CLINICAL & FORENSIC

Toxicology News

ISSN 2326-3253

March 2021

An AACC/CAP Educational Newsletter for Toxicology Laboratories

Update on Psychedelic-Assisted Therapies for Mental Health

By Benjamin Lewis, MD, and Kevin Byrne, MD

After a prolonged political and social moratorium on the study of psychedelic drugs, we are currently witnessing a renaissance in psychedelic research. Recent work in psychiatry—though admittedly involving mostly small studies and limited control groups—has shown remarkably promising, large-magnitude therapeutic effects, even after single drug administrations. Targets with such evidence include: existential distress or anxiety in cancer patients (1, 2), smoking cessation (3, 4), treatment-resistant major depressive disorder (MDD) (5, 6), alcohol use disorder (AUD) (7), and obsessive-compulsive disorder (OCD) (8). As of this writing, there are currently 61 psilocybin clinical trials in various stages registered with the Federal Drug Administration (FDA) addressing a range of psychiatric diagnoses including MDD, OCD, anorexia nervosa, AUD, and migraine headaches (9). The FDA has granted 'Breakthrough Therapy' designation for both 3,4-methyl-enedioxy-methamphetamine (MDMA, also known as "ecstasy" or "molly") and psilocybin (the active ingredient in so-called "magic mushrooms"), in conjunction with psychotherapy, for treatment of post-traumatic stress disorder (PTSD) and treatment-resistant depression, respectively, signaling that they may be available for clinical use within the next few years.

Background

The term 'psychedelic'—coined by Humphrey Osmond in 1956—translates from the Greek *psyche* and *delos* to 'mind-manifesting,' which denotes the particular alterations in conscious experience occasioned by these compounds. The study of psychedelics can be divided into three relatively distinct historical waves. The first wave refers to the study and use of classic psychedelics, primarily in spiritual practices, by indigenous cultures dating back millennia (and ongoing today). The second wave can be traced back to the 1938 synthesis of lysergic acid diethylamide (LSD) by Albert Hoffman, and involved a burst of research in the 1950s and 1960s. This research was halted by a cultural, political, and legal backlash against recreational use of psychedelics (particularly LSD). The resulting research hiatus lasted until the third wave of psychedelic research, which began with a trickle of research in the mid-1990s, and has crescendoed into the explosion of research ongoing today.

The psychedelic landscape is now growing and changing rapidly. Psilocybin- and MDMA-assisted psychotherapy appears poised for FDA approval. There are a growing number of dedicated research institutions investigating psychedelic science, including the Johns Hopkins Center for Psychedelic and Consciousness Research, the Imperial College Centre for Psychedelic Research, and the University of California Berkeley Center for the Science of Psychedelics. Recent years have seen decriminalization measures for plant- and fungi-based psychedelic compounds in Denver, Oakland, Ann Arbor, and Santa Cruz, and most recently Washington D.C. This past November, Oregon passed Measure 109 to legalize psilocybin-assisted psychotherapy. There are now several pharmaceutical companies, including Usona and Compass Pathways, pursuing large-scale production of psilocybin for clinical research. Now there are several companies dedicated to psychedelics that have gone public with associated financial speculation estimating that the industry is currently worth up to $100 billion (10).

Continued on page 2

Inside...

Increasing Trends of Drug Abuse and Overdose Deaths Driven by a Global Pandemic 6

2020 AACC Annual Scientific Meeting: Virtual Scientific Events Showcase Toxicology through a Multi-Disciplinary Lens 8

ACCENT Credit 9

Update on Psychedelic-Assisted Therapies for Mental Health

Continued from page 1

This review will focus on the so-called 'classic' psychedelics, compounds understood to have pharmacological action via agonism or partial agonism at the serotonin-2A (5-HT2A) receptor. Many compounds with this pharmacological property have not been studied in any depth, however the informal term 'classic psychedelic' typically refers to the most common and well-known of this class, including: plant-derived indolamines [N,N-dimethyltryptamine (DMT), 5-methyoxy-N,N-dimethyltryptamine (5-MeO-DMT), and psilocybin], phenylalkylamines [mescaline and synthetic amphetamines such as 2,5-dimethoxy-4-bromophenethylamine (2C-B)], and semi-synthetic ergolines such as lysergic acid diethylamide (LSD). MDMA, or 3,4-methylenedioxymethamphetamine, is a phenethylamine analogue which acts as a general serotonin releasing agent rather than a serotonin-2A agonist, and therefore is considered by many to belong in a distinct category from classic psychedelics. This schema leaves out a range of other compounds that are understood as 'psychedelics' or having overlapping effects in subjective alterations in consciousness, such as ketamine, cannabinoids, entactogens (such as MDMA), salvinorin A (the latter being the active ingredient in the ceremonial psychedelic plant Salvia Divinorum). MDMA is currently being explored in phase III trials for PTSD with anticipated FDA approval by 2022. It will not be discussed in depth here.

