Promise
The jury is out on the safety of e-cigarettes.

BY HOWARD BELL

Bobbi Kruse, a program administrator at the University of Minnesota Medical Center, Fairview, smoked cigarettes for 38 years. "I enjoyed smoking and had no desire to quit," she says. But last July's price hike that came as a result of an increase in the state's tax on tobacco products pushed her over the edge. Rather than give up cigarettes altogether, she switched to less expensive e-cigarettes. "I have no cravings and still get the enjoyment of smoking without smoking," she says.

Kruse is among a growing number of e-cigarette users. According to the Centers for Disease Control and Prevention (CDC), one out of every five cigarette smokers say they have tried e-cigarettes. E-cigarette sales in the United States exceeded $1 billion in 2013, doubling since 2012, and tobacco companies are placing big bets on them. A Wells Fargo market analysis predicts e-cigarette sales may exceed tobacco cigarette sales in 10 years. Three U.S. tobacco companies have already bought brands and deployed their considerable marketing muscle, unaffected by regulation, to glamorize e-cigarettes through celebrity endorsements, TV and print ads, online ads, social media, NASCAR sponsorships and product giveaways.

The rapid rise of e-cigarettes prompts the question—Are we beginning a new chapter in the fight against smoking?

Although some question their safety, others view e-cigarettes as a legitimate tool to help tobacco smokers kick the habit. As Mayo-Scottsdale's Cancer Prevention and Control Program co-director Scott Leischow, Ph.D., sums it up: "We are in the midst of a national experiment that could dramatically lower the risks of smoking."

Playing with fire?
Electronic cigarettes are battery-operated devices that often look like regular cigarettes. Invented by a Chinese pharmacist in 2004 as an aide for quitting smoking, they have been sold in the United States since 2007 and generally cost less than half the price of regular cigarettes.
Drug delivery devices

E-cigarettes are legally defined as tobacco products, but in reality they’re drug-delivery devices. Between 2008 and 2010, the Food and Drug Administration (FDA) tried to regulate them as such because manufacturers were claiming e-cigarettes could help people quit or cut back on tobacco cigarettes.

One e-cigarette maker sued the FDA in federal court, which ruled in 2010 that e-cigarettes can only be regulated as tobacco products under the 2009 Family Smoking Prevention and Tobacco Control Act unless the manufacturers make therapeutic claims. In September 2010, the FDA sent letters to several e-cigarette makers warning them to stop making unsubstantiated claims that e-cigarettes can help people stop smoking tobacco.

“If the FDA had gotten its way and regulated e-cigarettes as a drug-delivery device, the e-cigarette makers would have to fund at least three randomized clinical trials that prove they’re safe and effective,” says Richard Hurt, M.D., director of Mayo Clinic’s Nicotine Dependence Center.

Instead, the FDA is expected to eventually regulate e-cigarettes as tobacco products, which means there will be rules about what they contain and how they’re made and marketed, but they will not be subjected to the “safe and effective” standards used for drugs and medical devices—as long as manufacturers don’t make claims that they help people quit or cut back on tobacco smoking.

Puffing an e-cigarette activates a heating element that vaporizes a solution of nicotine (the cartridge in the “filter” end of an e-cigarette can contain as much as 24 milligrams), flavoring (eg, bubblegum, cookies and cream, fruit punch) and propylene glycol into a cloud that looks similar to tobacco smoke. An LED light, usually blue, green or orange, at the tip of the battery glows like the end of a tobacco cigarette. Because they produce vapor instead of smoke, using e-cigarettes is often referred to as “vaping.”

Although e-cigarettes contain far fewer toxins and carcinogens than tobacco cigarettes, no one has the answer to the safety question yet, says Kola Okuyemi, M.D., M.P.H., who researches e-cigarettes at the University of Minnesota in his role as director of the university’s Program in Health Disparities and the Minnesota Center for Cancer Collaborations. “We just don’t have the science to answer these questions, and until the FDA starts regulating the content of e-cigarettes, researching these questions is going to be hard.”

