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# All Young Cannabis Users Face Psychosis Risk

Pauline Anderson

June 15, 2018

Cannabis use directly increases the risk for psychosis in teens, new research suggests.

A large prospective study of teens shows that "in adolescents, cannabis use is harmful" with respect to psychosis risk, study author Patricia J. Conrod, PhD, professor of psychiatry, University of Montreal, Canada, told *Medscape Medical News.*

The effect was observed for the entire cohort. This finding, said Conrod, means that all young cannabis users face psychosis risk, not just those with a family history of schizophrenia or a biological factor that increases their susceptibility to the effects of cannabis.

"The whole population is prone to have this risk," she said.

The study was [published online](https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2681642?utm_source=facebook&utm_medium=social_jamapsyc&utm_campaign=article_alert&utm_content=automated) June 6 in JAMA Psychiatry.

### Rigorous Causality Test

Increasingly, jurisdictions across North America are moving toward cannabis legalization. In Canada, a marijuana law is set to be implemented later this year.

With such changes, there's a need to understand whether cannabis use has a causal role in the development of psychiatric diseases, such as psychosis.

To date, the evidence with respect to causality has been limited, as studies typically assess psychosis symptoms at only a single follow-up and rely on analytic models that might confound intraindividual processes with initial between-person differences.

Determining causality is especially important during adolescence, a period when both psychosis and cannabis use typically start.

For the study, researchers used random intercept cross-lagged panel models (RI-CLPMs), which Conrod described as "a very novel analytic strategy."

RI-CLPMs use a multilevel approach to test for within-person differences that inform on the extent to which an individual's increase in cannabis use precedes an increase in that individual's psychosis symptoms, and vice versa.

The approach provides the most rigorous test of causal predominance between two outcomes, said Conrod.

"One of the problems in trying to assess a causal relationship between cannabis and mental health outcomes is the chicken or egg issue. Is it that people who are prone to mental health problems are more attracted to cannabis, or is it something about the onset of cannabis use that influences the acceleration of psychosis symptoms?" she said.

The study included 3720 adolescents from the Co-Venture cohort, which represents 76% of all grade 7 students attending 31 secondary schools in the greater Montreal area.

For 4 years, students completed an annual Web-based survey in which they provided self-reports of past-year cannabis use and psychosis symptoms.

Such symptoms were assessed with the Adolescent Psychotic-Like Symptoms Screener; frequency of cannabis use was assessed with a six-point scale (0 indicated never, and 5 indicated every day).

Survey information was confidential, and there were no consequences of reporting cannabis use.

"Once you make those guarantees, students are quite comfortable about reporting, and they become used to doing it," said Conrod.

### Marijuana Use Highly Prevalent

The first time point occurred at a mean age of 12.8 years. Twelve months separated each assessment. In total, 86.7% and 94.4% of participants had a minimum of two time points out of four on psychosis symptoms and cannabis use, respectively.

The study revealed statistically significant positive cross-lagged associations, at every time point, from cannabis use to psychosis symptoms reported 12 months later, over and above the random intercepts of cannabis use and psychosis symptoms (between-person differences). The statistical significances varied from P < .001 to P < .05.

Cannabis use, in any given year, predicted an increase in psychosis symptoms a year later, said Conrod.

This type of analysis is more reliable than biological measures, such as blood tests, said Conrod.

"Biological measures aren't sensitive enough to the infrequent and low level of use that we tend to see in young adolescents," she said.

In light of these results, Conrod called for increased access by high school students to evidence-based cannabis prevention programs.

Such programs exist, but there are no systematic efforts to make them available to high school students across the country, she said.

"It's extremely important that governments dramatically step up their efforts around access to evidence-based cannabis prevention programs," she said.

Currently, marijuana use in teens is "very prevalent," she said. Surveys suggest that about 30% of older high school students in the Canadian province of Ontario use cannabis.

"I'd like to see governments begin to forge some new innovative policy that will address this level of use in the underaged," Conrad said.