This review will highlight the most significant recent clinical trials and discuss several interesting aspects of this emerging field. Discussion of these compounds requires some space devoted to a review of risks.

Risks/Safety

Psychedelic drugs have a long history of portrayal in the media as extremely dangerous drugs. This is reflected in (and possibly partially responsible for) the classification of these agents as Schedule 1 controlled substances (as defined by the United States Controlled Substances Act), which are defined as drugs with no currently accepted medical use and high potential for abuse. While there are certainly psychological risks associated with psychedelic use, particularly in uncontrolled settings, the classic psychedelics are physiologically very safe compared to other medications (11). Classic psychedelics (whose pharmacological action is via agonism or partial agonism at the 5HT-2A receptor) are unlikely to lead to addiction or dependence and are not considered to be reinforcing due to the absence of direct engagement of the brain's dopaminergic system (12). There have been no reported overdose deaths after ingestion of typical doses of LSD, psilocybin, or mescaline. Similarly, there are several case reports of individuals who have inadvertently consumed massive doses of LSD and survived without long-term medical sequelae (13). Krebs and Johnansen published a population-based study using data drawn from the National Survey on Drug Use and Health (NSDUH) from 2001–2004 examining possible associations between lifetime use of psychedelics and mental health outcomes in the U.S. population. There were no significant associations identified between lifetime use of any psychedelic, past year use of a psychedelic, and an increased rate of any mental health outcome. Rather, lifetime psychedelic use was associated with a lower rate of (self-identified) mental health problems (14).

Because psychedelics can cause such profound alterations in conscious experience there are associated psychological and behavioral risks which have led to suggested clinical practice procedures designed to maximize safety and potential benefit. Johnson et al. emphasize the need for structured use within a safe and comfortable physical environment, the presence of 2 trained guides throughout the duration of the session (8 h for psilocybin), careful subject preparation prior to the drug session with robust education and discussion as to the range of possible experiences, and the availability of an licensed medical doctor in the unlikely event of a medical complication (15). There is also an emphasis in these guidelines on subsequent integration of the experience in sessions following the active drug session, as well as robust screening of study participants.

Modern Trials

With the exception of a series of experiments with intravenous DMT on normal adult volunteers at the University of New Mexico by Rick Strassman, MD in the mid-1990s, the third wave of psychedelic research started in 2006 at Johns Hopkins. A team there performed a double-blind study which demonstrated that psilocybin, when administered under supportive conditions, can occasion experiences similar to other spontaneously occurring mystical experiences with enduring personal meaning and significance (16). This trial, and subsequent analyses, compared psilocybin to an active comparison compound (methylphenidate) in 36 hallucinogen-naive adults and demonstrated that the degree of achieved mystical experience during the psilocybin sessions (2–3 sessions per participant) predicted downstream increased life satisfaction and well-being (assessed at 14 months). Of the study participants administered psilocybin at a dose of 30 mg/70 kg 58% met the criteria for having had a "complete" mystical experience, and 67% rated the psilocybin-occasioned experience as being

among the five most personally meaningful and the five most spiritually significant experiences of their lives (17). This study was a direct extension of the 'Good Friday' experiment carried out at Boston University's Marsh Chapel in 1962 by Walter Pahnke, which administered either 30 mg psilocybin or 200 mg of nicotinic acid as an active placebo in a double blind fashion to divinity students with a goal of comparing experiences induced by psilocybin to naturally occurring mystical or spiritual experiences. A subsequent study by the Johns Hopkins group used a similar protocol with 18 volunteers to examine dose effects for psilocybin ranging from 0–30 mg/70 kg to show that there is a dose-response effect to the ability of psilocybin to occasion mystical experiences. Similarly, long-term effects on positive mood ratings and prosocial effects also increased directly as a function of dose and were sustained at 14 months (18).

Of note, the majority of modern clinical trials utilize psilocybin, the active ingredient in "magic mushrooms." While there are some practical reasons for focusing on psilocybin (drug effect duration is approximately 8 h vs 12–18 h for LSD), another primary explanation for this is that psilocybin does not carry the same cultural baggage as LSD, which has been associated with the countercultural transgressions of the 1960s and media-amplified perceptions surrounding risks. In the 1950s and 1960s, prior to rescheduling of all classic psychedelics under the Nixon administration, there were thousands of human subjects administered LSD (as well as mescaline) in various studies across a range of diagnoses and hundreds of papers published (19). DMT has recently been studied in human subjects in relation to electroencephalographic (EEG) and magnetoencephalographic (MEG) changes (20). Its very short duration of action (15–30 min) suggests possible pragmatic utility in clinical settings; however, to date there are no clinical trials completed investigating it as a single therapeutic agent (outside of studies of ayahuasca, the traditional South American DMT-containing beverage briefly discussed below).

