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Vaping Trends in the United States

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Modern electronic cigarettes (ECIGs), referred to as vapes, vaping pens, tank systems, mods, and electronic nicotine delivery devices, were invented and designed by a Chinese pharmacist named Hon Lik in 2003 (1–3). The design was internationally patented in 2007 (US patent 20070267031 A1). By 2018, 21% of high school students reported to have used an ECIG. Recently, *Morbidity and Mortality Weekly Report* documented a multistate epidemic of lung injuries related to ECIG use. As of this printing, there have been at least 805 confirmed cases of lung injury reported from 45 states in the US, of which 91% of patients experienced symptoms severe enough to be hospitalized (1, 3). Tetrahydrocannabinol (THC) and nicotine-containing ECIGs were both implicated in the CDC report. As investigations are still ongoing, it is difficult to draw conclusions about the toxicological impact of firsthand or secondhand exposure to ECIG vapors. However, as ECIG use in the general population has dramatically increased, there is an urgent need for clarity on the risk of short-term and long-term exposure.

Vaping has been shown to cause acute and chronic inflammatory responses including activation of biochemical pathways, such as mitogen-activated protein kinase and Janus tyrosine kinase/signal transducers, and activation of transcription and nuclear factor-κB signaling (4). These inflammatory pathways are similar and overlap with those activated by traditional smoking. This article reviews the current available knowledge on the toxicology of e-liquid components, the pathology of vaping-related lung injury, and the public health impact of ECIG use. In addition, we also review issues surrounding smoking cessation, public perception, marketing, and policies for regulating ECIGs.

ECIG Design

The basic components of an ECIG include a mouthpiece, cartridge, heating element (also called the atomizer), and a battery (Figure 1). Currently, the most common type of battery used is rechargeable lithium-ion batteries. Some ECIG devices contain nonrechargeable batteries, but these are less popular among customers. Two types of battery options are available: manual actuation and automatic (5). The automatic models can have a sensor that is triggered by increased airflow when the user starts inhaling. In the manual model, once the switch is activated, the atomizer is energized, which allows the e-liquid in the reservoir to be heated. Temperatures up to 500 °F can be reached in the atomizer coil. The heated e-liquid is then converted to an aerosol that is inhaled by the user via a mouthpiece. Adjacent to the tip of the vaporizer is the e-liquid tank or "cartridge." This refillable tank stores the e-liquid that is aerosolized and inhaled. In some models, cartridge and atomizer are combined into one component called the cartomizer. The tank or the cartridge on some models has a transparent body (clearomizer), making it easy for the user to know when to replace the cartridge or refill the tank.

The ECIG design has significantly evolved over the past few years. First-generation ECIGs were completely closed systems with 3.2- to 4.2-V batteries that were nonreplaceable. These were followed by second-generation open models, which offered higher powered (3.7–6 V) rechargeable lithium-ion batteries. The ECIG models from this version onward offered refillable or tank-style cartridges. The third generation featured tank-style devices called "mods," which can cost upward of $200. The battery power in the third-generation ECIG devices offered 3 to 8 V, allowing users to

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attain higher nicotine intake that can be similar to that seen with traditional cigarettes. The latest generation of ECIG devices offers enhanced customization for tank size and temperature control, including batteries that can offer variable power output. The battery can deliver 1 to 75 W of power to the atomizer. However, higher voltage can result in overheating, causing release of toxic compounds from the e-liquid components. Likewise, another complication factor associated with larger battery packs is the vulnerability to short-circuit catastrophic failures causing explosion of the device, which have been associated with a number of documented deaths (6).

Trtchounian et al. studied the characteristics of traditional cigarettes and ECIGs and reported that compared with traditional cigarettes, more suction was needed in ECIGs to release aerosols (7). This need translates to greater inhaling pressure that is required to sustain aerosol density. One implication of this finding is that the density of the aerosol varies significantly during smoking, causing inconsistent doses of the aerosolized compounds to reach the lung tissue. This may result in a greater concentration of e-liquid vapors in certain puffs compared with others, causing adverse effects on the lungs.

Smoking performance was compared in another study in which various brands of ECIGs were tested. A number of performance indicators were examined, including airflow rate required to produce aerosol, pressure drop across ECIGs, and aerosol density. Interestingly, each of the factors studied was found to be variable among devices of the same brand. In fact, performance was variable even across different devices of the same model within a brand (8). The authors of this study concluded that the variability was attributed to poor quality control around the manufacturing processes, increasing the risk of adverse events.

