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REVIEW

Managing intoxications with nicotine-containing e-liquids

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ABSTRACT

Introduction: Nicotine is an addictive and poisonous agent. The recent development of e-cigarettes has caused a new demand for highly concentrated nicotine-containing solutions. These concentrated nicotine solutions have also increased the risk of nicotine overdoses.

Areas covered: Essential factors for nicotine exposure are the concentration of the nicotine-containing e-liquid solution and its pharmacokinetics. Liquid nicotine refills contain nicotine in varying concentrations, which vary widely between and within products. The pharmacokinetics of nicotine are dependent on the route of administration, renal/hepatic clearance and urinary pH. The dose is another essential determinant of nicotine exposure. There is a considerable discrepancy between the generally accepted lethal dose and symptoms reported in case studies. Ingested doses correlate poorly to clinical symptoms. Symptoms of liquid nicotine toxicity vary from mild to severe between patients and are the result of overstimulation of nicotinic acetylcholine receptors, which may lead to fatal respiratory failure and cardiovascular collapse.

Expert opinion: The literature on nicotine-containing e-liquid intoxications originating from vaping device refills are mainly case reports. Based on these case reports, we propose a treatment plan which is primarily symptomatic. Research should focus on providing insight on its toxicity, based on oral and transdermal pharmacokinetics and on toxicodynamics.

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E-cigarettes; intoxications; nicotine-containing e-liquid; treatment plan

1. Introduction

Nicotine is an addictive and toxic compound that has been known to man for a long time. Until the recent introduction of e-cigarettes, nicotine was never smoked or ingested as a single compound, but always as part of smoking or ingesting tobacco. The tobacco plant, *nicotiana tabacum* was named after Jean Nicot de Villemain after the introduction of nicotine leaves and seeds for medicinal purposes in 1560. The first isolation of nicotine from tobacco took place in 1828 by the German chemists Posselt and Reimann [1]. Not long after this introduction, researchers discovered the neurotoxic action of nicotine. Therefore, nicotine was used as a potent pesticide in agriculture as well. The amount of nicotine used as an insecticide was over 2500 tons worldwide from World War II until the 1980s [2]. However, because of fatal intoxications as a result of inhalation, ingestion or skin contact, the use and production of nicotine decreased drastically over the last decades [3].

Nicotine originating from tobacco is estimated to be the second most widely used drug in the world after caffeine from coffee and tea. Nicotine is consumed regularly across all cultures, countries and almost all religions [4]. In the last 40 years, smokers have been under increasing pressure to quit smoking. This pressure has been increasing because of the many carcinogens and oxidizing chemicals that are present in tobacco smoke and the increased risk of diseases, including cancer, cardiovascular disease and COPD [5,6]. Based on the high use of nicotine and the rich history of the compound, a considerable amount of knowledge on smoking prevalence is available [7].

Since e-cigarettes are advertised to contain fewer carcinogens, they quickly gained popularity among smokers. Additionally, e-cigarettes have also been marketed as supporting in the cessation of smoking, as well as providing additional health benefits over cigarettes [8]. The appearance of e-cigarettes has generated a whole new market for nicotine, however. E-cigarettes use nicotine in a highly concentrated solution (nicotine-containing e-liquid) to release nicotine. The generation of this market has resulted in unprecedented access to potentially toxic doses of nicotine in the home environment [9]. There are several reports of accidental nicotine intoxications in young children [10] but also reports of suicide attempts by adults using nicotine-containing e-liquids and of accidental transdermal absorption during handling of the liquid nicotine [11]. One study using the National Poison Data System (NPDS) for nicotine and tobacco product exposures among children younger than 6 years showed that between January 2012 through April 2015, the child exposure to e-cigarette products increased ~1500% [12]. Children exposed to e-cigarettes had a higher chance of