Reducing access to and demand for cannabis among youth could lead to reductions in risk for major psychiatric conditions, she said.

A limitation of the study was that cannabis use and psychosis symptoms were self-reported and were not confirmed by clinicians. However, as the authors note, previous work has shown positive predictive values for such self-reports of up to 80%.

### Unique Research

Commenting on the findings for Medscape Medical News, Robert Milin, MD, child and adolescent psychiatrist, addiction psychiatrist, and associate professor of psychiatry, University of Ottawa, said the study is at "the vanguard" of major research investigating cannabis use in adolescents over time that is being carried out by that National Institute on Drug Abuse in the United States.

"The study is at the forefront because it is specifically looking to measure psychosis symptoms and cannabis use in adolescents, and the model they are using strengthens the study," said Milin.

That model uses "refined measures or improved measures to look at causality,

vs what we call temporal associations," he said.

The fact that the study investigated teens starting at age 13 years is unique, said Milin. In most related studies, the starting age of the participants is 15 or 16 years.

He emphasized that the study examined psychosis symptoms and not psychotic disorder, although having psychotic symptoms increases the risk for a psychotic disorder.

*The study was supported by grants from the Canadian Institutes of Health Research. Dr Conrod and Dr Milin have disclosed no relevant financial relationships.*

*JAMA Psychiatry.* Published online June 6, 2018*.*

[Medscape Medical News](http://www.medscape.com/news) > [Neurology](http://www.medscape.com/index/section_10172_0)

**Structural Brain Differences Seen in Casual Marijuana Users**

Megan Brooks April 16, 2014

Even occasional marijuana smoking appears to be associated with significant structural differences in key brain regions involved in motivation, emotion, and reward compared with nonsmoking controls, a new study indicates.

The researchers found dose-dependent differences in gray matter density, volume, and shape of the nucleus accumbens and amygdala in young healthy recreational marijuana smokers vs never-users of marijuana.

"Most studies have looked at long-term heavy marijuana users and show brain changes," Jodi Gilman, PhD, from the Department of Psychiatry, Massachusetts General Hospital, Boston, told *Medscape Medical News*.

"Our study is different in that it looks at young adult recreational users who are not addicted based on a psychological interview and we found observable brain changes in this group. This is concerning, given that there are roughly 18.5 million recreational users," she said.

Dr. Gilman and colleagues [report their findings](http://jn.sfn.org/press/April-16-2014-Issue/zns01614005529.pdf) April 16 in the *Journal of Neuroscience*.

**Altered Brain Organization**

The researchers assessed brain morphology using high-resolution MRI in 40 young adults aged 18 to 25 years recruited from Boston-area colleges; 20 used marijuana recreationally (mean, 11.2 joints per week) and 20 did not use the drug at all.

Comparing the scans, the researchers found abnormalities in all 3 structural measures assessed (gray matter density, volume, and shape) in casual marijuana users relative to nonusers.

The study is "quite elegant and appears to be the first study to associate recreational cannabis use with brain abnormalities," Matthew Smith, PhD, assistant research professor in psychiatry and behavioral sciences, Northwestern University Feinberg School of Medicine, told *Medscape Medical News*. Dr. Smith wasn't involved in the study but has also found brain changes with marijuana use in his own studies.

This new study, Dr. Smith said, "appears to demonstrate that increasing amounts of cannabis used recreationally are associated with increasing severity in brain abnormalities. Their findings are also consistent with my recent work in young adults who were daily cannabis users as teens, as both studies observed abnormalities in the nucleus accumbens," Dr. Smith said.

**Marijuana Use Linked to Schizophrenia-like Brain Changes**

Megan Brooks December 19, 2013

Long-term marijuana use has been linked to structural brain changes similar to those observed in schizophrenia patients, and these changes correlate with poorer working memory, new research shows.

A study conducted by investigators at Northwestern University Feinberg School of Medicine in Chicago, Illinois, showed that teens who smoked marijuana daily for about 3 years performed poorly on tests of working memory and had abnormal changes in brain structures akin to those seen in patients with schizophrenia.