The design of ECIG devices has evolved rapidly, and more customizable models are expected on the horizon. Each element of the ECIG device has undergone improvement to serve a growing user base. However, the quality control processes surrounding the manufacturing of these devices often appears suboptimal, and the high-powered batteries have resulted in explosions and related adverse events. Much more thorough research and development are needed to optimize the various aspects of the ECIG design, making them safer and standardized for public use.

Components in Vaping Mixes and Vape Smoke, and Public Health Concerns

The composition of e-liquids varies greatly depending on user preferences. Additionally, the composition of the exhaled components varies dramatically in terms of particulate matter and the chemical composition of the vapor. The harms of vape smoke have yet to be thoroughly researched. Some liquids and vapor do contain potentially toxic constituents that are also found in cigarette smoke but generally at lower concentrations (9–11).

Nicotine content in e-liquids varies widely and includes some products advertised as nicotine-free. Vendors may classify the nicotine content as a range of concentrations with classifications such as zero, low, medium, and high. Nicotine concentration ranges from 6 to 12 g/L (low), 13 to 18 g/L (medium), and 24 to 36 g/L (high). Vaping vendors can buy a nicotine solution with a concentration of nicotine as high as 1000 g/L and dilute it to the desired ranges, although reports of errors in compounding are common (5). Studies that have analyzed contents of e-liquids of popular brands have shown

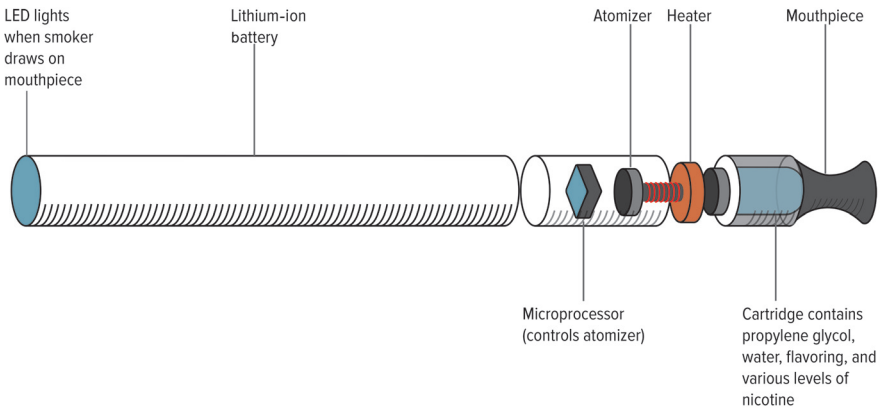

Figure 1. How a common e-cigarette works.
First, the user inhales from the mouthpiece, turning on the device and activating the LED light. Then, the battery sends a charge to the atomizer and heater, which vaporize liquid from the replaceable cartridge, producing flavored nicotine-containing vapor, which is consumed and exhaled by the user. Reproduced with permission from Blanding (39).

wide disparities in nicotine content between refills and similarly labeled e-liquid mixes (12–16). Additionally, nicotine content often differs greatly from that listed on the package labeling. Of note, nicotine has been shown to be present in e-liquids that are labeled as nicotine-free (16).

In addition to nicotine, there are numerous flavoring agents that are added to the e-liquids. Popular flavors include chocolate, peppermint, and vanilla, with thousands of flavors being available. The majority of the flavoring agents (approximately 75%) contain diacetyl, propylene glycol, and glycerin (5). Unfortunately, in addition to the abovementioned chemicals, e-liquids contain aldehydes like formaldehyde, benzaldehyde, acetaldehyde, acrolein, and others. These may not be added to the e-liquid itself but are formed during the vaping process (17).

Trace amounts of heavy metals and other compounds that are known carcinogens have been identified in e-liquids. The chemical profile of the vapor from an e-liquid can include toxic carbonyl compounds, heavy metals including mercury, cadmium, and lead, and volatile organic compounds such as benzene and toluene. Other toxic compounds like nitrosamines have been identified in e-liquid as well. One well-known toxic byproduct of heated and aerosolized propylene glycol is formaldehyde, which is a known biocide. Chronic inhalation of toxic aldehydes, heavy metals, and other toxic components known to be a part of vaping can cause significant respiratory complications (18).