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Article highlights

- E-cigarettes contain nicotine in a highly concentrated solution. The generation and increasing popularity of the e-cigarette market has resulted in unprecedented access to potentially toxic doses of nicotine in the home environment.
- Nicotine pharmacokinetics are crucial in predicting nicotine exposure and blood plasma concentrations. Researchers have performed many studies into the absorption, distribution, metabolism and excretion of nicotine in the last few decades.
- Nicotine and cotinine serum or saliva concentrations may be useful for confirming nicotine-containing e-liquid intoxications, but are not useful for guiding therapy due to the rapid onset of symptoms.
- Nicotine is estimated to have a human oral LD_{50} of 6.5–13 mg/kg.
- The symptoms of nicotine toxicity are not dose-dependent and resemble the cholinergic toxidrome. Symptoms of severe toxicity typically occur within 4 hours and consist of lethargy, convulsions, and coma and finally respiratory paralysis.
- Treatment for nicotine-containing e-liquid intoxications is mostly supportive and symptomatic. Most life-threatening aspects of nicotine poisoning are respiratory muscle weakness and respiratory arrest. Monitoring of respiratory function and consideration of intubation if indicated is the most important aspect of care. In the case of dermal exposure, however, exposed skin should be washed thoroughly with water and soap to avoid continued absorption of nicotine.

This box summarizes key points contained in the article.

hospitalization and a higher chance of a severe outcome. The authors attributed this rise in e-cigarette exposure by the increased use of the products. A retrospective study between 2012 and 2018 showed 5277 exposures, of which 3033 involved combustible cigarettes, 1489 involved e-cigarettes and 818 involved other nicotine containing devices in California (e.g. nicotine patches) in California [13].

Evidence-based treatment protocols for acute nicotine poisoning from liquid formulations are currently lacking. Therefore, this study's main objective is to provide a summary of the literature on the toxicity and propose a treatment plan for intoxications with nicotine-containing e-liquids.

2. Methods

Relevant literature was obtained using literature databases PubMed, Web of Science and Google Scholar in the period of December 2019 to May 2020. The main search terms used included 'liquid nicotine' and 'intoxications.' These search terms were supplemented with combinations of 'electronic nicotine delivery systems,' 'ENDs,' 'pharmacokinetics,' 'pharmacodynamics,' 'lethality,' 'lethal dose,' 'symptoms,' 'plasma concentration,' 'case,' 'case report' either alone or combined. The results were evaluated on quality and fit with the main objective. Also, cross-references were used.

3. Electronic nicotine delivery systems

E-cigarettes, or better, electronic nicotine delivery systems (ENDS) are the largest source for liquid nicotine exposure in the home environment. In the context of this review, the term ENDS will be used as a carrier device for liquid nicotine. ENDS are handheld devices that produce an aerosol from a solution which the smoker inhales. The aerosol typically contains nicotine, chemicals for flavor and carrier solvents. Examples of carrier solvents found in ENDS are propylene glycol and vegetable glycerin (glycerol) [14]. Although the components of the aerosol are more or less similar, wide variations exist in terminology, design and engineering of ENDS.

Some ENDS have an illuminating diode, simulating the burning end of a traditional cigarette. Newer ENDS, however, are designed to resemble other everyday objects like pens or flashlights. In 2014, more than 460 different brands of ENDS were on the market [15,16]. All these different brands vary substantially in quality and price. The ENDS are sold in various places like gas stations, online stores or specialized stores called 'vape shops.' They can be disposable or reusable. Recent case reports have identified several serious pulmonary diseases among people who have reported the use of nicotine or cannabis extracts in e-cigarettes [17]. Documented case reports described several severe pulmonary diseases among people who reported nicotine together with cannabis extracts being used in e-cigarettes [17]. It is suspected that this pulmonary disease is due to the presence of vitamin E acetate, which is utilized as a diluent in illegal cannabis vapes [18].