This study links the long-term use of marijuana to "concerning brain abnormalities that appear to last for at least a few years after people stop using it," lead investigator Matthew Smith, PhD, assistant research professor in psychiatry and behavioral sciences, said in a statement.

"With the movement to decriminalize marijuana, we need more research to understand its effect on the brain," he added.

In addition, memory problems and brain changes were observed 2 years after the teens stopped smoking marijuana, suggesting long-term use has long-term, negative effects.

**Early Marijuana Use: A More Harmful Impact on Brain Structure**

Deborah Brauser November 11, 2014

The link between long-term marijuana use and altered brain structure may depend on the age at first use and duration of use, new imaging research suggests. A study of 110 adult participants show that long-term marijuana users have reduced gray matter volume and increased structural and functional connectivity in the orbitofrontal cortex (OFC), a brain region responsible for decision making, compared with nonusers. The findings also suggest that early onset of regular marijuana use may be associated with increased functional connectivity in white matter, whereas long duration of marijuana use might be tied to decreased structural connectivity.

"This was a much more comprehensive approach than has been done in the past," lead author Francesca M. Filbey, PhD, associate professor in the School of Behavioral and Brain Sciences at the University of Texas (UT) at Dallas and director of cognitive neuroscience research in addictive disorders at UT's Center for BrainHealth, told *Medscape Medical News.*

Dr Filbey noted that the findings show that clinicians should be aware of these long-term effects, as well as the fact that "the picture is very complex."

"Another important point from the paper is that there was a direct relationship with age of onset. So those who began regular use at adolescence seemed to have the greater effects on these brain measures, including greater volume reduction," she said.

The study was [published online](http://tinyurl.com/lsv4q2a) November 10 in the *Proceedings of the National Academy of Sciences of the United States of America.*

Legalized Marijuana Boosts High School Dropout Rates

Fran Lowry

October 20, 2016

Legalizing medical marijuana may have an adverse effect on educational attainment, new research shows.

A study examining the impact of laws that legalize marijuana on educational attainment shows that states with these laws had an increase in the high-school dropout rate among 12th graders.

In addition, among those who did graduate from high school, fewer went on to attend college or to graduate from college.

The study was [published online](http://www.drugandalcoholdependence.com/article/S0376-8716(16)30882-1/abstract) October 11 in *Drug and Alcohol Dependence*.

**Direct Link**

"More than anything, what we have done is provided good, solid evidence that there is a direct link between marijuana policies and education," lead author Andrew Plunk, PhD, from Eastern Virginia Medical School, Norfolk, told *Medscape Medical News*.

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"With these policy changes, we need to be mindful about how young people might view marijuana. As it becomes approved for medical indications, are kids going to be viewing it as less risky?" Dr Plunk said.

"This is not to say that there are not legitimate reasons for medical marijuana, and also decriminalization. But just because we allow medical marijuana, and if we do decriminalize it, that doesn't mean that there are not also negative consequences associated with marijuana use. Alcohol is legal, and we know there are tons of negative things that can happen to people who abuse alcohol. Cigarettes are legal to buy, and smoking is one of the worst things you can do for your health, so we need to have a dialogue with our kids about these dangers and pitfalls," he said.

Dr Plunk and his team looked at the potential impact of medical marijuana laws by examining the relationship between those laws and educational attainment.

They used datasets from the US Census and the American Community Survey for years 1990 through 2012. The datasets included 5,483,715 individuals of high-school age.

The researchers examined the level of education attained by individuals aged 14 to 18 years who were exposed to medical marijuana by virtue of living in states with medical marijuana laws, as well as those who were not exposed.

Specifically, they looked at the effects of medical marijuana laws on three educational attainment outcomes:

* Getting a high school diploma after completing 12th grade
* Beginning college but not necessarily completing a degree
* Obtaining any college degree after having begun college

They found that exposure to medical marijuana laws was associated with a 0.40 percentage point increase in the probability of failing to get a high school diploma or general educational development (GED) certificate completing the 12th grade (from 3.99% to 4.39%; odds ratio [OR] = 1.11; 95% confidence interval [CI], 1.05 - 1.17).

