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ORIGINAL ARTICLE

Opioid-Associated Hearing Loss: A 20-Year Review from the New Jersey Poison Center

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Abstract

Background Opioid-associated ototoxicity is a known complication of opioid exposure, although the mechanism remains unclear. While historically most closely linked to heroin and oxycodone, evolving reports suggest that it may be a class effect of opioids. However, the evidence is limited to case reports.

Methods A retrospective review of the New Jersey Poison Center records (ToxiCALL®) identified cases that included both hearing loss and recent opioid exposure between January 1, 1999, and September 21, 2018.

Results Forty-one cases were identified, mean age 29.4 years, 51% ($n = 21$) were male. Reported heroin exposures comprised 51% ($n = 22$), 18 of which were heroin alone. The next most commonly cited opioids were oxycodone ($n = 7$), methadone, ($n = 4$), and tramadol ($n = 3$). Hearing loss was described as tinnitus in 24% of cases, hypoacusis in 37% of cases, deafness in 29% of cases, and mixed tinnitus/hypoacusis in 10% of cases. Only 34% ($n = 14$) of cases were associated with a potential hypoxic event. Of the cases that documented resolution data, 21% ($n = 4$ of 19) reported no improvement at time of hospital discharge.

Discussion Opioid-associated ototoxicity appears to be a hypoxia-independent adverse effect since most of the reported cases did not involve a known contributory hypoxic event. It occurs with a wide array of opioids, which supports an opioid receptor-mediated mechanism. The ototoxic effect may be self-limited in many patients.

Conclusion Opioid-associated ototoxicity was most commonly associated with heroin exposure and appeared independent of hypoxic events. Further investigation that clarifies the risk factors and long-term outcomes is needed.

Keywords Opioid · Ototoxicity · Hearing · Toxicology · Poison center

Introduction

Opioid-associated ototoxicity is a known complication of opioid exposure, but many questions remain regarding the pathophysiology, risk factors for development, and prognosis. It is described in association with many opioid agonists and often occurs in the context of chronic exposure [1]. Symptoms vary from hypoacusis to overt deafness. While some patients may regain their hearing, in others the loss is permanent [2–4].

Most commonly, patients report a precipitous onset of unilateral or bilateral hearing loss, and audiometric testing demonstrates flat, profound sensorineural hearing loss with absent otoacoustic emissions and normal vestibular function [1, 2, 5, 6]. These findings, coupled with the curative success of cochlear implants, suggest a direct cochlear injury, most likely to the delicate hair cells of the organ of Corti or disruption of the nutritive stria vascularis required for their function [1, 7]. The implication of opioids as a class suggests an opioid receptor-mediated effect; all three opioid receptor subtypes are present in the cochlea [8]. Of interest, some patients developed ototoxicity after exposure following a period of abstinence, causing some authors to posit a potential mechanistic effect of receptor upregulation [3]. Alternatively, injury to the hair cells or stria vascularis as a result of hypoxia or hypotension has been suggested, although several cases are described in the absence of any apparent hypoxic event [1]. As yet, the etiologic mechanism remains unclear.

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The risk factors for this adverse outcome are equally unclear, in large part because published evidence is limited to case reports and small case series. Nonetheless, ototoxicity is associated with virtually every opioid, including codeine, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, propoxyphene, and tramadol [1–3, 5, 9, 10]. There does not appear to be an age or gender predilection. Cases described are generally in the context of either chronic heavy use or after an acute overdose. The prognosis is variable although some authors have suggested that acute overdose-related cases are more likely to resolve [6, 8].

We sought to determine the factors associated with opioid-associated ototoxicity, as well as the details regarding symptoms described and outcome, where known.

Methods

The New Jersey Poison Information and Education System (NJPIES) database (ToxiCALL®) was queried in November 2018 for all cases of opioid exposure in which an associated new onset of hearing dysfunction was reported between January 1, 1999 and September 21, 2018. An a priori search algorithm was used for retrospective chart review. Initial search was performed using two approaches including an advance search for "tinnitus" and "deafness" coded under clinical effects in the ToxiCALL® database, as well as a free-text entry for "deaf," "deafness," "hearing," and "sensorineural". A single abstractor unblinded to the hypothesis was trained on the study variables and how to navigate the database, as well as the inclusion and exclusion criteria, prior to the initiation of the retrospective review. The search results were analyzed to exclude any cases without documented opioid exposure and then to determine if there was a description consistent with new-onset and temporally associated auditory dysfunction. Cases were included if they had new-onset auditory dysfunction with documented opioid exposure; cases were excluded if there was no history of change in auditory status or opioid exposure. Cases were followed until hospital discharge. Schematic depiction of chart selection process is shown in Fig. 1.

