drug Administration (15).

Conclusion

Many commonly prescribed NGAs have narrow therapeutic indices. TDM has the potential to improve the use of these drugs, especially in vulnerable populations such as elderly and pediatric patients. CYP3A4, CYP2D6, and CYP1A2 metabolize a large proportion of NGAs, making drug–drug interactions likely and genetic polymorphisms relevant.

Guidelines strongly recommend TDM for clozapine, olanzapine, and amisulpride, and recommend TDM in specific cases for all other NGAs. Indications for NGA TDM include a lack of clinical response from the target dose, confirmation of adherence, monitoring of formulary or dose changes, and investigation of patient tolerance issues and drug–drug interactions. Increased availability of monitoring methods is likely to lead to wider adoption of monitoring and increased knowledge about these therapies. As more methods become available, future research should investigate the utility of TDM to predict therapeutic response, accelerate effective treatment, decrease the incidence of adverse effects, and improve the quality of life for patients prescribed these drugs.

Learning Objectives

After reading this article, the reader should be able to describe the main differences between first-generation and newer-generation antipsychotics and discuss the primary clinical indications for obtaining plasma drug concentrations of newer-generation antipsychotics.

References

1. Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. Pharmacoepidemiol Drug Saf 2011;20:177–84.
2. ClinCalc DrugStats Database. The top 200 drugs of 2018. http://clincalc.com/DrugStats (Accessed September 2018).
3. U.S. Department of Health and Human Services. Agency for Healthcare Research and Quality. Medical Expenditure Panel survey. Prescribed drug estimates: 2015. https://meps.ahrq.gov/data_stats/summ_tables/hc/drugs/2015/hcdrugest_totexp2015.shtml (Accessed September 2018).
4. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018;51:9–62.
5. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000;157:514–20.
6. Law S, Haddad PM, Chaudhry IB, et al. Antipsychotic therapeutic drug monitoring: psychiatrists' attitudes and factors predicting likely future use. Ther Adv Psychopharmacol 2015;5:214–23.
7. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–23.
8. Spina E, Hiemke C, de Leon J. Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opin Drug Metab Toxicol 2016;12:407–22.
9. Mauri MC, Paletta S, Di Pace C, et al. Clinical pharmacokinetics of atypical antipsychotics: an update. Clin Pharmacokinet 2018 Jun 19 doi: 10.1007/s40262-018-0664-3. [Epub ahead of print].
10. Urban AE, Cubala WJ. Therapeutic drug monitoring of atypical antipsychotics. Psychiatr Pol 2017;51:1059–77.
11. Müller MJ, Regenbogen B, Härtter S, et al. Therapeutic drug monitoring for optimizing amisulpride therapy in patients with schizophrenia. J Psychiatr Res 2007;41:673–9.
12. Khan AY, Preskorn SH. Examining concentration-dependence toxicity of clozapine: role of therapeutic drug monitoring. J Psychiat Pract 2005;11:289–301.
13. Bondolfi G, Morel F, Crettol S, et al. Increased clozapine plasma concentrations and side effects induced by smoking cessation in 2 CYP1A2 genotyped patients. Ther Drug Monit 2005;27:539–43.
14. Kirchherr H, Kuhn-Velten WN. Quantitative de-

termination of forty-eight antidepressants and antipsychotics in human serum by HPLC tandem mass spectrometry: a multi-level single-sample approach. J Chromatogr B Analyt Technol Biomed Life Sci 2006;843:100–13.
15. Business Wire. 2018. Saladax signs licensing agreement with Janssen for antipsychotic drug testing patents. https://www.businesswire.com/news/home/20180626005084/en/Saladax-Signs-Licensing-Agreement-Janssen-Antipsychotic-Drug (Accessed September 2018).

Bridgit O. Crews, PhD, DABCC-TC, is assistant professor of pathology and laboratory medicine at the University of California Irvine and director of clinical chemistry and toxicology at UCI Medical Center in Orange. Email: crewsb@uci.edu.

The author has nothing to disclose.