Of the flavors that have been studied, cinnamon flavor was shown to exhibit cytotoxicity. In animal models, e-liquid components have been shown to have some physiologic effects, including weight loss, oxidative stress, and neurological changes. Data on the impact of secondhand exposure are still unclear, although the impact has been shown to be significantly less compared with secondhand exposure to smoke from traditional cigarettes. Some evidence for cytotoxicity related to exposure to e-liquid components has been published in the literature (17). Some physiologic impact has been shown in large animal studies, but these have not been replicated in humans. Studies have compared physiologic parameters such as exhaled carbon monoxide, complete blood count, cognitive function, and weight in people using ECIGs (4). There seems to be a short-term favorable impact on cognitive function, which is consistent with initial use of traditional cigarettes (17).

Pathology of Vaping-Associated Lung Injury

As of the writing of this article, at least 12 deaths were attributed to vaping-related products and lung injury. The CDC recently published characteristics of a multistate outbreak of lung injury associated with ECIG use. As of October 2019, there were 1888 cases of vaping-related lung injury reported (19). These respiratory complications have been generally termed vaping-associated pulmonary illness (VAPI) or vaping-associated lung injury. Many possible etiologies have been suggested; however, further investigation is currently underway. Many cases of lung injury have been linked to the vaping of THC and cannabidiol (CBD) products, and of the patients with suspected lung injury, about 500 had reported using THC-containing products. Specifically, adulterated and unlicensed marijuana-associated vape cartridges have fillers, such as vitamin E acetate, that may contribute to the respiratory disease (19, 20).

Although the definitive mechanism of injury is unknown, a medical literature review has shown specific patterns of symptomology, pathophysiology, and histology associated with VAPI cases. Individuals with VAPI have nonspecific symptoms, affecting the respiratory and gastrointestinal systems. Individuals commonly complain of dyspnea, cough, chest pain, nausea, vomiting, and fever (19, 21, 22). E-liquids, including the previously mentioned propylene glycol and glycerol, are believed to be contributors to this symptomology. Several in vitro models, including cell-based assays, have been used for assessing toxicity arising from e-liquid and vapor exposure. Specifically, cytotoxicity of the most common e-liquid components—propylene glycol and glycerin—has been studied in several in vitro models. Propylene glycol and glycerol, being alcohols, have been shown to dehydrate the respiratory surfactant, causing epithelial damage, obstruction, and inflammation of the airway. These alcohols can induce cytokine activation and trigger proinflammatory pathways that cause airway constriction and microvascular leakage. Collectively, these effects damage the epithelial surfaces of the lung, decreasing surface tension, leading to airway collapse and disruption of gas exchange. However, the specific cytotoxic effects have yet to be completely elucidated in human cell-based systems (17, 23).

A recent, randomized clinical trial has shown similar findings, specifically evidence of small airway constriction and disruption of pulmonary gas exchange (24). A variety of nonspecific histopathological patterns of acute lung injury are seen in VAPI, including diffuse alveolar damage, organizing pneumonia, and acute interstitial lung disease (25). In diffuse alveolar damage, a neutrophilic mediated inflammation is initially seen causing hemorrhage and edema, followed by myofibroblastic proliferation, leading to fibrosis, alveolar collapse, and decreased pulmonary compliance presenting clinically as acute respiratory distress syndrome (22, 26). The use of nicotine-containing e-liquids has been associated with the broadly termed acute interstitial lung disease, a group of disorders characterized by remodeling

of airspaces causing lung fibrosis. Specific entities of acute interstitial lung disease seen in VAPI include hypersensitivity pneumonitis, fibrinous pneumonitis, and eosinophilic pneumonitis (22, 25). Hypersensitivity pneumonitis is an immune-mediated process, causing peribronchiolar inflammation and fibrosis (27). Fibrinous pneumonitis is characterized by intraalveolar fibrin deposition (28), and eosinophilic pneumonitis, as the name implies, has alveolar and interstitial infiltration by eosinophils (20). Although somewhat variable, these cases have shown similar histological features, including sloughing of the respiratory epithelium, mucosal edema, and macrophage infiltration of the alveolar and bronchiolar airspaces (20).