Exposure to medical marijuana laws from ages 14 to 18 was also linked to a 1.84 percentage point increase in the probability of not enrolling in college (from 31.12% to 32.96%) and a 0.85 percentage point increase in the probability of not getting a college degree (from 45.30% to 46.15%).

"The impact of medical marijuana laws was not immediate, so if the policy change occurred when someone was 13 or 14, he or she did not immediately drop out of high school. Instead, there was a delayed impact; the law did not affect kids until they were in the 12th grade," Dr. Plunk said.

"College enrollment and college completion with obtaining a degree were also affected by medical marijuana laws. These results are consistent with a longer-term developmental effect. As our study implies, legalizing medical marijuana could be associated with an additional 120,000 high school dropouts over a 17-year span," he said.

Medical marijuana cannot be prescribed to youth, Dr Plunk noted.

However, it is likely that young people are getting the medical marijuana that is legitimately prescribed for an adult through diversion, he said.

"There is research that suggests that 12th graders and older teens are using diverted medical marijuana meant for other people. So we really need to be cautious."

**Equating "Legal" With "Safe"**

Commenting on this study for *Medscape Medical News*, David C. Rettew, MD, director, Pediatric Psychiatry Clinic, University of Vermont College of Medicine, Burlington, said that as states consider legalizing cannabis, "one issue that often comes up is the tax revenue that can be generated from legal sales. Aside from the obvious human costs, this study indicates that a lot of that increased income could be offset by decreased tax revenues as people reduce their level of education."

This study adds to the growing scientific literature that demonstrates that cannabis, legal or not, is associated with a large number of negative outcomes, Dr Rettew added.

"As we tend to equate 'legal' with 'safe,' it is going to be more and more important that the public does not receive a whitewashed version of the true risks of cannabis use," he said.

*The study was sponsored by the National Institutes of Health. Dr Plunk and Dr Rettew report no relevant financial relationships*.

*Drug Alcohol Depend*. Published online October 11, 2016

Secondhand Marijuana Metabolite in Children's Urine

Ricki Lewis, PhD

December 09, 2016

Children exposed to secondhand marijuana smoke have measurable amounts of a metabolite of Δ9tetrahydrocannabinol, according to results of an investigation published online December 2 in *Pediatric Research*.

With medical marijuana now legal in 28 states plus the District of Columbia, and recreational use decriminalized in 20 states plus the District of Columbia, childhood exposure could become a public health concern. The effect of secondhand marijuana smoke on children has not been studied, although it contains particulates, toxins, and carcinogens.

Karen Wilson, MD, and colleagues used a new, sensitive analytical method developed by the Centers for Disease Control and Prevention to quantify 11nor9carboxy(COOH)THC in the urine of young children exposed to secondhand marijuana smoke.Dr Wilson is the Debra and Leon Black Division Chief of General Pediatrics and vice chair for clinical and translational research, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York City. The researchers also measured urine cotinine, a metabolite of nicotine.

The investigators sampled urine from 43 healthy babies aged from 1 month to 2 years who were hospitalized in Colorado for bronchiolitis between 2013 and 2015. The parents completed a survey that asked, "Does anyone who lives in your home or who cares for your child smoke marijuana (yes or no)?" Marijuana use is approved for both medicinal and recreational use in Colorado.

Levels of THC and another major active ingredient, cannabidiol, were undetectable in the urine samples. However, COOHTHC was found in 16% of them, ranging from 0.03 to 1.5 ng/ml, with only two children exceeding 1 ng/mL. As expected, these levels were lower than would be seen in the urine of a person directly smoking marijuana.

Exposure did not differ by sex or age (77% of the children were boys, and 52% were younger than 1 year). However, more nonwhite children had COOHTHC in their urine than did white children (44% vs 9%; *P* = .026). Of children whose parents reported marijuana use or exposure in the home, 75% had detectable COOHTHC; 10% of children whose parents reported no exposure had detectable levels (*P* < .016).