That’s because each of the 250 e-cigarette brands sold today contains a different amount of nicotine as well as other chemicals. Literally no two are alike. “Right now,” says Okuyemi, “we’re living in an e-cigarette Wild West, with no laws controlling their sale, content, advertising or manufacturing process.”

In July of 2009, the Food and Drug Administration analyzed a small sample of e-cigarette cartridges from two leading brands and found they contained nitrosamines, a known carcinogen, and heavy metals, but in far lower amounts than are found in regular cigarettes. One cartridge contained diethylene glycol, a toxic chemical used in antifreeze.

Propylene glycol and the flavor chemicals used in e-cigarettes are generally recognized as safe for use in food. But no big studies have been done on what happens when these chemicals are vaporized. One study presented at the European Respiratory Society in 2012 showed that e-cigarettes can cause airway irritation and inflammation in some users at least for a short period after vaping. A 2012 case report published in the journal Chest described a 42-year-old woman with asthma who developed a rare lipid pneumonia, causing chronic dyspnea and a cough that began when she started using e-cigarettes. “We know propylene glycol causes airway irritation in some individuals,” Okuyemi says. But studies so far show that the vapor produced by e-cigarettes is not inhaled deeply into the lung, nor does it produce an arterial spike of nicotine the way smoke from cigarettes does.

Another 2012 study, published in Toxicology, found the flavorings used in e-cigarettes contained cytotoxins in amounts that ranged from very low to “fairly significant,” depending on the brand and flavor. The amount of nicotine varied widely as well. And yet another 2012 study, published in Tobacco Control, found that nicotine levels in 35 different brands were often lower and sometimes higher than what the label listed. Three different e-cigarette cartridges of the same brand each produced a different amount with each puff.

The same study found six toxic chemicals in e-cigarettes, but the amounts were far less than those found in regular cigarettes. For example, formaldehyde concentrations were nine times higher in tobacco cigarettes, and acetaldehyde was 450 times higher than in the e-cigarettes tested. Likewise, the volatile organic compounds acro-
lein and toluene, and two types of nitrosamines were all present in e-cigarettes, but in far smaller quantities than in tobacco cigarettes. The researchers concluded that “substituting tobacco cigarettes with e-cigarettes may substantially reduce exposure to selected tobacco-specific toxicants.”

“Tobacco cigarettes contain more than 7,000 chemicals,” says Richard Hurt, M.D., director of Mayo Clinic’s Nicotine Dependence Center. “Sixty of them cause cancer. E-cigarettes contain two to three tobacco-specific carcinogens.”

Hurt says that although we can say with certainty that e-cigarettes contain fewer toxins than tobacco cigarettes, it doesn’t mean they’re safe or don’t cause harm. “We haven’t studied the short-term health effects enough, and we don’t have any studies on long-term effects,” he says.

A better way to quit?
Whether e-cigarettes are a good way to help people quit smoking remains to be seen as well. A 2013 New Zealand study published in *Lancet* concluded that e-cigarettes worked as well as nicotine patches in helping people stop smoking tobacco cigarettes. The study’s authors divided 657 adult smokers who wanted to quit into three groups: one that used nicotine patches, one that used e-cigarettes and one that received a placebo (e-cigarettes with no nicotine). Seven percent of the e-cigarette users quit for at least six months, compared with 6 percent of nicotine patch users and 4 percent of the placebo users.

The study got a lot of positive media attention, but Hurt points out its limitations. “If there’s not a doubling of the quit rate compared to placebo, then the nicotine-containing e-cigarette would not be considered effective,” he says.

After six months, one-third of participants continued using e-cigarettes. Many who relapsed to smoking tobacco also kept using e-cigarettes and so significantly reduced their tobacco cigarette consumption. In addition, nine out of 10 people in the e-cigarette and placebo groups said they would recommend e-cigarettes to friends trying to quit, where only 56 percent of the patch users said they would recommend patches.

Okuyemi found similar preferences among 50 African-American adults enrolled in his ongoing menthol cigarette quit study. “When we let people choose from different ways to quit, three out of four choose e-cigarettes,” he says. “They may be more appealing because they’re more like smoking than patches, sprays or lozenges. We can’t ignore this. If it can be shown that switching to e-cigarettes helps lots of people quit or cut back on tobacco cigarettes, we’re going to have to take a serious look at e-cigarettes.”