Cannabinoid Hyperemesis Syndrome
Drug Legalization Could Lead to Increase in this Paradoxical Effect

By Grace Mahony Kroner, PhD

In June, Canada became the second nation in the world to legalize and regulate cannabis for recreational use (1). Although it remains a Class I scheduled drug at the federal level in the U.S., 30 states permit cannabis for medical use, and nine others plus Washington, D.C., allow recreational use (1). Several states will vote on measures to legalize cannabis for medical or recreational use this November.

Cannabis has been used medicinally to treat nausea and vomiting in chemotherapy patients, HIV-associated anorexia/wasting, chronic pain, convulsions, headache, depression, and glaucoma (2,3). Given its well-known antiemetic properties, healthcare providers need to be aware that in some long-time users a paradoxical effect known as cannabinoid hyperemesis syndrome (CHS) can occur.

Prompt recognition and diagnosis can avoid unnecessary and expensive medical investigations and provide relief to the patient. Recent studies have documented that CHS patients are diagnosed on average 4.1 years after developing symptoms, and visit the emergency room an average of 17.3 times in two years, resulting in a median cost of $95,023 per patient (3,4).

Diagnosis

Since CHS was first described in 2004, case reviews have clarified the typical presentation. Symptoms include cyclic episodes of abdominal pain, severe nausea, and vomiting that usually last one to two days, but can extend up to 10 (2,4). A history of long-term cannabis use, at least weekly for one to five years, is required for diagnosis. Patients reporting that their symptoms are relieved by hot baths or showers is pathognomonic for CHS (2,3). Other supportive evidence for a CHS diagnosis includes weight loss, normal bowel habits, predominance of symptoms in the morning, lack of significant gastrointestinal findings, and patient age of less than 50 years (2).

In a recent cumulative analysis, the median age at which CHS patients started using cannabis was 16, suggesting that CHS may be more likely in patients who commence cannabis use as a teenager (3). Because hot baths and showers relieve their symptoms, patients will often bathe compulsively. The mechanism by which hot showers relieve nausea and vomiting is unclear, but two main hypotheses exist. First, the hot water may correct cannabinoid-mediated disruption of the hypothalamic thermoregulatory system, thus decreasing symptoms (2). Second, the diversion of blood from the abdominal circulation to the skin due to the temperature increase may relieve symptoms (2).

Consequences of CHS can include burns from exposure to scalding water, acute renal failure, and esophageal injury (2). Lab findings may include ketonuria, electrolyte imbalances, and mild leukocytosis (4). If there is a strong suspicion of CHS, imaging studies are not recommended because they are not specific for a diagnosis of CHS (4).

An alternative cause to consider in the process of differential diagnosis is chronic vomiting syndrome (CVS), the symptoms of which are not relieved by hot showers. In addition, CVS patients generally have a personal or family history of migraines or psychological disease. However, some CHS patients may be misdiagnosed with CVS due to lack of awareness about CHS (3).

Treatment

Treatment of CHS includes intravenous hydration and supportive therapy. In some cases, treatment with an antipsychotic, such as haloperidol or olanzapine, or topical capsaicin has provided some relief from abdominal pain and nausea (2,4). Capsaicin and heat are known activators of the G-protein coupled receptor $TRPV_1$; $TRPV_1$ and cannabinoid receptor signaling interact, suggesting a more specific mechanism by which hot showers may alleviate symptoms (4). Capsaicin 0.075% applied to the abdomen and back of the arms may therefore be an inexpensive and low-risk way to provide relief (4).

In general, standard antiemetics, including antihistamines, serotonin antagonists, benzodiazepines, and dopamine antagonists, have exhibited mixed efficacy (4). Caution must be used in treating patients with opiates to relieve abdominal pain because opiates can themselves cause nausea and have dangerous addictive properties; therefore, if a diagnosis of CHS is clear, opiates are not advised (4).

Abstinence from cannabis is the only true cure, and elimination of symptoms upon stopping cannabis confirms a diagnosis of CHS (2,3). Patient education is therefore critical, and patients should be informed that it may take up to 10 days for symptoms to disappear after stopping use of cannabis (4).

Source of the Paradox

How can a drug known for antiemetic effects also cause extreme nausea and vomiting? The mechanism is unclear, but our understanding of how cannabis produces antiemetic effects is an important place to start in understanding this disease. The cannabis plant contains hundreds of compounds that contribute to its medical and psychoactive effects; the most critical mediator is Δ^9-tetrahydrocannabinol (Δ^9-THC) (2). It and other cannabinoids are agonists of the CB_1 and CB_2 cannabinoid receptors.