Depression and Anxiety Associated with Terminal Illness

Roland Griffiths' group at Johns Hopkins has gone on to examine the effects of a single high dose of psilocybin on depressive and anxiety symptoms for patients with a life-threatening cancer diagnosis (21). This 2015 study included 51 patients with life-threatening cancer diagnoses who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for a mood or anxiety disorder related to their cancer diagnosis. The study utilized a double-blind cross-over design comparing high dose psilocybin (22 or 30 mg/kg) to very low dose (1 or 3 mg/70 kg) and demonstrated significant improvement at 5 weeks (roughly 60–70% remission of symptoms) which appeared to be maintained at 6 month follow-up. This is a remarkable result for a population that has demonstrated limited response to standard antidepressant treatments. Similar results for this population have been demonstrated by Grob et al. and Ross et al., with a convergent finding among these studies that magnitude of therapeutic response is predicted by the degree of complete mystical experience reported in the psilocybin sessions (1, 2, 18). None of these 3 trials showed any serious adverse effects. Limitations of these studies include small sample sizes, selection bias (approximately half of the study subjects had prior exposure to psychedelics, suggesting the possibility of expectancy effects), and difficulties with blinding of placebo control (a significant challenge in studying psychedelics given associated profound alterations in consciousness that are difficult to otherwise replicate with active placebos such as niacin, which is used in some studies). Despite these limitations these studies have been remarkably promising in identifying therapeutic options for a common and largely treatment-refractory set of conditions associated with terminal cancer.

Treatment-Resistant Depression/Major Depressive Disorder

The Imperial College group led by Robin Carhart-Harris, PhD has completed an open-label, non-controlled trial investigating the benefits of psilocybin for 12 patients with treatment-resistant depression. Study subjects were in an active depressive phase and met criteria for treatment resistance in virtue of no improvement in symptoms following 2 adequate trials (in terms of dose and duration) of 2 antidepressants from separate classes. Following 2 psilocybin sessions, 67% of patients met the criteria for full remission and 58% continued to meet the criteria for treatment response at 3 month follow-up. There were no serious adverse events reported (22). The Imperial College group is finishing up a double-blind placebo-controlled trial comparing psilocybin to 6-weeks of escitalopram for major depressive disorder with anticipated publication early in 2021.

The group at Johns Hopkins recently published a randomized, waiting list-controlled clinical trial investigating 2 psilocybin sessions (session 1: 20 mg/70 kg, and session 2: 30 mg/70 kg) for adults (N = 27) with a diagnosis of major depressive disorder. At the 4 week follow-up, 71% of participants had a clinically significant response (≥50% reduction in GRID Hamilton Rating Scale for Depression (GRID-HAMD score) and 54% were in full remission (>7 GRID-HAMD score) (23).

There has been one NIH-registered clinical trial on ayahuasca for patients with treatment-

resistant depression. Ayahuasca is a traditional beverage used in spiritual ceremonies by indigenous groups in the Amazon Basin. It is prepared using (at least) 2 plants, one of which contains the classic psychedelic substance DMT and another which contains reversible monoamine oxidase inhibitors that prevent gut metabolism of DMT and facilitate oral bioavailability. A group from Brazil published a double-blind, randomized placebo-controlled trial on 29 patients with treatment resistant depression that was designed to assess the possible 'rapid-acting' antidepressant properties of ayahuasca (24). Participants received a single dose of ayahuasca or placebo with tracking of depression severity using the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D) on days 1, 2, and 7. At day 7, 64% of subjects in the experimental group vs 27% in the placebo group demonstrated a reduction of ≥50% from baseline. Limitations in this study included a significant placebo effect (46% response in placebo group on day 1). It was also notable that there was a high rate of personality disorder diagnoses (cluster B) in the study group (76%).

There are currently multi-site trials underway investigating psilocybin for major depressive disorder and anticipated possible FDA approval for treatment-resistant depression within the next 5 years.

Smoking Cessation

Matthew Johnson's group at Johns Hopkins group published an open-label pilot study looking at psilocybin-assisted therapy for patients (N = 15) with tobacco-use disorder. This study involved 3 psilocybin sessions within a 15-week cognitive-behavioral therapy smoking cessation program for patients with an average of 30-pack year smoking history. At 6-month follow-up 80% of participants demonstrated biologically-confirmed abstinence and 67% continued to demonstrate biologically-confirmed abstinence at 12 months (3, 4). This represents a massive improvement over standard evidence-based therapies which demonstrate an approximate 30% success rate. As with other trials, there were no reported significant adverse events.