Urine cotinine levels exceeded 2.0 ng/mL in 23% of the children. The results for cotinine suggest that households that expose children to cigarette smoke may also expose them to marijuana smoke: 56% of children whose cotinine levels exceeded 2.0 ng/mL were positive for COOHTHC, but only 7% of children who had lower cotinine levels (*P* < .004) were positive for the marijuana metabolite.

The increase in prevalence of detectable COOHTHC after legalization during the studied period, from 10% to 21%, was not significant.

The study demonstrates exposure to secondhand THC among the children, but does not examine health consequences. However, the well known dangers of exposure to secondhand tobacco smoke (cognitive effects and respiratory illness) suggest that increased exposure to marijuana smoke could pose problems. "In the interim, parents should be cautioned not to smoke marijuana in the presence of their children," the researchers conclude.

"In areas where marijuana use is legal, or common, education is needed to counsel parents on the dangers posed to their children by secondhand smoke," Dr Wilson said in a Mount Sinai news release.

"Parent reported screening questions in areas where marijuana is legal is a helpful first step. While we do not know yet whether this exposure poses a health risk to children, this study highlights the urgency of further investigation." Limitations of the study include the use of samples previously collected to assess effects of exposure to secondhand cigarette smoke from parents who consented to future research, which might have selected out some who use the drug. The use of existing samples limited investigation of other factors that might have contributed to marijuana use or the presence of COOHTHC in the children's urine.

Marijuana Not Benign: Warn Teens, Parents, AAP Says

Norra MacReady, Feb. 27, 2017

As the legal status of marijuana evolves, pediatricians should counsel teenagers and their parents about its potential for harm,

write the authors of a new clinical report from the American Academy of Pediatrics.

Despite the impression among many teenagers and their parents that marijuana is a fairly benign drug, it has some real risks

that can have a longstanding effect on an individual's health and function, write Sheryl A. Ryan, MD, and Seth D. Ammerman,

MD, and colleagues in the clinical report published online February 27 in *Pediatrics*.

A key area of concern is "the effect of its use on brain development," Dr Ammerman told *Medscape Medical News*.

There is also the concern that younger children may be exposed to marijuana in the form of edibles such as brownies that may

be in the home, he noted. Already, there have been a few reports of children overdosing in this fashion in states where

marijuana is legal.

As a result, "a lot of pediatricians now are being asked, 'is marijuana safe?' " he said.

The report arms clinicians with some information to answer that question. It addresses the effects of adolescent marijuana use

and offers suggestions for conducting brief, officebased

interventions aimed at identifying problem users and helping them

stop.

It also provides a list of 10 talking points for pediatricians to remember when talking with parents and teenagers. The points

stress the addictive nature of marijuana and its effect on the brain, the dangers of driving under the influence of marijuana, the

toxicity of secondhand marijuana smoke, and the influence parents can exert as role models for their children.

WellDocumented

Adverse Effects

The view of marijuana as a harmful substance has diminished among adolescents in recent years, the authors explain.

According to the National Survey on Drug Use and Health conducted by the US Department of Health and Human Services,

only 41% of participants 12 to 17 years of age perceived "great risk" in smoking marijuana once or twice a week in 2015, down

from 55% in 2007.

Yet many of its adverse effects are "welldocumented,"

such as impaired shortterm

memory and concentration; alterations in

judgment, coordination, and motor control; diminished lung function; and a heightened risk for mental health disorders such as

depression and psychosis.

In addition, some studies have shown alterations in brain development in areas such as the amygdala, hippocampus, and

prefrontal cortex, said Dr Ammerman, clinical professor, Division of Adolescent Medicine, Department of Pediatrics, Stanford

University School of Medicine and Lucille Packard Children's Hospital, Stanford, California.

The clinical implications of these findings are unclear, he added, "but they're probably not good."