The endogenous endocannabinoid system influences many processes, including gastrointestinal motility, appetite, vomiting, inflammation, sleep, pain, and mood (3). CB_2 receptors exist on immune cells; their downstream effects are unclear (2). Activation of CB_1 in the central nervous system and enteric nerves is thought to be the main mechanism by which cannabinoids exert their antiemetic effect because activation of these receptors inhibits emetic neurotransmitter signaling (2). However, the physiological control of nausea and vomiting is complex, so there are likely other influences on cannabis' antiemetic effect.

Strong evidence for mechanisms of cannabis pathophysiology is lacking, but several possibilities exist. Cannabinoids are lipophilic and thus stored in fat tissues (2). Their buildup in fat or variant metabolism may contribute to an emetic effect. Individual differences in CYP P450 genetic profiles may predispose some people to CHS, which would explain why many long-term cannabis users do not experience CHS (2).

In animal models, administration of Δ^9-THC always suppressed vomiting, but high concentrations of a different cannabinoid, cannabidiol, increased vomiting (5). Additionally, researchers have proposed that downregulation or desensitization of the CB_1 receptors due to excessive exposure to their cannabinoid ligands may produce an emetic effect by disrupting the endogenous cannabinoid system (4). Some studies have suggested that a cannabis-induced decrease in gastric motility might cause hyperemesis, but gastrointestinal motility is not always altered in CHS patients (3). Although smoking of cannabis, e-cigarettes, waxes, oils, and synthetic cannabinoids is known to cause CHS, eating cannabis has led to no documented cases (4).

Prompt Diagnosis

Prompt recognition that episodic vomiting in patients with a long history of cannabis consumption may be due to CHS, especially if symptoms are relieved by hot bathing, is critical to avoid unnecessary medical testing and a delay in treatment. Since cannabis legalization in Colorado, there has been an increase in patient visits to the emergency room for cyclic vomiting (4). In addition, among 155 self-reported frequent cannabis users admitted to the emergency room for reasons unrelated to nausea or vomiting, 33% met guidelines for CHS diagnosis, namely that they had instances of nausea and vomiting that were relieved by hot showers (6). If this number is extrapolated to the estimated number of cannabis users nationwide, some 2 to 3 million people may have CHS symptoms (6). Given that cannabis legalization and consumption are continuing to increase, the number of cases of CHS is likely to grow nationwide.

Learning Objectives

After reading this article, the reader will be able to recognize the symptoms of cannabinoid hyperemesis syndrome and describe the possible mechanisms that cause it.

References

1. Sapra B. Canada becomes second nation in the world to legalize marijuana. CNN, June 20, 2018. https://www.cnn.com/2018/06/20/health/canada-legalizes-marijuana/index.html (Accessed August 2018).
2. Richards JR. Cannabinoid hyperemesis syndrome: pathophysiology and treatment in the emergency department. J Emerg Med 2018; 54:354–63.
3. Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment: a systematic review. J Med Toxicol 2017;13:71–87.
4. Lapoint J, Meyer S, Yu CK, et al. Cannabinoid hyperemesis syndrome: public health implications and a novel model treatment guideline. West J Emerg Med 2018;19:380–6.
5. Parker LA, Kwiatkowska M, Burton P, et al. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). Psychopharmacology (Berl) 2004;171:156–61.
6. Habboushe J, Rubin A, Liu H, et al. The prevalence of cannabinoid hyperemesis syndrome among regular marijuana smokers in an urban public hospital. Basic Clin Pharmacol Toxicol 2018;122:660–2.

Grace Mahony Kroner, PhD, is a clinical chemistry fellow at the University of Utah/ARUP Laboratories in Salt Lake City. Email: grace.kroner@aruplab.com.

The author has nothing to disclose.