As previously mentioned, the use of unapproved fillers in THC/CBD cartridges has been suspected as a cause for the lipoid pneumonitis seen in VAPI. Lipid-laden macrophages found in these cases are suggestive of possible aspiration of exogenous lipoid substances, such as vitamin E oil, a filler found in unlicensed THC/CBD cartridges (4). A recently published article by the Mayo Clinic has refuted these findings; in their study, none of the lung biopsies from 17 patients had histologic or radiologic evidence of lipoid pneumonia (5). The significance of this study in the understanding of VAPI is currently unknown. These contrasting findings are evidence that more rigorous investigation of the pathophysiology and histopathology is warranted.

Smoking Cessation, Public Perception, Marketing, and Policies

One area of research in which ECIGs have been studied extensively is in the field of addiction and smoking cessation. Randomized controlled trials have been conducted to assess the efficacy of ECIGs for aiding in smoking cessation and to compare nicotine replacement therapy with ECIG use. Rates of cessation with ECIGs were significantly higher compared with the nicotine replacement therapy (4, 5, 17). Overall, well-designed randomized controlled trials have shown an increase in smoking cessation when users switch to ECIGs compared with nicotine replacement. Additionally, many cross-sectional and longitudinal studies without control groups have also shown similar findings that ECIGs can assist in quitting or reducing smoking. However, there are studies that have shown a negative correlation between ECIG use and smoking cessation. Some authors have suggested that the studies showing negative correlation between ECIG use and smoking cessation are wrought by selection bias, confounding factors, and inadequate measures of exposure (4, 17). The statistics for correlation between ECIG use and smoking cessation are similar to those for correlation between smoking cessation and nicotine replacement therapy. About 80% of trials showed a favorable impact of ECIG use on smoking cessation (5). Overall, although some isolated studies differ in their conclusions, a majority of well-designed longitudinal and cross-sectional studies have shown a favorable impact of ECIG use with smoking cessation (29, 30).

Public perception of ECIGs is evolving from that of positive "ECIGs help people quit" to mixed "Are ECIGs really safe?" and "Are ECIGs gateway to smoking and other drugs?" However, the overwhelming perception of ECIGs is that they are safer than cigarettes and considered less addictive and more convenient than traditional cigarettes. Common concerns include lack or paucity of research on long-term use and potential for use as a gateway mechanism to nicotine and other drugs, especially for minors. Users cite many reasons for using ECIGs, including tobacco cravings and smoking cessation, to circumvent smoke-free policies and to avoid social stigma of traditional smoking and secondhand smoke, and the general belief that vaping devices are safer than traditional cigarettes.

ECIGs have been available to consumers via vape shops, at traditional cigarette outlets, and via Internet vendors. Fifty percent or more of tobacco outlets now sell ECIGs. Pricing on ECIGs can vary widely, and some vape shops may sell these devices at up to 200% markup compared with manufacturer-suggested retail prices (5, 31). For this reason, frequent smokers tend to buy ECIGs that are available from the Internet.

There seems to be a correlation between vape shop locations and neighborhood demographics, wherein vape shops appear to be concentrated in neighborhoods with higher median incomes. However, the unregulated nature of Internet marketing of ECIGs is problematic. Studies have reported that successful youth ECIG purchases can be made without any age verification (32, 33). Factors that drive the pricing of ECIGs are currently unknown but may be, in part, driven by the increasing cost of traditional cigarettes.

Local, state, and national policies around regulation of ECIGs are widely inconsistent. Efforts to characterize the health impact of components of ECIGs other than nicotine must be made to better characterize and regulate these products. Additionally, nicotine amount in ECIG devices will likely require stricter regulation, similar to traditional cigarettes that are classified as full flavor, light, and ultralight based on the nicotine content. Of note, some recent policies like the ban of menthol cigarettes have raised concerns and increased demand on ECIG use. Additionally, smoke-free indoor air laws differ broadly across states and federal guidelines. The impact of smoke-free policies on ECIG demand in the near future remains uncertain (34).

Conclusion

ECIGs were first patented in 2007 and started becoming available from traditional tobacco outlets and via the Internet. Partly because of the ease and wide availability and widespread marketing, ECIG use in the general population is increasing. Randomized controlled trials and cross-sectional studies have shown marketing exposure from ECIGs can promote ECIG use and uptake in the general population (35–38). A recent epidemic in vaping-related adverse events has come to light. Since their first appearance in the market, vaping products have evolved in their design over the past few years and can deliver more e-liquid content with greater user control. More recently, completely customizable ECIG devices with ability to vary the power that is delivered to the atomizer have come to the market—all with apparently little quality control. These models have been shown to overheat and have caused explosions and related adverse events. Animal model studies have shown cytotoxicity from at least one flavoring agent, and several hundred flavoring agents are newly available every month. Yet, the health impact of these agents is relatively unknown. The CDC has reported on a few hundred cases and 12 deaths related to use of vaping devices; the respiratory impact of ECIG use is now beginning to be characterized.