Included cases were reviewed to collect descriptive information across several variables as follows: year of exposure, gender, age, opioid agonist(s), co-exposures, route of opioid exposure, description of auditory dysfunction, presence of hypoxic event, naloxone administration, and resolution of auditory dysfunction. These variables were abstracted on a standardized form. A random sample of the included cases was evaluated by a second abstractor to generate inter-rater reliability scores for the following variables: description of auditory dysfunction, presence of a hypoxic event, need for ventilatory support, and resolution of hearing dysfunction.

Several definitions were developed prior to data analysis and employed by the study team to characterize the results. We defined opioid exposure on the basis of historical information captured in the medical chart. Auditory dysfunction was assessed in two ways based on the subjective reported findings of the medical chart as follows: symmetry and clinical presentation. Symmetry of auditory dysfunction was categorized as unilateral or bilateral. The clinical variants of auditory dysfunction were described as "deaf," "hypoacusis," "tinnitus," or "mixed." In cases where auditory dysfunction type was not coded in the chart, the study team used the case description to classify the effect based on the following definitions. "Deaf" signified a presentation consistent with a complete loss of hearing. "Hypoacusis" signified a partial loss of hearing. "Tinnitus" signified a presentation with patient-reported "ringing" in his/her ear(s). "Mixed" was applied to any presentation that described features consistent with "hypoacusis" and "tinnitus."

The presence of a hypoxic event was categorized into three groups based on the reported findings as follows: "presence of hypoxic event," "no presence of hypoxic event," or "unknown presence of hypoxic event." The grouping "presence of hypoxic event" signified a patient case that included documentation of at least one of the following: [1] loss of consciousness, [2] receipt of cardiopulmonary resuscitation, or [3] need for ventilatory support. Further, "need for ventilatory support" was defined as any breathing supplementation via invasive or non-invasive mechanical support or with exogenous oxygen. "No presence of hypoxic event" signified patient cases where the patient was "awake and alert" throughout the management, without the criteria for a hypoxic event. The definition of "unknown hypoxic event" signified patients that did not met the criteria for "presence of hypoxic event" nor for "no presence of hypoxic event."

Descriptive statistical analysis was performed across variables. Inter-rater reliability scores were reported using the unweighted Cohen's kappa.

This study was approved by the Rutgers Newark Health Sciences Institutional Review Board.

Results

The initial search of the NJPIES ToxiCALL® database between January 1, 1999, and September 21, 2018 for cases coded as "deafness" and "tinnitus," as well as those with free-text mentioning "deaf," "deafness," "hearing," or "sensorineural," resulted in 2336 cases within the preset date range. Of these, 2201 were removed due to lack of documented opioid exposure. The remaining 135 cases were then evaluated for a new-onset, temporally associated auditory dysfunction. After this review, 60 cases remained