Despite the variations in terminology and design, ENDS products generally have various components in common. These components include an aerosol generator, flow sensor, solution storage area and battery [19]. ENDS can be of disposable or reusable nature that contain either an open or a closed system. When a user inhales the aerosol (or vapes) from the device, the flow sensor identifies a change in pressure and triggers the aerosol generator. This generator draws the nicotine solution from the storage area. In the storage area, the nicotine solution is heated or dispersed, generating the aerosol [20].

In open delivery systems, nicotine is supplied in the form of containers (canisters) with a concentrated solution of nicotine (liquid nicotine refills). Closed ENDS do not allow refilling. The liquid nicotine refills are available in different concentrations ranging from 0.5 mg/ml to a maximum of 100 mg/ml [21,22]. Nicotine-containing e-liquid refills are generally small and can contain up to 10 ml of this solution. According to the EU Tobacco Product Directive, such a refill can contain up to 200 mg. Due to a recent change in policies of the EU Tobacco Product Directive [23], significant advances have been made in for example child-resistant packaging and tamper-proof vials. However, the products did not completely comply to the policies yet [24]. Manufacturers in the United States are prohibited from making false health claims, though manufacturers of e-cigarette refills are subject to fewer restrictions [25]. The variable nicotine concentrations allow users to adjust the nicotine exposure to fit their needs [26]. However, there may be a large discrepancy between the stated nicotine concentration on the label and the actual concentration. For example, a study of 35 liquid refills showed that the actual nicotine concentration was substantially different from the label statement in up to 89% of the cases [21,24,27]. The

measured nicotine concentrations in the ENDS solution ranged from 0 to 36 mg/mL in the different sized cartridges. Concentration differences between the label and actual nicotine content ranged from 1% to 31% for different batches of the same brand of e-cigarettes [28,29]. In comparison, the amount of nicotine in the tobacco in a traditional cigarette varies between 10 and 30 mg [30], and the actual exposure to nicotine for a smoker by smoking a cigarette is estimated between 0.05 and 3 mg per cigarette [31,32]. Besides the dose, the users' actual exposure to nicotine is also determined by nicotine pharmacokinetics.

4. Nicotine pharmacokinetics & pharmacodynamics

Nicotine pharmacokinetics are crucial in predicting nicotine exposure and blood plasma concentrations. Researchers have performed many studies into the absorption, distribution, metabolism and excretion of nicotine in the last few decades.

Nicotine absorption through biological membranes is pH dependent. Since nicotine is a weak base (pKa = 8.0), it is present in its ionized form under acidic conditions, and it does not cross membranes very easily [33]. Therefore, manufacturers increase the pH to facilitate the absorption of nicotine through the cell membrane. The newer nicotine salt liquids have a lower pH (as low as 5) to facilitate inhalation and allow for effective dosing of high nicotine concentrations in small aerosol volumes [34]. Data on the absorption of nicotine-containing e-liquids is scarce. The bioavailability of nicotine via the oral mucosa is 20–45% [35,36], and this is based on a study with nicotine replacement therapy (nicotine gum, for example). The skin absorbs the nicotine as a base dependent on the pH of the liquid, which may, therefore, be a potential risk for nicotine intoxications [37]. This concept was proved by Maina et al. [38]. The authors filled chambers of a Franz diffusion system, a model for percutaneous absorption, with liquid nicotine and donated skin cells for 24 hours. The nicotine was detectable after 2 hours and the absorbed amount gradually increased.

After absorption, nicotine enters the systemic circulation. At pH 7.4, nicotine is about 69% ionized and 31% unionized. Less than 5% of the nicotine in the bloodstream binds to albumin [39]. The body distributes nicotine extensively to tissues with a steady-state volume of distribution averaging 2.6 L/kg. The highest affinity for nicotine is found in the liver, kidney, lung and spleen. The lowest affinity for nicotine is found in adipose tissue, based on human autopsy samples from smokers [40]. Nicotine accumulates in gastric juice and saliva. Most essential for nicotine intoxications is the accumulation of nicotine in the brain, which accounts for the addictive effects. The time course of nicotine accumulation in the brain is highly dependent on route and rate of dosing. For example, after a single cigarette puff, nicotine enters the brain in 10–20 s. The intake of nicotine during smoking depends on the length of the puff, depth of inhalation, degree of dilution with room air and the rate and strength of the puffing [35].