Hair Drug Testing in Brazil

Testing with Wide Time Window Now Mandatory for Professional Drivers

By Jennifer Collins

The World Health Organization (WHO) *Global Status Report on Road Safety 2015* reported that more than 1.2 million people die each year in traffic accidents, ranking accidents among the leading causes of death globally and a significant public health issue (1). Brazil reported more than 40,000 road traffic fatalities in 2013 or about 23.4 per 100,000 population. This compares with 13.6 per 100,000 in Argentina, 12.4 in Chile, and 10.6 in the United States in the same data set. The Brazilian rate had increased from 19.5 fatalities/100,000 in 2009.

The report includes a number of recommendations to improve traffic safety and reduce fatalities, including improving automobile safety standards, reducing speed limits, increasing motorcycle helmet use, and reducing drug- and alcohol-impaired driving. The report points out that, compared with alcohol-related traffic incidents, much less is known about drugged driving and the effectiveness of policies to deter it.

Current policies aimed at countering driving under the influence of drugs tend to mirror those directed at driving under the influence of alcohol—a combination of laws, enforcement, and prevention—but addressing drug use is more complex. This complexity stems from the variety of prescribed and illicit substances taken, more technical methods required for measurement, and the lack of scientific evidence linking drug levels, impairment, and crash risk (2).

For these reasons, and backed by evolving evidence, countries are enacting legislation that includes setting tolerance limits for some drugs, training police to recognize drugged driving, and introducing random roadside screening for drugs.

Drug Testing of Professional Drivers

In March 2016, the Brazilian Transportation Department and National Traffic Council implemented drug testing of all professional drivers who apply for or renew a commercial driver's license using a method with an extended detection window of at least 90 days (3). Scalp hair, other hair, or nail samples may be used to meet the requirement, although hair is the predominant matrix. In addition to the WHO report, the regulation is also a response to reports that the use of not only alcohol but also illicit drugs is a significant problem among Brazilian professional drivers (4,5,6).

A survey found that 58% of Brazilian truck drivers reported use of amphetamines in their lifetime, with 29% reporting use within a year and 14% within the previous month (7). Many drivers reported using amphetamines to overcome fatigue while driving for extended periods. A study that analyzed blood samples from 230 traffic accidents found illicit drugs or alcohol in 45% of the samples, with cocaine the most frequently detected substance other than alcohol (8). Of note, the cost of the testing is borne by individual drivers and may be as much as U.S. $100.

Initial estimates were that as many as 2.4 million hair tests would be performed annually from a professional driver population of 13 million. Because of the large volume, laboratory capacity within Brazil is insufficient, and laboratories in the U.S. such as Quest Diagnostics, Psychemedics, and Omega Laboratories have provided services.

The test panel screens drivers for amphetamines/methamphetamines, cocaine and metabolites, marijuana metabolite, opiates, and phencyclidine.

Positive Rates

In the first year (March 2016 to March 2017), about 56,000 tests were performed by Chromatox Laboratories in Brazil and results were presented at the Society of Hair Testing annual meeting in June 2017 (9). About 60% of the samples were body hair rather than head hair. Evidently, because the legislation does not specify which hair should be collected, most drivers choose to provide body hair.

Drugs were detected in 1,684 samples for a positive rate of 3%. The most prevalent finding was cocaine (approximately 2.4% prevalence), followed by cannabinoids, amphetamines, and opioids. The high prevalence of cocaine was similar to that observed by Quest Diagnostics, which found that about 70% of positive tests were due to cocaine (10).

The positive rates reported by Chromatox may have been affected by the large percentage of body hair in the sampling. Because body hair potentially represents a longer than 90-day detection window, the positive rate may be higher than if only head hair were used.

The Brazilian minister for transport presented combined data from all the labs at the same meeting (11). Almost 1.4 million drivers were tested in the first year, with a positive rate of 1.5%.

Impact of the Program

These low positive rates are somewhat surprising given that hair analysis provides a wide detection window and previous studies using oral fluid or urine samples collected randomly from professional drivers on Brazilian roads demonstrated positive rates of 5.2% to 9.3% (5,6,12).

The reasons for the discrepancy are not clear; however, the government believes that the hair-testing requirement coupled with the fact that the drivers bear the cost of the tests has been a deterrent

to drug use. In addition, a significant number of drivers reportedly opted not to renew their professional licenses rather than submit to testing.