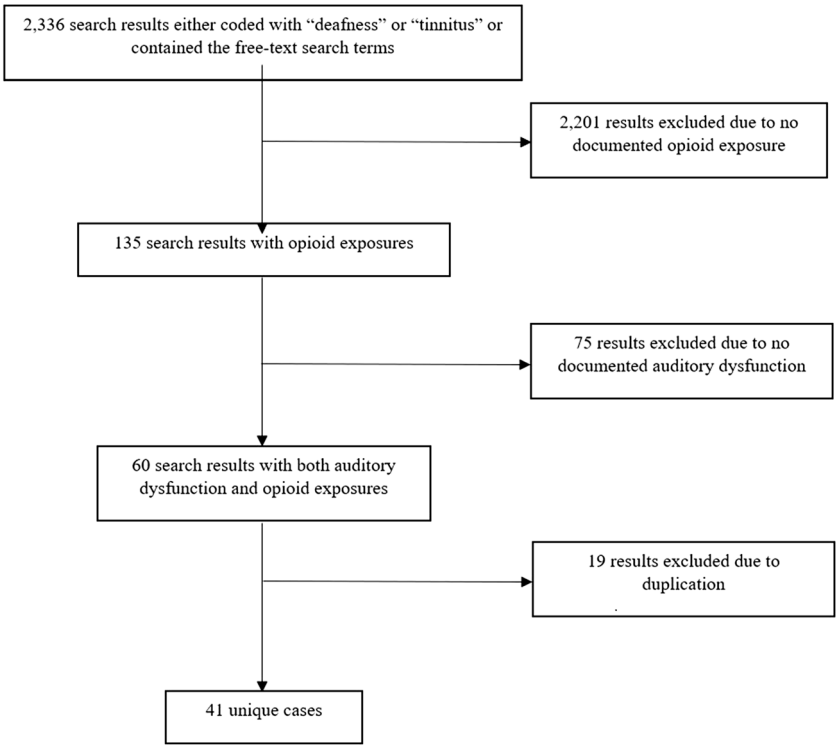

Fig. 1 Schematic representation of inclusion and exclusion of cases.

that met inclusion criteria. These were then cross-referenced to exclude any duplication, resulting in a total of 41 unique cases for our study (Fig. 1). Cases were evenly distributed by sex (51% male). Mean patient age was 29.4 years, with a median age of 26 years. Case overview information is presented in Table 1.

Of the 41 cases included, 36 (88%) had a single and known opioid exposure reported. Of the remaining five cases (12%), four (10%) had multiple opioid agonists documented, and one (2%) was recorded as an opioid agonist not otherwise specified. For the four cases with multiple opioid agonist exposures, two were heroin with oxycodone (5%), one was heroin with fentanyl (2%), and one was tramadol with codeine (2%). Agents implicated in cases with a single, known opioid exposure included 18 heroin cases (44%), 7 oxycodone cases (7%), 4 methadone cases (10%), 3 tramadol cases (7%), 2 hydrocodone cases (5%), 1 fentanyl case (2%), and 1 morphine case (2%). Eleven of the cases (27%) reported a co-exposure of another potentially ototoxic agent. These co-exposures included allopurinol, aspirin, cocaine, ibuprofen, furosemide, quinine, ranitidine, and valproic acid. Route of administration was not documented for 26 cases (63%). Of the 15 cases with a reported route, 9 were oral (22%), 4 intranasal (10%), 1 intravenous (2%), and 1 transdermal (2%).

Auditory dysfunction was characterized for all 41 cases. One case (2%) had unilateral dysfunction, while the remaining 40 (98%) were bilateral in nature. Of the 41 total cases, 12 (29%) reported deafness, 15 (36%) reported hypoacusis, 10 (24%) reported tinnitus, and 4 (10%) reported a mixed auditory dysfunction (Fig. 2). Of these cases, 7 (17%) reported complete resolution, 8 (20%) reported partial resolution, 4 (10%) reported no resolution, and 22 (54%) did not include data regarding resolution at the time of hospital discharge. Naloxone administration was documented for 16 cases (39%). Of these 16 cases with documented naloxone administration, 2 (13%) were among those that reported complete resolution of auditory dysfunction at time hospital discharge, 5 (31%) were among those that reported partial resolution, 2 (13%) were among those that reported no resolution, and 7 (44%) were among those that did not provide documentation.

Of the 41 cases, 12 (29%) reported presence of a hypoxic event, 25 (61%) reported no presence of a hypoxic event, and 4 (10%) were coded as unknown presence of a hypoxic event. Specifically, for the 16 cases that had documentation of naloxone administration, 13 (81%) were associated with documentation of a hypoxic event, 2 (13%) were associated with unknown hypoxic event, and 1 (6%) was associated with no hypoxic event.

A second abstractor reviewed a randomized sample of 10 cases (24%). The two abstractors were in complete agreement for description of auditory dysfunction, presence of a hypoxic event, and need for ventilatory support with unweighted Cohen's kappa scores of 1. For resolution of auditory dysfunction, the abstractors generated an unweighted Cohen's kappa value of 0.8, indicating substantial to near perfect agreement.

Table 1 Characteristics of patients with auditory dysfunction exposed to opioid agents.