There is also clear evidence that marijuana is addictive, Dr Ryan, professor of pediatrics and associate clinical professor of

nursing, Yale School of Medicine, New Haven, Connecticut, and colleagues write in the report. Overall, 9% of people who try

marijuana become addicted, but that rises to 17% of people who try it during adolescence and anywhere from 25% to 50% of

adolescents who smoke marijuana daily.

The risk is especially high among adolescents who are regular or heavy users of cannabis. Regular use is defined as 10 to 19

times per month, and heavy use is defined as 20 or more times per month.

Office Screening Suggested

Marijuana Not Benign: Warn Teens, Parents, AAP Says

Norra MacReady

3/9/2017 www.medscape.com/viewarticle/876347\_print

http://www.medscape.com/viewarticle/876347\_print 2/2

The report urges pediatricians to screen adolescent patients for substance use, as recommended in the previously published

Screening, Brief Intervention, and Referral for Treatment policy statement.

Screening should occur at all wellteen

visits, or "whenever there is a concern that marijuana use might be an issue," Dr

Ammerman said. He also suggested that even before they start screening, pediatricians should raise the issue with patients in

an ageappropriate

way.

Motivational interviewing techniques can be used either to support patients who have chosen to abstain or to discourage use

among adolescents who do smoke marijuana. Some patients may require one or more followup

visits or a referral to a mental

health counselor, the authors write.

Clinicians can use the talking points to emphasize the drawbacks of marijuana: not only the adverse mental and physical

effects, but also the fact that its use by people younger than 21 years is still illegal. Prosecution may result "in a permanent

criminal record, affecting schooling, jobs, etc.," the authors state.

In addition, the talking points remind parents that they are role models for their children. "Actions speak louder than words," Dr

Ammerman warned. "It's very clear that if parents use marijuana in front of their kids, those kids are more likely to use it

themselves, regardless of what the parent says."

Adults who view marijuana as relatively harmless may be thinking of the product they used in the 1970s and 1980s, he added.

Back then, the average dose of marijuana had about 4% tetrahydrocannabinol, or THC, the compound that gives marijuana its

euphoric properties.

However, today's marijuana has 16% THC. "So the drug that we experienced is much less potent than what our children are

using, and we know much more today about its potential problems."

On average, adolescents who become addicted to marijuana remain addicted for about 10 years, Dr Ammerman said. "So

you've lost 10 years of your life, perhaps doing poorly in school or on the job, or in your relationships. We don't want anyone to

throw their life away like that."

*The authors have disclosed no relevant financial relationships.*

*Pediatrics*. Published online February 27, 2017.

**Vaping is blamed for mounting deaths, lung injuries. Here’s what it’s doing to kids’ brains.**

[**by Rita Giordano**](https://www.inquirer.com/author/giordano_rita/), Updated: October 29, 2019

With more than 1,600 cases of vaping-related lung injuries and 34 deaths reported by the U.S. Centers for Disease Control and Prevention, there is plenty that’s worrisome about the health effects of e-cigarettes.

But the pulmonary harm — so concerning that the [CDC website](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information) is updating the toll weekly — isn’t the only thing alarming pediatricians about their young patients and vaping. There also is the damage the practice might be doing to their brains.

A growing body of research suggests that nicotine is a potent gateway drug to other substances, as well as other troubling behaviors, especially in the high doses delivered by many e-cigarettes. Researchers, as well as clinicians, increasingly say they are seeing an increase in attention difficulties, irritability, volatility, even aggression and addiction, in young vapers whose brains are still forming.

“We have this burgeoning evidence base that nicotine exposure, especially early on, might increase your brain’s risk of getting addicted to not only nicotine but other substances like marijuana, alcohol, and cocaine,” said Brian Jenssen, a faculty member with the Children’s Hospital of Philadelphia’s PolicyLab and an expert in tobacco/e-cigarette treatment and policy.