There are significant concerns about ECIG devices available to youth via the Internet without age verifications, and complete bans on ECIG use are being discussed in local governments across the US. Public opinions about ECIGs have been mixed. The CDC recommends avoiding the use of ECIG devices, as the risk from the short-term or long-term exposure to e-liquid components is unknown. More detailed population-based studies assessing the long-term risk of ECIG use in various vulnerable populations are needed.

Learning Objectives

After reading this article, the reader will be able to describe the evolution of vaping and its associated technologies. The reader will be able to list the patterns of lung pathology related to Vaping Associated Lung Injury (VAPI). The reader will be describe the contents of vaping e-liquids.

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Overdose Death Associated with Vaping Designer Fentanyl Analogs

By Katherine Maloney, MD, and Milad Webb, MD, PhD

We recently examined a 33-year-old white male with a history of drug dependency who was found dead at home after a suspected drug overdose. At the scene, the decedent's mother informed investigators that in addition to conventional injection of illegal drugs, the decedent would also vape these drugs, allegedly making his own vaping liquids with illicit street drugs. A vaping device was discovered on the bed next to the decedent and was submitted for toxicological analysis.

The social interest in vaping has fueled an exponential rate of evolution within vaping technology and consumer customization of vaping devices. These devices allow vaping liquids to be made into a vapor via contact with a heating element, and then

inhaled—sometimes referred to as an electronic cigarette. Although vaping liquids generally contain nicotine and a variety of flavors, other substances have been incorporated into vaping liquid, such as tetrahydrocannabinol (THC) (1). In fact, a brief search on the Internet will yield hundreds of do-it-yourself guides and products for the manufacturing of "DIY E-Juice." The typical ingredients include vegetable glycerin, propylene glycol, diluted nicotine or nicotine salts, and flavor concentrates; however, there are now emerging reports of other illicit drugs finding their way into vaping mods, which are larger devices than traditional vape pens owing to their modifications and enhancements. With recent reports of vaping-associated lung injury and deaths, there is now mounting scrutiny of what is a largely unregulated industry.

Independent of the vaping craze, there has been an epidemic in opioid-related deaths escalating over the past decade. These deaths, which were initially driven by heroin and prescription opioid abuse, are now rising because of a common anesthetic and pain management therapeutic: fentanyl (2). Because of its potency and wide availability, fentanyl has been abused and misused for the past several decades. In addition, clandestinely manufactured fentanyl and designer analogs are introduced into illicit markets on a monthly basis (3). Two such analogs are butyrylfentanyl and valerylfentanyl. Like parent fentanyl, both are μ-receptor agonists but with lower affinities (4, 5).

Postmortem toxicology performed on the decedent's peripheral blood revealed the presence of fentanyl (20.7 ng/mL), butyrylfentanyl (4 ng/mL), valerylfentanyl (0.93 ng/mL), β-hydroxyfentanyl, cocaine (330 ng/mL), buprenorphine (0.52 ng/mL), and sertraline (190 ng/L). Fentanyl is reported to be up to 200-fold more potent than morphine (6, 7). The use of fentanyl is associated with numerous adverse effects, including somnolence, severe respiratory depression, seizures, coma, hypotension, and sudden death. In fatalities from fentanyl toxicity, blood concentrations have been reported as low as 3 ng/mL (8).

Concomitant testing of the liquid from the vaping device revealed the presence of nicotine, butyrylfentanyl, and valerylfentanyl. The decedent also had a syringe in his pocket that was collected by police.

Vaping illicit substances is not a new phenomenon and has been reported previously with heroin (9), but to our knowledge this is the first case of a vaping device being used as a delivery mechanism for fentanyl or fentanyl analogs. It is unknown at this time if this route of administration is associated with an increased risk of morbidity or mortality. Given the nature of this case, it is recommended that vaping devices found at death scenes be collected and the contained vaping liquid tested for the presence of illicit substances.

Learning Objectives

The reader will be able to describe the characteristics of the current trends in vaping and potential adulterants present in such products.