Patient no.	Age (years)	Gender	Opioid agent	Co-exposure	Route	Type of auditory dysfunction	Naloxone[±]	Hypoxic event[β]	Resolution
1	15	F	Oxycodone	Ibuprofen	–	Tinnitus	–	–	–
2	16	F	Tramadol	Quinine	–	Tinnitus	–	–	–
3	17	F	Methadone	–	–	Deaf	+	–	–
4	18	F	Morphine	Cocaine	PO	Mixed	–	–	–
5	19	M	Heroin	–	IN	Tinnitus	–	–	–
6	19	F	Oxycodone	–	–	Tinnitus	–	–	–
7	20	F	Heroin	–	–	Hypoacusis	+	+	No change
8	20	F	Methadone	–	–	Tinnitus	–	–	–
9	20	F	Methadone	–	–	Tinnitus	+	+	–
10	21	M	Heroin Oxycodone	Alprazolam Ethanol	–	Deaf	–	–	–
11	21	F	–	Cocaine Ethanol Marijuana	–	Deaf	+	?	–
12	21	M	Heroin	Marijuana	–	Hypoacusis	+	–	–
13	22	M	Heroin	Cocaine Marijuana	–	Deaf	+	+	Partial
14	22	M	Heroin Oxycodone	Alprazolam	IN	Deaf	–	–	–
15	22	F	Heroin	Alprazolam	–	Hypoacusis	+	?	Complete
16	22	F	Heroin	Acetaminophen	–	Hypoacusis	–	–	Partial
17	23	M	Heroin	Alprazolam Clonazepam Fluvoxamine	–	Hypoacusis	+	+	Partial
18	23	M	Heroin	–	–	Hypoacusis	+	+	Partial
19	25	M	Heroin	–	–	Deaf	–	–	–
20	26	M	Heroin	–	IV	Hypoacusis	+	+	Complete
21	27	M	Heroin	Valproate	–	Deaf	–	–	–
22	28	M	Oxycodone	Alprazolam Diazepam Quetiapine	–	Deaf	–	–	Complete
23	28	M	Heroin	–	–	Hypoacusis	+	+	No change
24	28	M	Oxycodone	Acetaminophen Aspirin	PO	Mixed	–	–	Partial
25	29	M	Fentanyl Heroin	Marijuana	IN	Deaf	+	+	–
26	29	F	Tramadol	Cyclobenzaprine Ranitidine	PO	Hypoacusis	–	–	Complete
27	30	F	Heroin	Ethanol	PO	Deaf[ǂ]	–	?	–
28	34	M	Heroin	–	IN	Deaf	+	–	Partial
29	34	M	Hydrocodone	Aspirin Eszopiclone	–	Tinnitus	–	–	–
30	35	M	Heroin	–	–	Mixed	–	?	No change
31	36	F	Tramadol	Ibuprofen	PO	Hypoacusis	–	–	Complete
32	36	M	Oxycodone	–	–	Tinnitus	–	–	Complete
33	40	M	Oxycodone	–	PO	Hypoacusis	–	–	Partial
34	42	F	Oxycodone	Furosemide Hydrochlorothiazide	–	Hypoacusis	–	–	–
35	42	F	Heroin	–	–	Hypoacusis	+	+	–
36	44	M	Fentanyl	–	TD	Deaf	+	+	–
37	44	F	Hydrocodone	–	–	Tinnitus	–	–	–
38	56	M	Methadone	*	PO	Hypoacusis	+	+	Partial
39	94	F	Codeine	–	–	Hypoacusis	–	+	No change

Table 1 (continued)

Patient no.	Age (years)	Gender	Opioid agent	Co-exposure	Route	Type of auditory dysfunction	Naloxone[±]	Hypoxic event[β]	Resolution
40	–	F	Tramadol Heroin	Clonidine Diazepam Ethanol	–	Mixed	–	–	–
41	–	F	Heroin	–	–	Tinnitus	–	–	Complete

*Allopurinol, asenapine, bupropion, clonazepam, lamotrigine, lithium, trazodone, valacyclovir, vilazodone

[ǂ] Only unilateral auditory dysfunction case, all other are bilateral processes

[±] – denotes no documented naloxone administration, + denotes documented naloxone administration

[β] – denotes no hypoxic event, + denotes hypoxic event,? denotes unknown hypoxic event

IN intranasal, *IV* intravenous, *PO* oral, *TD* transdermal

Discussion

Overall, our study characterized the phenomenon of opioid-associated ototoxicity using two decades of statewide Poison Center data. Our findings illustrate that ototoxicity occurs irrespective of hypoxia and across the class of opioid agonists. Further, our study illustrated that the clinical presentation of ototoxicity is variable, with an equal distribution of tinnitus, hypoacusis, and deafness. Given a lack of documentation, the value of naloxone in the reversal of opioid-associated hearing loss remains unknown.