At a meeting at the United Nations in April, Brazilian policymakers presented data showing a 38% drop in the number of fatal accidents involving trucks on Brazilian federal highways since the program was initiated (13). Whether this drop can be attributed to the new hair-testing requirement is disputed by some who argue that most research demonstrates significant reductions in traffic accidents do not occur until several years after adoption of evidence-based programs (14).

Hair Testing in the U.S.?

This initiative is being closely monitored by proponents of hair testing in the transportation industry in the U.S. Some stakeholders in the trucking industry have been advocating for the addition of hair as an alternative matrix in the federal workplace drug-testing program, and some companies have implemented pre-employment hair testing in addition to the federally required urine drug test (15).

Hair was one of the alternate matrices proposed for inclusion in the Mandatory Guidelines for Federal Workplace Drug Testing Programs in 2004 along with oral fluid, sweat, and point-of-collection urine tests (16). No alternative matrices ended up in the final version implemented in October 2010, but the Department of Health and Human Services (DHHS) and the Substance Abuse and Mental Health Services Administration Drug Testing Advisory Board have continued to work toward establishing guidelines for their use (17).

Signed into law in December 2015, the Fixing America's Surface Transportation Act includes a provision for use of hair in transportation workplace drug-testing programs once DHHS establishes scientific and technical guidelines (18). The law directs the agency to issue guidelines within one year, and that effort is currently in progress.

Learning Objectives

After reading this article, the reader will be able to describe the drug-testing program recently implemented for professional drivers in Brazil and list some of the most frequently encountered drugs.

References

1. Global status report on road safety 2015. World Health Organization, Geneva, Switzerland. http://www.who.int/violence_injury_prevention/road_safety_status/2015/en/ (Accessed August 2018).
2. Reisfield GM, Goldberger BA, Gold MS, et al. The mirage of impairing drug concentration thresholds: a rationale for zero tolerance per se driving under the influence of drugs laws. J Anal Toxicol 2012;36:353–6.
3. Brazilian Federal Law No. 13.103. http://www.planalto.gov.br/ccivil_03/_Ato2015-2018/2015/Lei/L13103.htm (Accessed August 2018).
4. Leyton V, Sinagawa DM, Oliveira KCBG, et al. Amphetamine, cocaine and cannabinoids use among truck drivers on the roads in the state of Sao Paulo, Brazil. Forensic Sci Int. 2012;215:25–7.
5. Yonamine M, Sanches LR, Paranhos BA, et al. Detecting alcohol and illicit drugs in oral fluid samples collected from truck drivers in the state of Sao Paulo, Brazil. Traffic Inj Prev 2013;14:127–31.
6. Leyton V, Andreuccetti G, de Almeda RM, et al. Hair drug testing in the new Brazilian regulation to obtain professional driver's licence: no parallel to any other law enforcement in the world. Addiction 2015;110:1207–8.
7. de Oliveira LG, de Souza LM, Barroso LP, et.al. Occupational conditions and the risk of the use of amphetamines by truck drivers. Rev Saude Publica 2015;49:61.
8. Pelicao FS, Peres MD, Pissinate JF, et al. Predominance of alcohol and illicit drugs among traffic accidents fatalities in an urban area of Brazil. Traffic Inj. Prev 2016;17:663–7.
9. Andraus M, Tsanaclis L, Salvadori M, et al. Hair analysis in driving license issue and renewal in Brazil. Presentation at the 22nd scientific meeting of the Society of Hair Testing, Cardiff, England, June 12–14 2017. https://blog.cansfordlabs.co.uk/the-drug-and-alcohol-testing-blog/what-do-you-find-when-you-test-57000-professional-drivers-for-drugs (Accessed August 2018).
10. Jupe N. Why Brazil chose hair drug testing. DATIA focus, Spring 2018. Drug and Alcohol Testing Industry Association, Washington, D.C. https://content.yudu.com/libraryHtml/A4395w/DATIAFocusSpring2018/reader.html?page=40&origin=reader (Accessed August 2018).
11. Garonce F. The world's largest drug-control program for drivers uses hair testing. Presentation at the 22nd scientific meeting of the Society of Hair Testing, Cardiff, England, June 12–14, 2017. https://prezi.com/qyrn1pcg0wts/soht-cardiffuk-2017/ (Accessed September 2018).
12. Peixe TS, de Almeida RM, Girotto E, et al. Use of illicit drugs by truck drivers arriving at Paranagua port terminal, Brazil. Traffic Inj Prev 2014;15:673–7.
13. The use of technology to promote road safety: the Brazilian experience. International Congress at the United Nations, April 27, 2018, New York,