What should physicians tell patients?
The considerable debate within the scientific community about the pros and cons of e-cigarettes makes knowing what to say to patients a challenge. Kola Okuyemi, M.D., M.P.H., director for the University of Minnesota’s Program in Health Disparities and the Minnesota Center for Cancer Collaborations, says an honest discussion with patients has to include mention of potential benefits and harms.

**Potential benefits:**
- E-cigarettes are less toxic and, therefore, presumably less harmful than tobacco cigarettes.
- Studies show there is a good chance that you will reduce the number of tobacco cigarettes you smoke if you switch to e-cigarettes. It’s possible, but far less likely, that you will completely quit smoking.
- E-cigarettes are cheaper, cleaner and generally less annoying to others.

**Potential harms:**
- You may end up using both e-cigarettes and tobacco cigarettes. There is some evidence that using both makes it less likely you will quit tobacco.
- E-cigarettes contain known carcinogens and other potentially harmful ingredients whose long- and short-term effects on health have not been adequately studied.
- You will remain addicted to nicotine.
- Nicotine is a potential poison. (Physicians should remind e-cigarette users with young children that they should treat e-cigarettes as they do other poisons and keep them out of reach.)

Richard Hurt, M.D., director of Mayo Clinic’s Nicotine Dependence Center, tells patients who want to quit that there are other products available that have been proven to help stop smoking. “All of them have gone through clinical trials that show they’re safe and effective. When used in combination with counseling, they increase your chances of quitting even more. Try those first.”
Okuyemi says if nicotine replacement therapies (NRT) and other quit methods worked better, e-cigarettes might not even be considered as a possible quit device. “The fact is we don’t have any good quit treatments. They’re all lousy.” He points out that even if e-cigarettes aren’t any more effective than other quit methods, they may work better simply because more people may be willing to try them and stick with them because they satisfy the psychosocial reasons people smoke.

One way to improve e-cigarettes as a quitting aide is to enable them to deliver nicotine into the arterial blood more efficiently. In the New Zealand study, e-cigarettes delivered only about 20 percent of the nicotine delivered by an equivalent amount of cigarette smoking. For this reason, smokers using e-cigarettes to quit may find them ineffective. Phillip Morris and British American Tobacco Company both recently purchased nicotine inhaler technology that promises “pulmonary delivery.”

“We would love to have a metered dose nicotine inhaler to help people quit,” Hurt says. “If we had such a device that was safe and effective, we would use it to help people stop smoking tobacco. They’d still be addicted to pure medicinal nicotine, but studies show no serious harm from medicinal nicotine.”

Before e-cigarettes can become a legitimate way to quit tobacco smoking, far more research is needed not only to determine their harmfulness but also to determine if they may actually encourage tobacco smoking or make it harder, rather than easier, to quit tobacco. “There is some evidence,” Okuyemi says, “that tobacco cigarette smokers who try e-cigarettes are more likely to be unsuccessful quitters compared to smokers who never tried e-cigarettes.” The CDC fears that “if a large number of adult smokers start using both traditional and e-cigarettes, rather than quitting tobacco, there will be a net negative public health effect.”

Another concern is whether e-cigarettes are a gateway to tobacco cigarettes, especially for young people. A 2013 University of Oklahoma survey of 1,300 college students concluded that e-cigarettes are not. “For now,” Okuyemi says, “the idea that e-cigarettes are a gateway to tobacco cigarettes is pure speculation. What we do know is that many tobacco smokers who start using e-cigarettes end up smoking both, but they smoke fewer tobacco cigarettes than they used to.”

Dorothy Hatsukami, Ph.D., a professor of psychiatry at the University of Minnesota who is studying toxin intake among users of e-cigarettes, believes e-cigarettes may have benefits over tobacco cigarettes. “If e-cigarette product standards are imposed, if e-cigarettes don’t prompt former tobacco smokers to start again or keep smokers who want to quit from quitting, and if they don’t tempt nonsmokers to start smoking tobacco, I think public health may benefit from these products,” she says. However, until more studies shed more light on these “ifs,” the CDC’s official stance is that “there is no conclusive scientific evidence that e-cigarettes are an effective way to quit tobacco smoking long term.”