As sound waves travel through the external auricle and auditory canal, they reverberate off the tympanic membrane transferring their energy to the bones of the middle ear [11]. This energy is thereby transmitted to the inner ear through the oval window after which it propagates through the perilymphatic fluid before being transferred to the endolymphatic fluid [11]. Here the fluid waves cause mechanical deflections of the hair cells of the organ of Corti, which are tethered via the stria vascularis [11]. In a complex physiological process, these deflections translate the energy, by the influx of potassium cations, into neural signals, which eventually are processed by the auditory cortex in the temporal lobe [11].

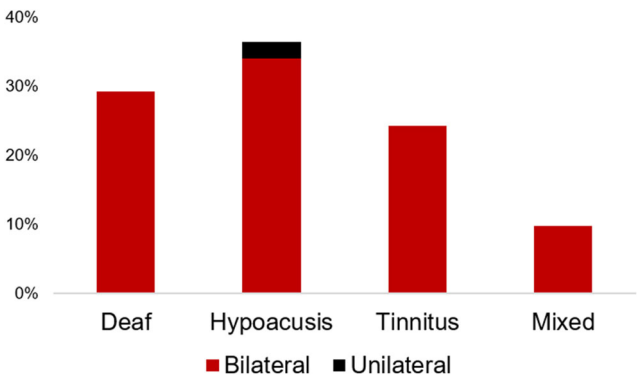

Fig. 2 Descriptive analysis of auditory dysfunction by case.

Although the exact pathophysiological mechanism of opioid-associated ototoxicity is not known, several postulates include genetic variations in metabolism, transport and channel alterations that impact homeostasis, ischemic damage to the auditory system, and a direct opioid receptor effect [4, 8, 12]. In the past, potential differences in genetic polymorphisms, either in regard to enzymatic metabolism or receptor activity and expression, were proposed as a potential etiology for opioid-associated ototoxicity [7, 8]. However, as demonstrated in our study and prior medical literature, this phenomenon has been described throughout the class of opioid analgesics, of which many have differing metabolic pathways, and given the lack of a common toxic metabolite, this potential mechanism has largely been discarded [1, 2, 5, 7–9]. There may be some agent-specific metabolites or variations in anatomic location where these compounds accumulate that make certain opioids more likely to cause ototoxicity. Another potential cause involves disruption of the blood-labyrinth barrier of the inner ear [12]. As an organ system, the inner ear is highly subject to dysfunction secondary to homeostatic changes, such as oxygen supply and endolymph composition, a fact which supports this etiologic theory.

As previously described, the inner ear structures are highly metabolic due to the intense energy requirements needed to maintain endolymphatic and electrochemical gradients, thereby making them susceptible to ischemic damage. Hypoxia may cause ototoxicity due to sensitivity of the cochlea to ischemic insult [8]. Currently, hypoxia-induced ototoxicity is believed to occur secondary to damage to the stria vascularis or the hair cells of the organ of Corti [8, 12]. Further, hypoxic injury may also occur as a result of opioid-induced endothelin production leading to cochlear vasoconstriction [13]. Less commonly, hypoxic insult can damage the neural audition pathways and processing centers, such as the temporal lobe, causing auditory dysfunction independent of cochlear damage [8, 12]. However, our study demonstrates through numerous case reports that ototoxicity occurred in the absence of a documented hypoxic event.

Another emerging mechanism with a growing body of evidence is a direct opioid receptor effect. This hypothesis is congruent with the results from our study, which clearly demonstrate that opioid-associated ototoxicity occurs across the class of opioid agonists. Opioid receptors are located in the inner ear of rats and guinea pigs, [14, 15] and they appear to exist in the spiral (cochlear) ganglion of mice and humans [12, 16]. Activation of these receptors by endogenous opioid compounds therefore likely has a role in the neuro-modulation of sound. Further, it is possible that effects on these receptors following an opioid overdose may result in the development of cochlear damage and auditory dysfunction.