“We know nicotine [use through e-cigarettes] is not only impacting the parts of the brain to do with addiction,” said Sharon Levy, director of Boston Children’s Hospital’s adolescent substance use and addiction program and an associate professor with Harvard Medical School. “It’s impacting other parts of the brain, too, and we’re seeing effects we haven’t seen with cigarette smokers. We’re seeing lots of kids who have problems with attention, concentration, and a lot of behavioral dysregulation. We’ve seen it with marijuana addiction. We’ve seen it with opioid addiction. We have not seen it with cigarettes.”

And the likelihood is we’ll be seeing more of these problems given the rapid growth of vaping among young people. According to research published in October in the New England Journal of Medicine, the prevalence of e-cigarette use among students in the eighth, 10th, and 12th grades more than doubled from 2017 to 2019.

### Critical time for brain growth

As physicians and scientists continue to [seek explanations about what is causing serious lung problems in people who vape](https://www.inquirer.com/health/vaping-juul-cdc-lung-illness-20190928.html), including some who have used cannabis products, the impact of nicotine on the developing brain, especially in high doses, is still being learned. But the ever-growing implications are troubling.

Nicotine is highly addictive. Any smoker who has tried to quit cigarettes can attest to that. However, research has found the younger an adolescent starts using nicotine, the more likely he or she will continue into adulthood, even more so than users of other addictive substances.

Adolescence into young adulthood is a critical time for brain development. Studies suggest nicotine alters chemical pathways in the brain and boosts dopamine, a neurotransmitter associated with reward-seeking, pleasure, and the risk for various addictions.

An analysis of more than 20 studies recently published in JAMA Pediatrics found that youth with a history of vaping were 3.5 times more likely than those who do not vape to become marijuana users. Other research has found people who use nicotine are more likely to try other substances.

Meanwhile, a landmark study by Columbia University medical school researchers viewed as the closest to biological proof of the gateway theory found that mice given nicotine in their water over a period of time showed addiction-related gene changes and increased vulnerability to cocaine dependence. Denise Kandel, a professor of sociomedical sciences in psychiatry at Columbia’s Irving Medical Center and a lead author on the study, said she and her colleagues have also found in subsequent research that alcohol and cannabinoids seem to have gateway-like relationships to cocaine use in mouse studies. Kandel said it’s not yet known if all the same molecular changes take place in humans, but because adolescents’ brains are still forming, young people are likely to be especially susceptible to the gateway effect.

For the young, nicotine is the most likely gateway. Adolescent alcohol consumption rates have decreased in recent years. The prevalence of tobacco use is greater than marijuana use, Kandel said, and the decreases in young people smoking combustible cigarettes have been undone by the “explosive increase” in vaping.

“Whatever its source, nicotine is nicotine,” Kandel said. “It will adversely affect the brains of adolescents and increase their susceptibility to the reward effects of other drugs.”

### ‘To the point of seizures’

The research is especially shocking given the super-doses of nicotine adolescents are getting from e-cigarettes like Juul, a popular brand among young people. One Juul pod has as much nicotine as a pack of cigarettes and young vapers tend not to partake sparingly.

“Many of these kids are using one, two, three pods a day,” Jenssen said.

Ironically, Jenssen said, it’s not unusual for these youngsters, priced out of their vaping habit, to start turning to conventional cigarettes — the very products e-cigarettes were marketed as an alternative to.

“There are reports consistent with nicotine toxicity even to the point of seizures in some kids,” Levy, of Boston Children’s, said.

Taken in low doses, nicotine, a stimulant, can seem to aid concentration. But in high doses, the opposite is true.

”We’ve got a lot of kids coming in the clinic saying, ‘I think I’ve developed ADHD,’ ” Levy said. “You don’t develop ADHD at age 15 or 16.”

Even before vaping-related lung injuries swept the nation, the pediatrician said her clinic’s staff members were seeing behavioral problems that suggested brain impacts from high-dose vaping.

“If you develop problems with your concentration or behavior dysregulation, is all that going to get better? And the answer to that is we don’t know,” Levy said. “There are a lot of unknowns, and it’s all part of a scary landscape.”