The quantitative aspects of human nicotine metabolism are well known. Nicotine is primarily metabolized by the liver and undergoes extensive metabolism [36]. Therefore, enterohepatic recirculation is unlikely. There are six primary metabolites of nicotine identified so far, which are inactive. The lactam derivative cotinine is the most important metabolite, which accounts for nearly 90% of a systemic dose of nicotine in urine [35]. Other nicotine metabolites in urine include nicotine N′–oxide (4–7% of a nicotine dose) and nicotine glucuronide (3–5%). The liver metabolizes 70–80% of the ingested nicotine to cotinine via a mechanism involving cytochrome P450 isoform 2A6 (CYP2A6). Cotinine can be excreted unchanged in the urine (10–15% of the nicotine) but can also be further metabolized by the liver. Cotinine metabolites found in urine include trans–3′–hydroxycotinine glucuronide (7–9%), cotinine glucuronide (12–17%) and trans–3′–hydroxycotinine (33–40%). The plasma half-life (t1/2) of nicotine averages between 100 and 150 min [36]. Metabolism of nicotine can be influenced by various characteristics, including gender, age, food intake and medication use [41].

Glomerular filtration and tubular secretion by the kidney are the main excretion routes for unmetabolized nicotine [36]. The renal clearance of unmetabolized nicotine varies between 17–600 ml/min [42] and is dependent on urine pH and urinary flow. In acidic urine, the nicotine is mostly ionized, thereby minimalizing tubular reabsorption. For example, when the urinary pH is 4.4, renal clearance of nicotine can increase up to 600 ml/min. In alkaline urine, however, renal clearance can become as low as 17 ml/min due to tubular reabsorption.

Elimination of cotinine is mainly through metabolism to 3-hydroxy-cotinine [33,41]. The cotinine metabolites are excreted unchanged in the urine. Extreme urinary acidification increases the glomerular filtration of cotinine up to 50%. Cotinine is less alkaline and therefore less sensitive for physiological pH changes. The urinary flow rate influences the excretion of cotinine, as is the case with nicotine [43].

In summary, nicotine pharmacokinetics depend on the route of administration, renal/hepatic clearance and urinary pH. As with every other drug, total nicotine exposure and plasma concentrations depend on the dose and pharmacokinetics.

Pharmacodynamic effects of nicotine are mediated via nicotinic acetylcholine receptors (nAChRs). nAChRs are located on the cell membrane of cells in the central nervous system, autonomic ganglia (sympathetic and parasympathetic nervous system), and neuromuscular junctions. Similar to acetylcholine, binding of nicotine to the postsynaptic nAChRs results in the opening of the cation (Ca^{2+}, Na^{+} and K^{+}) permeable ion channels, resulting in the rapid depolarization of target cells. Depolarization subsequently opens voltage-dependent calcium channels. In contrast to acetylcholine, nicotine is not readily deactivated by acetylcholinesterase resulting in prolonged activation of the nAChRs. Persistent activation of nAChRs by nicotine may lead to receptor desensitization and depolarization blockade. In summary, exposure to nicotine may initially result in a stimulation of the nAChRs, followed by a blockade. In addition to its effects on nAChRs, chronic nicotine exposure may also change the expression of muscarinic AChRs [44].

5. Toxicity of nicotine

5.1. Intoxication

There is a weak relation between the dose of nicotine and the clinical symptoms of nicotine-containing e-liquid intoxications. Therefore, differentiation between mild and severe intoxications is based on clinical symptoms.