The clinical and long-term health outcomes of opioid-associated ototoxicity have yet to be fully elucidated, namely, the severity and duration of auditory dysfunction [6, 8]. Further, anecdotal evidence has suggested that naloxone administration has a limited role, if any, in improving the clinical outcomes of opioid-associated ototoxicity. While our results demonstrated that a majority of patients had at least partial improvement in hearing function following the administration of naloxone, a significant portion had no documentation of resolution of auditory dysfunction, thereby severely limitation the generalizability of these results. Therefore, at this time, the role of naloxone and its potential role in the extent and/or duration of auditory dysfunction resolution remains unknown.

The phenomenon of opioid-associated ototoxicity has long been described in the literature through case reports. This study approached this clinical syndrome in a larger retrospectively derived cohort of patients. Our study used a state-wide poison center database, in lieu of an institution-specific set of cases, increasing the generalizability of our results. This, in conjunction with its span of two decades, offers a more longitudinal description of this phenomenon that is not limited to a specific set of societal, demographic, and temporal considerations. Further, employing two search functions relying on different objective datapoints increases our likelihood of capturing all appropriate cases for inclusion. Because several of the clinical presentations discussed, including hypoacusis and deafness, manifest organically with age, the younger population identified in the study allowed for a stronger conclusion regarding our ototoxic, opioid-dependent hypothesis.

We must acknowledge the limitations of this present study. Our most significant limitation arose within the study design itself, which utilized a retrospective approach and information from a database. Given the nature of our record review, we must consider the potential implications of human error and recording bias that may exist and those that may be exacerbated by our single abstractor review design. Further, while necessary for the feasibility of a large database study, using a manual search function for this record review introduces a potential selection bias, namely, that cases meeting the inclusion criteria were not identified. Another limitation to our study is that the impact of chronicity and route of exposure could not be fully captured within the ToxiCALL® database. Finally, our study does include several cases where several co-ingested ototoxic agents were implicated, which may have altered the threshold for opioid-associated hearing loss. Nonetheless, most of the study subjects did not have such co-exposures. Further, it is also imperative to consider the potential for adulterated agents, in particular with exposures reporting the illicit use of heroin. This consideration is especially important in our study, given that nearly half of our cases reported exposure to heroin. Both co-ingested ototoxic agents and adulterated opioid agents present confounding variables that limit the conclusions that can be made about the causality or association between opioids and ototoxicity. However, given the nature of descriptive studies, these confounding variables cannot be isolated out of the study population; thus, studies with larger sample sizes, such as ours, are necessary to describe these phenomena. While a prospective observational study would provide the best data to evaluate the impact of these variables, it is not practical given the low frequency of ototoxic events.

A logical future direction in the investigation of opioid-associated ototoxicity should attempt to elucidate its exact pathophysiologic mechanisms in order to better comment on prevention, prognosis, and treatment options. Further, subgroup analysis involving acute, chronic, and acute-on-chronic exposures, as well as the route of exposure, should follow these results to capture the impact of chronicity and route on clinical outcomes. Unfortunately, this may not be feasible given the rarity of this clinical syndrome. Resolution of this opioid-associated ototoxicity should also be further characterized. Finally, while the state-wide study design was strong, a national study, including between-cohort matching, would greatly assist in approaching these more nuanced endeavors.

Conclusion

While prior literature described the clinical phenomenon of opioid-associated ototoxicity through individual case reports or small case series, our study characterized this event on a larger scale. While the majority of cases were associated with heroin exposure, we demonstrated that ototoxicity occurs with agents across the opioid class and is irrespective of hypoxic events. Further investigation is needed to clarify the impact of risk factors, such as chronicity and route, the long-term health outcomes, and the potential therapeutic role of naloxone.

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Compliance with Ethical Standards

Conflict of Interest Authors Dr. Alexander Mozeika, Dr. Bruce Ruck, Dr. Lewis Nelson, and Dr. Diane Calello declare they have no conflicts of interest.

Ethical Approval This study was approved by the Rutgers Newark Health Sciences Institutional Review Board.

Previous Publications/Presentations American College of Medical Toxicology, Annual Scientific Meeting 2019 – Lighting Oral Presentation.

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