Discussion

There are several things worth noting about this emerging field. First, recent clinical trials are designed as a form of assisted or catalyzed psychotherapeutic process: drug administration is incorporated within a robust framework of preparatory meetings and subsequent integration sessions. The psychotherapeutic work during the session itself (an 8 h session with 2 therapists present for the duration) is supportive and non-directive: participants utilize eye-shades during the session and listen to a selected music track and are instructed generally to 'go inward' rather than direct attention externally.

Secondly, it is of interest that psychedelic-assisted psychotherapy appears to be potentially effective across a wide range of psychopathology, from substance use disorders to mood disorders, to existential distress associated with terminal illness. This is perhaps less surprising than it might initially appear given limitations in current psychiatric classification in terms of biological causation and the fact that many forms of mental illness seem to have underlying common neurobiological features. While beyond the scope of this article, there is emerging work by Robin Carhart-Harris and others that characterizes psychedelic therapeutic effect in terms of alterations in default mode network (DMN) functional connectivity. The DMN involves a set of higher-level association cortices and has been implicated in a wide range of psychiatric conditions.

Thirdly, a current principle of psychedelic-assisted psychotherapy is that the occurrence of a profound transformative experience is essential for the treatment's efficacy (25). Of course, this remains an empirical question that bears future study (there are currently efforts underway to develop psychedelic analogues that do not produce alterations in consciousness). And yet a recurring feature of these described studies is the fact that certain experiential qualities of psychedelic states are the most reliable marker, as well as predictor for the magnitude of therapeutic change: that is, specific aspects to the altered state of consciousness induced by psychedelics that can be reliably tracked (via a range of rating scales and self-reports) appear critical to what is often termed a 'quantum change,' or a dramatic shift in perspective that leads to behavioral and emotional change. This stands in marked contrast to standard psychotropic interventions where the attributed causal levers for therapeutic change are typically understood at sub-personal levels and do not necessarily rely directly on specific alterations in consciousness: "the idea that a single discrete experience can result in lasting beneficial effects in an individual's attitudes of behavior is highly unusual, if not unprecedented within the modern biomedical paradigm" (27). This is a significant shift from prescription of, say, selective serotonin reuptake inhibitors (SSRIs) for major depressive disorder. These powerful psychological experiences can be phenomenologically indistinguishable from spontaneously arising 'mystical' or 'spiritual' experiences (17, 26). This proposed mechanism—i.e., the altered state of consciousness (ASC) being the primary mechanism for therapeutic effect—raises a host of questions regarding the relationship between mental and physical phenomena that have a long history in both philosophy of mind and in philosophy of psychiatry.

The emerging science of psychedelic medicine will have major implications for fields including psychiatry, psychology, neuroscience, and philosophy. While these medicines hold promise for difficult to treat mental health conditions there is still much we do not know about these compounds, how they work, and the optimal ways to maximize their therapeutic impact.

Learning Objectives

After reading this article, the reader will be able to summarize important current research with classic psychedelics for psychiatric conditions. The reader will be able to describe challenges that this emerging field faces.