In low doses, comparable to cigarette smoking, nicotine exposure produces an increase in heart rate, blood pressure and respiratory rate. Besides cardiovascular effects, a low nicotine dose induces a slight tremor, cutaneous vasoconstriction, nausea and increased gastrointestinal motility [45]. In the central nervous system, stimulation of nicotinic receptors causes increased alertness and euphoria.

With mild intoxication and in the early phase of moderate/severe intoxication, symptoms such as headache, dizziness, confusion, agitation, anxiety, restlessness, sweating and tremors may occur. Also, tachycardia, pallor (due to vasoconstriction) and hypertension may develop [44,46,47]. Since nicotine is quickly metabolized, mild symptoms are likely to disappear within 4 to 6 hours. Patients with symptoms of nicotine toxicity after transdermal nicotine patch application are an important exception to this rule, as a drug reservoir may remain in the skin after patch removal and may serve as a source of continuing absorption [45].

In moderate/severe intoxication, the stimulation phase will be followed by depression of organ functions. Early-stage symptoms, such as headache, dizziness, confusion, agitation, anxiety, restlessness, and tremors, may be followed by lethargy, convulsions, and coma. Weakness, fasciculations, hypotonia, and hyporeflexia can result in paralysis, including respiratory paralysis.

In cases of severe nicotine poisoning, early symptoms are due to nicotinic cholinergic excess. This excess can cause an increase in salivation, nausea, vomiting and diarrhea. These symptoms can occur within minutes after systemic absorption [45]. Vasoconstriction is also a sign of early, severe nicotine poisoning, causing hypertension and pallor. Besides vasoconstriction, tachycardia is another cardiovascular symptom of severe nicotine poisoning in early stages. Nicotinergic stimulation can cause mild sinus tachycardia and a variety of cardiac dysrhythmias. These dysrhythmias can vary from somewhat innocent supraventricular tachycardia to severe electrophysiological toxicity with AV blocks and ventricular arrhythmias. Studies show a dose-dependent arrhythmogenicity of nicotine in dogs. Intravenous administration of nicotine induced supraventricular arrhythmias, atrioventricular junctional arrhythmias, and ventricular arrhythmias. In these studies, supraventricular bradycardia was found in 30 (83%) experiments, supraventricular arrhythmia in 30 (83%), sinus arrest in 18 (50%;), atrial ectopics in 24 (67%), and atrial tachycardia in 98 experiments (25%;) [48]. Case reports support this data in humans [49,50]. Neurologically, nicotine causes headache, dizziness, confusion, ataxia and perceptual distortion [45].

In moderate and severe intoxications, the nicotinic stimulation phase will be followed by depression of organ functions due to persistent blockage of the receptor. Symptoms during this second phase of a severe nicotine intoxication are potentially fatal. Lethargy, convulsions, and coma thus follow early-stage symptoms. Weakness, fasciculations, hypotonia, and hyporeflexia can result in paralysis, including respiratory paralysis. These symptoms of toxicity typically occur within 4 hours after exposure [10].

Additionally, nicotine is an irritant when ingested. Therefore, ingesting a high dose of nicotine-containing e-liquid can cause contraction of the throat muscles and burning in the mouth [45].

5.2. Lethal nicotine dose

Established by Mayer in 2014, there is a disagreement between the generally accepted lethal dose and documented cases of nicotine intoxications [51]. The typical databases and textbooks consistently indicate that the lethal ingested dose for adults is around 30 to 60 milligrams. However, this number is based on a textbook written by Rudolf Kolbert in 1906 who estimated the lethal nicotine dose of 60 mg as a result of dubious self-experiments [51]. This amount corresponds to five cigarettes or 10 ml of a diluted nicotine-containing e-liquid solution.