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The authors have nothing to disclose.

SOFT 2019 Highlights

By Jennifer Collins, PhD

The Society of Forensic Toxicologists (SOFT) annual meeting was held in San Antonio, Texas, on October 13 to 18, 2019. The meeting was headquartered at the Grand Hyatt in downtown San Antonio, close to both the Alamo and the River Walk. In addition to the plenary speaker, medical toxicologist Dr. Silas Smith, there were 52 platform presentations, 133 poster presentations, 12 workshops,

and multiple opportunities to network with colleagues and vendors.

Registration opened at 10 AM Sunday, October 13, followed by the annual National Laboratory Certification Program (NLCP) Laboratory Director and Inspector Training Workshop from 2 to 6 PM. The workshop traditionally covers current issues within the NLCP and the accompanying proficiency testing program, as well as presenting current research supported by the Substance Abuse and Mental Health Services Administration (SAMHSA) related to workplace drug testing programs. The SAMHSA Division of Workplace Program leaders took the opportunity to announce the impending publication of the final version of the Mandatory Guidelines for Federal Workplace Drug Testing Program—Oral Fluid. Those guidelines were published on October 25, 2019, with an effective date of January 1, 2020 (1). The NLCP is currently working on related documents and processes required to start the oral fluid laboratory certification process. In addition, the finalized testing cutoffs will require most reagent vendors to submit revised assays to the Food and Drug Administration for approval.

Monday and Tuesday comprised primarily workshops that covered method development, designer drugs, overdose deaths, cannabidiol and hemp, poisonous plants, oral fluid toxicology, and other topics relevant to the forensic toxicology discipline. The workshops provided excellent opportunities to earn continuing education credits. Vendor-sponsored "lunch and learn" sessions were held between workshops to demonstrate the latest products and technology. The welcome reception on Tuesday evening was an opportunity to network with colleagues and vendors, followed by the traditional Elmer Gordon Forum where laboratorians share analytical problems, difficult cases, and trends in their day-to-day forensic toxicology casework in an informal setting.

The meeting officially kicked off on Wednesday with the opening ceremony and plenary lecture, followed by scientific sessions 1 through 4 covering general and postmortem toxicology.

Dr. Marc Lebeau opened the scientific sessions with an update on Organization of Scientific Area Committees (OSAC) and the AAFS Standards Board (ASB). These are organizations comprising forensic science experts and practitioners who are engaged in strengthening forensic practice through developing and improving standards for forensic disciplines. Members include representatives from government, academia, and industry who facilitate development of science-based standards for the forensic science community through a formal process. The most recent approved toxicology standard is ANSI/ASB Best Practice Recommendation 037, First Edition 2019: Guidelines for Opinions and Testimony in Forensic Toxicology (2).

Scientific sessions 5 through 7 on Thursday, October 17 included presentations covering analytical toxicology and new psychoactive substances, a drugs and driving special session, and human performance toxicology. Synthetic cannabinoids continue to be a topic of interest; however, designer opioids such as U-type opioid series compounds and designer benzodiazepines are emerging with significant presence in forensic toxicology casework.

The U-type opioids, originally developed in the 1970s by the Upjohn pharmaceutical company, began to appear in casework in 2015. Compounds such as U-47700 and related isomers present analytical and interpretive challenges because of structural similarities and fragmentation patterns to conventional opioids (3). Likewise, designer benzodiazepines are rapidly increasing in prevalence. These compounds are agonists at the $GABA_A$ receptors, similar to other benzodiazepines, but are often missed in chromatographic analyses targeted to traditional prescription benzodiazepines. Compounds in this class include etizolam, delorazepam, phenazepam, clonazolam, and flualprazolam (4, 5).

The poster sessions Wednesday and Thursday covered wide-ranging topics, including drugs involved in overdose deaths, analytical method development and validation, prevalence of drugs of abuse in DUID (drug-impaired driving) cases, and case studies.

The meeting concluded on Friday, October 18, with scientific sessions 8 and 9, which included additional presentations on analytical toxicology and new psychoactive substances as well as alternative matrices such as oral fluid and hair.

Overall, the meeting was informative and topical, keeping with the tradition of gathering to share information and ideas among toxicology professionals. The SOFT advocates a high level of professionalism and ethics through its membership, certification, and accreditation programs. For additional information about SOFT and past and future annual meetings, visit the website at www.soft-tox.org.

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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.

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