References

1. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016;30:1165–80.
2. Grob CS, Bossis AP, Griffiths RR. Use of the classic hallucinogen psilocybin for treatment of existential distress associated with cancer. In: Carr B, Steel J, editors. Psychological Aspects of Cancer. Boston, MA: Springer. 2013. p. 291–308.
3. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 2014;28:983–92.
4. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse 2017;43:55–60.
5. Osório FD, Sanches RF, Macedo LR, Dos Santos RG, Maia-de-Oliveira JP, Wichert-Ana L, et al. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Braz J Psychiatry 2015;37:13–20.
6. Carhart-Harris RL, Bolstridge M, Day CM, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl) 2018;235:399–408.
7. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 2015;29:289–99.
8. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 2006;67:1735–40.
9. National Institutes of Health. U.S. National Library of Medicine. Clinicaltrials.gov. Accessed January 11th, 2021. https://clinicaltrials.gov/ct2/results?cond=&term=psilocybin&cntry=&state=&city=&dist=
10. Gonsalves T, McFarland S. Around the Corner: Emerging companies and industries to watch. 2020;1–35. https://www.docdroid.net/cdRrpWm/psychedelic-investing-pdf#page=22
11. Nichols DE. Psychedelics. Pharmacol Rev 2016;68:264–355.
12. O'Brien CP. Drug addiction and drug abuse. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York (NY): McGraw-Hill. 2001. p. 574–639.
13. Haden M, Woods B. LSD overdoses: three case reports. J Stud Alcohol Drugs 2020;81:115–8.
14. Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. PloS One 2013;8:e63972.
15. Johnson MW, Richards WA, Griffiths RR. Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008;22:603–20.
16. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 2006;187:268–83.
17. Griffiths RR, Richards WA, Johnson MW, McCann UD, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol 2008;22:621–32.
18. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology 2011;218:649–65.
19. The Medical History of Psychedelic Drugs. Multidisciplinary Association for Psychedelic Studies 2007. Available at https://maps.org/images/pdf/history_of_psychedelics.pdf
20. Timmermann C, Roseman L, Schartner M, Milliere R, Williams LT, Erritzoe D, et al. Neural correlates of the DMT experience assessed with multivariate EEG. Sci Rep 2019;9:16324.
21. Griffiths R. Psilocybin, mystical-type experiences, and the treatment of symptoms of anxiety and depression in patients with a life-threatening cancer diagnosis. In: *Presentation at the 168th Annual Meeting of the American Psychiatric Association, Abstract* 1162. May 16–20, 2015. Toronto, Canada.
22. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016;3:619–27.
23. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 2020;Nov 4:e203285.
24. Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med 2019;49:655–63.
25. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 2018;8:974.
26. Pahnke WN. An analysis of the relationship between psychedelic drugs and the mystical consciousness. Cambridge, United States: Harvard University, 1966;1–342 pp.
27. Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 2014;7:157–64.

Benjamin Lewis, MD, is an assistant professor of psychiatry at the Huntsman Mental Health Institute in Salt Lake City, UT. E-mail: ben.lewis@hsc.utah.edu. Kevin Byrne, MD, is a second-year psychiatry resident at the University of Utah in Salt Lake City, UT. E-mail: kevin.byrne@hsc.utah.edu.

The authors have nothing to disclose.

Increasing Trends of Drug Abuse and Overdose Deaths Driven by a Global Pandemic

By Bridgit O. Crews, PhD, DABCC

Since the global novel coronavirus (COVID-19) pandemic began there has been massive disruption to health care services and social support systems. Reports of increased rates of positive urine drug testing results and emergency department visits for nonfatal opioid overdoses (1, 2) provide a glimpse into the increasing toll that the COVID-19 pandemic is having on the prevalence of substance use, the resulting overdose deaths, and health disparities (3, 4).

In December, the Centers for Disease Control and Prevention (CDC) distributed a Health Alert Network (HAN) advisory regarding the observed increases in overdose deaths nationwide. Provisional data from the CDC National Center for Health Statistics (NCHS) showed that the largest 1-month increase in opioid overdose deaths ever recorded occurred between March 2020 and May 2020, coinciding with widespread mitigation measures related to the COVID-19 pandemic (5). While this is primarily driven by synthetic opioids such as illicitly manufactured fentanyl and fentanyl analogues (FFA), overdose deaths associated with psychostimulants such as methamphetamine and cocaine are also accelerating.

Prior to the COVID-19 pandemic, overall rates of drug overdose deaths increased between 2018 and 2019; however, the 2019 numbers were similar to those observed in 2017 (6, 7). Although deaths attributed to synthetic opioids increased nearly 10-fold between 2013 and 2019, much of the increase occurred prior to 2017. Deaths due to synthetic opioids such as fentanyl and fentanyl analogues increased on average by 75% per year from 2013 to 2017, but only by 9% per year from 2017 to 2019. Overdose death rates attributed to heroin actually decreased between 2016 and 2019, as did deaths attributed to semi-synthetic opioids such as oxycodone and hydrocodone. On the other hand, psychostimulant drug overdose deaths increased consistently. Deaths more than tripled for cocaine, and deaths due to methamphetamine increased on average by 29% per year between 2012 and 2019. In the 12-month period ending May 2020, methamphetamine deaths had increased by 34.8% compared to the prior 12-month period (5).

The concurrent use of opioids and stimulants elevates overdose risk, and more commonly, co-use of synthetic opioids may be a contributing factor for some psychostimulant deaths, particularly for cocaine related deaths. A recent analysis utilizing data from the National Forensic Laboratory Information System (NFLIS) also reported a small, but steady and significant, increase in seized illicit drug products containing mixtures of fentanyl and cocaine, or fentanyl and methamphetamine in selected jurisdictions (8). This also highlights a worrisome trend in increasingly risky illicit drug supplies.

The geographical distribution of synthetic opioids and overdose deaths due to synthetic opioids is also changing. Previous data from the NFLIS showed Northeastern and Midwestern states being most affected. This is attributed to different sources of heroin in different regions, with white powder heroin previously being more prevalent in the Northeastern and Midwestern regions and also being more likely to be mixed or substituted with illicit fentanyl (9).