Later experiments showed that the value from Kolbert is not accurate and that the LD_{50} value of nicotine varies considerably between species. For example, the LD_{50} of nicotine is 3.3 mg/kg in mice, whereas the LD_{50} value of nicotine is 50 mg/kg in rats [52]. The (controversial) postulated fatal dose of 60 mg dose in humans corresponds to an LD_{50} of 0.8 mg/kg, which is much lower. This low LD_{50} indicates that nicotine is a highly toxic and potentially lethal compound in e-liquids and patches [53,54]. However, fatal nicotine intoxications are relatively uncommon. Additionally, other nicotine overdose reports are barely compatible with the standard lethal dose of 60 mg or lower with a maximum nicotine intake of 20 mg [55–57].

Solarino et al. reviewed literature reports on fatal nicotine intoxications. This review of post-mortal findings indicates that nicotine concentrations of 2 mg/L or higher are lethal [47]. Reports from fatal intoxications showed plasma concentrations up to 4 mg/L, which would require a 500 mg of oral nicotine, according to Mayer [51]. Taken all this together, nicotine is estimated to have a human oral LD_{50} of 6.5–13 mg/kg. A case report that also presents an overview of more recent nicotine intoxication cases supports this statement [58].

6. Diagnosis

Plasma concentrations of nicotine and its metabolite cotinine are not convenient markers to confirm the exposure and estimate the expected degree of toxicity. Given the rapidity of nicotine toxicity, the time required for laboratory analysis precludes their use in treating an acutely poisoned patient. The main use for these concentrations is for forensic purposes and for use in tobacco regulations.

In the case studies on nicotine-containing e-liquid intoxications, various methods are used for the analysis of nicotine and metabolites. Examples of these techniques are gas chromatography, high-performance liquid chromatography, gas chromatography-mass spectrometry or liquid chromatography with mass spectrometry. All these techniques have their advantages and disadvantages like complexity the sample work-up and analysis, and time to result. A useful review of these techniques is described in detail by Rentsch et al. [59].

The metabolite cotinine might be a better biomarker for forensic purposes than nicotine in case of accidental ingestion. The half-life of cotinine is considerably longer (13–19 hours) than that of nicotine (100–150 minutes), resulting in higher serum concentrations. Secondly, cotinine is an important metabolite eliminated in the urine, facilitating its analysis. Because of this, clinicians often use cotinine as a biomarker for nicotine exposure [60]. In nicotine-containing e-liquid intoxications, however, the survival rates and clinical patterns do not always correlate with cotinine concentrations [61]. A possible explanation for this inconsistency could be that the metabolism rate of nicotine might differ between individuals. Another explanation could be that liver damage interrupts the metabolism of nicotine to cotinine. However, these explanations are not studied.

Additionally, cotinine levels may be relatively low early in the ingestion due to ongoing formation. Whereas later in the ingestion, cotinine levels may remain high while the nicotine has been fully metabolized.

To overcome the problem of diagnostic time, newer test are being developed. One suggestion is a point-of-care saliva test for nicotine [62]. This test reacts with metabolites of nicotine, including cotinine. Due to the nature of the test, it can only distinguish between exposed to nicotine or not exposed to nicotine in accidental exposures, and is thus only useful for confirmation and not for quantification. Therefore, this test may be useful for proving nicotine exposure but not for clinical guidance. In conclusion, nicotine and cotinine serum or saliva concentrations may be useful for confirming nicotine-containing e-liquid intoxications but are not useful for guiding therapy due to the rapid onset of symptoms. Its major limitations are the necessary time to perform the analysis and that the test is only useful if the patient is a nonsmoker. Treatment should, therefore, be based on the evaluation of the patient's symptoms and medical history.

7. Treatment

Age is an essential consideration in treating nicotine-containing e-liquid intoxications. Adult exposures are frequently caused by suicide attempts resulting in severe intoxication symptoms [63–66] In children, however, exposures are mainly accidental [67–69].

Treatment for nicotine-containing e-liquid intoxications is mostly supportive and symptomatic. In the case of dermal exposure, however, exposed skin should be washed thoroughly with water and soap to avoid continued absorption of nicotine.