Poison control centers see increase in e-cigarette calls

When misused, e-cigarettes can cause adverse reactions and injuries. Nationwide, poison control centers are reporting an increase in calls, either for ingesting cartridge liquid or getting it on skin, where the nicotine it contains is absorbed and can cause adverse effects. “Six milligrams of nicotine is enough to kill an infant,” says Richard Hurt, M.D., director of Mayo Clinic’s Nicotine Dependence Center. “Most cartridges contain a lot more than that. The refill bottles contain enough nicotine to kill an adult.”

In 2012, the Hennepin Regional Poison Center received eight calls about e-cigarettes; in 2013 it received 65 calls, says director Deborah Anderson, Pharm.D. Almost half of those calls were about children 5 years of age and younger who drank the cartridge fluid. In a few, an adult accidentally swallowed the fluid when the cartridge tip came off while they were vaping. Consumers also may report adverse events to the Food and Drug Administration (www.fda.gov/Safety/MedWatch/default.html).

Taming the Wild West

For e-cigarettes to earn a halo of legitimacy, they must be regulated. The FDA has the authority to regulate them as tobacco products but as of yet has not done so, although it sent a proposed rule to the
Office of Management and Budget last fall. “What the FDA should do,” Hurt says, “is regulate the contents to minimize public harm.” That includes eliminating flavorants that can appeal to children.

States, too, are acting on e-cigarettes. Minnesota has prohibited e-cigarette sales to minors since March 2011, under the state’s Tobacco Modernization and Compliance Act of 2010. The state also taxes e-cigarettes as tobacco products and requires e-cigarette sellers to have a license to sell tobacco.

State law still allows indoor use of e-cigarettes because vaping does not meet the definition of smoking in the Minnesota Clean Indoor Air Act. “Allowing substances with unknown harm into our indoor air is a huge step backward,” says Mike Sheldon, communications director for ClearWay Minnesota, a not-for-profit that sponsors smoking research and provides smoking-cessation programs. For that reason, Rep. Phyllis Kahn of Minneapolis plans to introduce a bill during the 2014 legislative session that adds e-cigarettes to the Clean Indoor Air law. Such an amendment would ban e-cigarette smoking in all public places.

Meanwhile, local governments are passing their own e-cigarette laws. Last October, Duluth became the first Minnesota city to ban use of e-cigarettes wherever tobacco cigarettes are banned. Restaurant owners asked for it because they found it difficult to enforce Minnesota’s indoor air law because it was hard to tell whether customers were smoking or vaping, says Terrence Clark, M.D., a recently retired pulmonologist at Essentia Health in Duluth, who testified in favor of the citywide ban.

Duluth officials also banned smoke shops from offering free samples. So did officials in Mankato. Housing authorities in St. Cloud, Eveleth and Worthington include e-cigarettes in their smoke-free housing policies. Bemidji requires e-cigarette sellers to have a tobacco seller’s license, and Beltrami County prohibits e-cigarette use wherever regular cigarette use is prohibited. Hennepin County Technical College and Target Field prohibit e-cigarette use on their grounds indoors and out.

If Kahn’s indoor vaping bill passes, it will help eliminate inconsistency and confusion over the patchwork of local ordinances and workplace rules.

Big tobacco companies fully expect e-cigarettes to be regulated, and some welcome it as a way to eliminate competition from smaller manufacturers who may not survive all the regulatory hoops, Okuyemi says. Until then, e-cigarette makers will be selling the “coolness factor” of vaping to young people, having all their marketing spigots open while they can.

Hurt believes the FDA needs to walk a fine line by regulating e-cigarettes without over-regulating them. “We need to minimize the harm and maximize the potential public health benefits by allowing people to use quality-controlled e-cigarettes, but only if research shows they’re safe and help smokers quit cigarette smoking, the effect of which we know in the U.S. is the equivalent of three fully loaded 747s crashing every day of the year with no survivors,” he says. E-cigarettes may help do that—but only if their promise outweighs their peril. MM

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