However, recent numbers show synthetic opioid deaths increasing nationwide. The majority of reporting jurisdictions observed increases of 25% or more in deaths due synthetic opioids. The largest increases were observed in Western states, which saw deaths due to synthetic opioids increase by 98% in the 12-month period ending May 2020, compared to the previous year. These geographical changes are likely due to changing illicit drug supplies and a market that is being dominated by white powder "heroin" (5).

Approximately 81 230 overdose deaths were reported in the 12 months prior to May 2020, marking the largest ever single year increase (5). In response, the CDC advisory includes recommended actions aimed to counteract the current crises. This includes raising awareness and expanding the provision and use of naloxone and overdose prevention education for patients, expanding access to treatment for substance use disorders, increasing early intervention for at-risk individuals, and improving detection of overdose outbreaks due to fentanyl, novel psychoactive substances, and other drugs.

Recommendations for laboratories include implementing opioid biosurveillance programs in line with the Association of Public Health Laboratories (APHL) guidance. The APHL guidance discusses the role that laboratories play in understanding the opioid epidemic and building a framework for reliable evidence to include data gathered from hospital, commercial, forensic, and public health laboratories together (10). Additional recommendations from the CDC include screening specimens for more synthetic opioid compounds both by using immunoassays with cross-reactivity to fentanyl and fentanyl analogues, and by using the CDC's Traceable Opioid Material Kits (TOM KITS®). TOM KITS include reference materials for more than 210 synthetic opioid compounds. Both an opioid certified reference material kit and a

fentanyl analog screening kit are available. The kits are designed to assist and enable laboratories in developing mass spectrometry analyses for synthetic opioids, and are designed to address the majority of fentanyl, fentanyl-related, and other new opioid cases based in part on the DEA Emerging Threats Reports and NFLIS (11, 12). For the most novel psychoactive substances non-targeted high resolution mass spectrometry (HRMS) testing is required. HRMS is currently available primarily in more advanced specialized laboratories, and even in the most advanced laboratories, identifying previously uncharacterized novel psychoactive substances is extremely challenging.

Immunoassays offer rapid turnaround time using instrumentation that is generally more readily available to a wider spectrum of laboratories. Several immunoassays for fentanyl screening are FDA-approved for use on automated analyzers. These may show significant cross-reactivity with some fentanyl analogues; however, many synthetic opioids will likely remain undetected with immunoassay-based approaches. Some prescription drugs or their metabolites are also known to cross-react and produce false-positive results on fentanyl immunoassays (13-16). This complicates the interpretation of immunoassay results; therefore, when laboratories lack the in-house ability to offer more comprehensive testing services by mass spectrometry, it is important they clearly communicate any testing limitations, as well as identify suitable referral laboratories that can provide a more comprehensive analysis when indicated.

For every overdose death there are numerous more nonfatal overdoses that go unaccounted. These individuals are at increased risk for future overdose, and improved drug screening has the potential to identify those individuals that may benefit from earlier intervention. Clinical and forensic toxicology laboratories also have the vantage to contribute substantial real-time information on local drug trends and have a major role to play in helping to counteract the current overdose epidemic.

Learning Objectives

After reading this article, the reader will be able to list the current types of illicit drugs that are driving increasing numbers of overdose deaths in the US. The reader will be able to discuss the current recommendations described by the most recent CDC health alert network advisory intended to combat rising numbers of overdose deaths observed nationally.