For both adults and children, treatment options consist of activated charcoal, atropine for bradycardia and benzodiazepines. In two case reports, activated charcoal was administered to the patients. In one case, the patients showed an improvement of consciousness in combination with atropine [61], and in the other case, there were no other adverse effects established [70]. Children that ingested small amounts of nicotine-containing e-liquid or only show minor symptoms should be observed and monitored until the symptoms have disappeared. Discharge is generally safe after 4 to 6 hours of observation since severe intoxication syndromes occur within 4 hours [9,19,71]. When a severe intoxication is suspected, the child should be brought to the hospital. Activated charcoal should only be administered if the child is still asymptomatic, alert, cooperative, and can be administrated within one hour after ingestion [22,71]. After this timeframe or when more severe symptoms are already present, charcoal should not be given because of the risk of aspiration [71]. One case describing the intoxication of an 18-month old child that ingested nicotine-containing e-liquid showed a decrease of symptoms after 6 hours of observation and supportive care [71]. The child was intoxicated with a 1 mg/kg dose. A fatal case was reported in a child swallowing 4 mg/kg. Despite symptomatic treatment, the child developed fatal hypoxic brain damage [68]. In adults, activated charcoal is always the treatment of choice, together with careful monitoring of cardiovascular and respiratory functions. The preferable dose for both children and adults is 1 g/kg without sorbitol since sorbitol can induce spontaneous vomiting [71].

In both adults and children, respiratory problems and bradycardia should be treated with 0.5–1.0 mg atropine in 5–10-minute intervals [61]. Other cardiac arrythmias should be treated according to clinical observations and the European resuscitation guideline [72]. Although atropine is a muscarinic cholinergic receptor antagonist and therefore may not block nicotine actions, it is still indicated for severe bradycardia as stated in the bradycardia algorithm from the European resuscitation guidelines [72]. Seizures should be treated by administering benzodiazepines [56]. In adults, hypotension is initially treated with fluid resuscitation and if refractory, expanded with vasopressors (dopamine or norepinephrine) [42,56]. Monitoring of heart and respiratory function combined with intubation are the most crucial aspects of care in nicotine-containing e-liquid intoxications.

8. Conclusion

The main objective of this review was to provide an outline of the literature on toxicity and propose a treatment for nicotine-containing e-liquid intoxications. Nicotine overdose is an increasing problem due to the widespread availability of e-cigarettes and nicotine-containing e-liquid. The symptoms of nicotine toxicity are not dose-dependent and resemble the cholinergic toxidrome. Analysis of nicotine and cotinine serum concentrations may be helpful in some circumstances, but are time-consuming and therefore of limited value in acute overdose settings concerning the short onset of the overdose symptoms. The treatment of nicotine-containing e-liquid intoxications is mainly symptomatic, and we

propose activated charcoal, atropine and benzodiazepines and fluid resuscitation when systemic symptoms arise. Cardiac and respiratory function should be monitored closely.

9. Expert opinion

The upcoming market of the e-cigarette has allowed for easy access to high doses of nicotine. This creates potential health risk in case of accidental ingestions, especially by children, or suicide attempts by adults. Additionally, spilling of the refill containers could lead to accidental transdermal absorption in both adults and children.

Currently, the research in the field on the toxicity and treatment of nicotine intoxications is limited and new research should focus on providing insight in its toxicity, based on oral and transdermal pharmacokinetics and on toxicodynamics. The refills should contain warnings regarding the maximum content based on the results from safety studies and case reports. The liquid nicotine containers should be provided with a proper list of ingredients and nicotine concentrations, volume and total dose. Also, the option of adding flavors and appealing packages should be limited to prevent attention of children as much as possible. Lastly, the design of the refills should be such, that accidental opening and swallowing by children is not possible. Regulations regarding these issues should be strengthened to limit the risk of accidental intoxications.

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