N.Y. http://www.itts.org.br/unitednations/file/CONGRESS%20RELEASE.pdf (Accessed August 2018).
14. Leyton V, Andreuccetti G, Souza Meira Junior AE, et al. Hair testing: an ineffective DUI strategy in Brazil. Addiction 2017;113:374–6.
15. Della Rosa, J. Trucking industry pushes feds for hair testing guidelines for drug testing. Talk Business & Politics, April 26, 2017. Fort Smith, Ark. https://talkbusiness.net/2017/04/trucking-industry-pushes-feds-for-hair-testing-guidelines-for-drug-testing/ (Accessed August 2018).
16. Proposed revisions to the mandatory guidelines for federal workplace drug testing programs, 69 FR 19673, April 13, 2004. Federal Register. https://www.gpo.gov/fdsys/pkg/FR-2004-04-13/pdf/04-7984.pdf (Accessed August 2018).
17. Mandatory guidelines for federal workplace drug testing programs. 73 FR 71858, Nov. 25, 2008. Federal Register. https://www.gpo.gov/fdsys/pkg/FR-2008-11-25/pdf/E8-26726.pdf (Accessed August 2018).
18. Fixing America's Surface Transportation Act, Public Law 114-94. https://www.gpo.gov/fdsys/pkg/PLAW-114publ94/html/PLAW-114publ94.htm (Accessed August 2018).

Jennifer Collins, PhD, F-ABFT, is the director of the forensic laboratory at MEDTOX Laboratories in St. Paul, Minn.; a member of the Clinical & Forensic Toxicology News *editorial advisory board; and a member of the Substance Abuse and Mental Health Services Administration Drug Testing Advisory Board. Email: jcollins@medtox.com.*

The author has nothing to disclose.

CFTN Readers Are Eligible To Receive ACCENT Credit

Readers of *Clinical & Forensic Toxicology News* are eligible to receive 4.0 ACCENT® credit hours per year of continuing education, at a rate of one credit per quarterly issue.

ACCENT credit allows you to document your continuing education to meet requirements for licensure or certification. ACCENT credit is recognized by a wide variety of organizations, including:

- American Association of Bioanalysts
- American Board of Clinical Chemistry
- American Society of Microbiology
- American Society for Clinical Laboratory Science
- American Society for Clinical Pathology
- American Medical Technologists
- Association of Clinical Scientists
- International Federation of Clinical Chemistry
- National Registry in Clinical Chemistry
- States of California, Florida, Louisiana, Montana, Nevada, North Dakota, Rhode Island, and West Virginia

How to Get Credit

It's easy to obtain credit. After reading this issue's articles, simply access the online evaluation form and print your continuing education certificate: http://apps.aacc.org/applications/apps2/CE/intro.aspx?actNum=44111655.

Clinical & Forensic Toxicology News provides practical and timely information on the clinical, forensic, technical, and regulatory issues faced by toxicology laboratories. Each issue includes articles authored by experts.

Clinical & Forensic Toxicology News is an educational service of the Forensic Urine Drug Testing (FUDT) Accreditation Program. Cosponsored by the American Association for Clinical Chemistry and the College of American Pathologists, the program includes three components: FUDT accreditation, the FUDT proficiency testing survey, and this newsletter. The accreditation program is the responsibility of CAP. The surveys are sponsored jointly by AACC and CAP. The digital newsletter is published quarterly by AACC, 900 Seventh St., N.W., Suite 400, Washington, DC 20001, (800) 892-1400 or (202) 857-0717. Email: custserv@aacc.org.

Clinical & Forensic Toxicology News does not accept advertising and is supported solely by its readers. The 2017 annual subscription price is $67, $47 for AACC members.

Opinions expressed are those of the authors and do not represent the position of AACC or CAP.