References

1. Wainwright JJ, Mikre M, Whitley P, Dawson E, Huskey A, Lukowiak A, Giroir BP. Analysis of drug test results before and after the US declaration of a national emergency concerning the COVID-19 outbreak. JAMA 2020;324:1674–77.
2. Ochalek TA, Cumpston KL, Wills BK, Tamas SG, Moeller G. Nonfatal opioid overdoses at an urban emergency departments during the COVID-19 pandemic. JAMA 2020;324:1673–74.
3. Haley DF, Saitz R. The opioid epidemic during the COVID-19 pandemic. JAMA 2020;324:1615–7.
4. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Mol Psychiatry 2021;26:30–9.
5. Centers for Disease Control; 2020. Health Alert Network (HAN). No.438–Increase in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. Available from: https://emergency.cdc.gov/han/2020/han00438.asp.
6. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2019. NCHS Data Brief, no 394. Hyattsville, MD: National Center for Health Statistics. 2020. Available from: https://www.cdc.gov/nchs/products/databriefs/db394.htm.
7. O'Donnell J, Gladden RM, Mattson CL, Hunter CT, Davis NL. Vital Signs: Characteristics of Drug Overdose Deaths Involving Opioids and Stimulants–24 States and the District of Columbia, January-June 2019. MMWR Morb Mortal Wkly Rep. 2020;69:1189–97.
8. Park JN, Rashidi E, Foti K, Zoorob M, Sherman S, Alexander GC. Fentanyl and fentanyl analogs in the illicit stimulant supply: Results from U.S. drug seizure data, 2011-2016. Drug and Alcohol Depend 2021;218:108416.
9. Jannetto PJ, Helander A, Garg U, Janis GC, Goldberger B, Ketha H. The fentanyl epidemic and evolution of fentanyl analogs in the United States and the European Union. Clin Chem 2019;65:242–53.
10. Opioids Biosurveillance Task Force. Model opioids biosurveillance strategy for public health practice. Association of Public Health Laboratories; 2020. Available from: https://www.aphl.org/aboutAPHL/publications/Documents/EH-2020-Opioid-Biosurveillance-Strategy.pdf.
11. Krajewski LC, Swanson KD, Bragg WA, Shaner RL, Seymour C, Carter MD, et al. Application of the fentanyl analogue screening kit toward the identification of emerging synthetic opioids in human plasma and urine by LC-QTOF. Toxicol Lett 2020;320:87–94.
12. Mojica MA, Carter MD, Isenberg SL, Pirkle JL, Hamelin EI, Shaner RL, et al. Designing traceable opioid material kits to improve laboratory testing during the U.S. opioid overdose crisis. Toxicol Lett 2019;317:53–8.
13. Warrington JS, Walsh A, Baker E, Lozier D, Belec A. Keeping up with fentanyl: Failure to do so is not an option. J Appl Lab Med 2018;3:148–51.
14. Guerrieri D, Kjellqvist F, Kronstrand R, Gréen H. Validation and cross-reactivity data for fentanyl analogs with the Immunalysis fentanyl ELISA. J Anal Toxicol 2019;43:18–24.
15. Budelier MM, Franks CE, Logsdon N, Jannetto PJ, Scott MG, Roper SM, Farnsworth CW. Comparison of two commercially available fentanyl screening immunoassays for clinical use. J Appl Lab Med 2020;5:1277–86.
16. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. Neuropharmacology 2018; 134(Pt A):121–32.

Bridgit O. Crews, PhD, DABCC, TC, is an associate clinical professor of pathology and laboratory medicine and director of clinical chemistry and toxicology at the University of California Irvine Medical Center in Orange County, Califor-

nia, as well as Chair of the Clinical & Forensic Toxicology News *board of editors. E-mail: crewsb@uci.edu.*

The author has nothing to disclose.

2020 AACC Annual Scientific Meeting: Virtual Scientific Events Showcase Toxicology through a Multi-Disciplinary Lens

By Yifei K. Yang, PhD

The American Association for Clinical Chemistry (AACC) annual meeting went virtual from December 13-17, 2020. During the 5-day conference, a variety of scientific topics covering numerous areas of interest among the *in vitro* diagnostics community were presented and discussed in both live and on-demand formats. Toxicology and therapeutic drug monitoring as a topic track was extensively represented by 11 scientific sessions and 40 poster presentations. Using a blend of on-demand sessions and live Q&A interactions, the AACC toxicology community drew special attention to the opioid epidemic and the growing use of other substances in 8 scientific sessions. The topics and speakers of these scientific sessions reflected the multi-disciplinary approaches employed to address the medical, legal, and social-economic impact of substance use disorders. In the session titled "Opioid-Use Disorders, from Brain to Clinical Treatment and Laboratory Testing," speaker Dr. Elizabeth Howell, a psychiatrist who specializes in substance use disorder treatment, comprehensively described the profound neurological impacts of substance use and dependence. She further explained key aspects of treatment for opioid use disorders (OUDs). Specifically, the under-utilization of pharmacotherapies involving buprenorphine and methadone for OUDs (1) and their efficacies in reducing overdose-related deaths were discussed in detail. The session demonstrated how to utilize toxicology testing as an interventional tool to support pharmacotherapies for OUDs. In the session "Controlled Substance Monitoring: Guiding Practice Change through Strategic Collaborations," speaker Dr. Sean Hoynes, a primary care physician, provided perspectives from a primary care setting on the requirements of prescribing controlled substances and the institutional monitoring guidelines. The session also offered additional views from the clinical laboratory on assay design strategies depending on clinical needs, and discussed consultative and educational opportunities to help bridge the knowledge gap between clinical providers and the laboratory. In the session titled "The Role of the Clinical Laboratory in Substance Treatment and Research," speaker Dr. Ju Park presented epidemiologic data on various harm reduction approaches to deescalate overdose risks. The application of test strips to check drugs and identify the presence of highly potent fentanyl and fentanyl analogues has been shown to raise awareness among substance users and potentially lead to a decrease in overdose risks (2, 3). In the session "Diagnostic Tools for the Detection of Fentanyl, Fentanyl Analogs, and Other Synthetic Opioids," Dr. Sarah Riley and Dr. Kara Lynch discussed recent progress in using both immunoassays and mass spectrometry approaches to detect and identify a growing number of synthetic opioids. Through high resolution mass spectrometry and an expanded synthetic opioids library, the session demonstrated improved regional surveillance capacities in both clinical and forensic toxicology laboratories.

On the traditional application of monitoring transplant patients on immunosuppressant (IS) medications, two scientific sessions offered new approaches from the molecular and cellular perspective. In the session titled "New Strategies in Transplant Patient Monitoring," speaker Dr. Michael Oellerich introduced the recent developments in measuring donor-derived cell free DNA to predict acute rejections. In the session titled "Is Therapeutic Drug Monitoring for Organ Transplantation on the Bleeding Edge?," Drs. Kamisha Johnson-Davis, Gwen McMillin, and Tiffany Roberts discussed how the analytical monitoring of IS and the metabolites can be interpreted in conjunction with pharmacogenomics and pharmacodynamics to offer individualized therapy. In addition, the plenary session, "Between Scylla and Charybdis: Navigating the Complex Waters of Machine Learning in Laboratory Medicine," presented by Dr. Ulysses Balis, further demonstrated how cellular and immunological responses from hematological assessment can be a potential better predictor for treatment responses of 6-mercaptopurine in the setting of Crohn's disease and ulcerative colitis.

Mirroring the diverse topics in the scientific sessions, the 2020 AACC meeting posters presented methods development and assay validation studies based on immunoassays and automated analyzers, point of care devices, and mass spectrometry platforms. Using retrospective data analysis, several poster presentations examined changing trends of opioids and other controlled substances in their local patient populations (poster B-267, B-294, B-300, and B-307). By leveraging additional clinical information, the poster presentations evaluated the utility of ceruloplasmin as an indirect indicator for serum copper (B-290),

and described identification of possible interfering substances in routine urine drug screens (B-291).

Overall, the scientific meeting of 2020 demonstrated the analytical advancements in clinical chemistry, but also the important values that laboratory data can bring to the wider medical and research community through multi-faceted approaches. Connected through the virtual platform of AACC, meeting attendees will continue to foster collaborations and bring the advancements to practice.

Learning Objectives

After reading this article, the reader will be able to discuss highlighted toxicology contents presented at the 2020 AACC Annual Scientific Meeting.

References

1. National Institutes of Heath. 10 percent of US adults have drug use disorder at some point in their lives. https://www.nih.gov/news-events/news-releases/10-percent-us-adults-have-drug-use-disorder-some-point-their-lives (Accessed January 3, 2021).
2. Krieger MS, Yedinak JL, Buxton JA, Lysyshyn M, Bernstein E, Rich JD, et al. High willingness to use rapid fentanyl test strips among young adults who use drugs. Harm Reduct J 2018;15:7.
3. Sherman SG, Morales KB, Park JN, McKenzie M, Marshall BDL, Green TC. Acceptability of implementing community-based drug checking services for people who use drugs in three United States cities: Baltimore, Boston and Providence. Int J Drug Policy 2019;68:46-53.

Yifei K. Yang, PhD, is an assistant professor at the Department of Pathology, University of Utah, and a medical director at ARUP Laboratories. Dr. Yang is a member of the Clinical & Forensic Toxicology News *Editorial Advisory Board. E-mail: yifei.yang@path.utah.edu.*

The author discloses grants/research and salary/consultant fees from ARUP Laboratories.

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

Learning Objectives

Learning objectives vary by article, but in general, after completing *Clinical & Forensic Toxicology News*, the reader will be able to:

- Describe emerging and changing trends in drug abuse, including new designer drugs, usage patterns, and contaminants/adulterants.
- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
- Evaluate methodologies for their utility and limitations relative to the needs of toxicology labs.
- Discuss relevant regulations, such as analytical performance requirements, or the legality of new drugs of abuse.
- Explain the analytical and regulatory issues unique to specific applications, including postmortem toxicology, workplace drug testing, and drug screening.
- Describe the medical implications of drug abuse, toxicity associated with therapeutic agents, and exposure to other toxicants.

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=27582103.

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: CFTNews@aacc.org.

Clinical & Forensic Toxicology News does not accept advertising and is supported solely by its readers. The 2021 annual subscription price is $84, $59 for AACC members. To subscribe, email custserv@aacc.org.

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