Aaron van Dorn (00:07):

Welcome to AJP Audio for February, 2025. I'm Aaron van Dorn. The February issue of The American Journal of Psychiatry takes a close look at issues surrounding addiction. For this month's episode, I spoke with Dr. Andrea King, Professor of Psychiatry and Behavioral Neuroscience at the University of Chicago Medicine. Dr. King and colleagues have a study in the February issue taking a close look at reward stimulation and negative affect in people with alcohol use disorder, with and without comorbid depression. Afterwards as always, AJP Editor-in-Chief Dr. Ned Kalin will put the rest of the February issue into context.

(00:35):

Dr. King, your study looked at the allostatic model of addiction as it relates to alcohol use disorder or AUD, with and without comorbid depressive disorder. What can you tell us about the theory?

Dr. Andrea King (00:45):

Well, first, as a step back, the term allostasis was first introduced by neuroscientists in the late 1980s. It signifies maintaining stability through change, how an organism can adjust set points based on environmental demand. In other words, as opposed to homeostasis, which refers to maintaining a constant internal environment for optimal functioning. Processes of allostasis may either benefit or harm an organism. Soon after allostasis was then applied to addiction. And the allostasis model of addiction has remained one of the leading neurobiological theories of addiction. It's based primarily on data from animal models of addiction which are good, but not a perfect fit with the human condition. And in a nutshell the theory states that alcohol initially produces pleasurable effects and reward. We call this positive reinforcement. But then with the continued onslaught of excessive drinking, adaptations and brain function render a waning of these rewarding effects. They call it a reward deficit that shifts to the dark side of addiction in which alcohol is consumed to relieve negative effective states or withdrawal symptoms.

(01:48):

And then there's a third stage, which is called preoccupation anticipation that reflects executive function deficits, which in our study we didn't test. We tested this transition from that first reward sensitive stage to this purported second reward deficit stage. And we did this in individuals who have alcohol use disorder and prone to negative affect by virtue of having a comorbid depressive disorder.

Aaron van Dorn (02:12):

Your study had four arms, a group with alcohol use disorder as we mentioned, with and without comorbid depression, and another comparative group with alcohol use disorders and also broken out by comorbid depressive disorder status. How did you gather your data and what did you find?

Dr. Andrea King (02:23):

Yeah. So we had 221 total participants. They were in their 20s or 30s, and there were 120 of them had past year alcohol use disorder and 101 did not have alcohol use disorder. They were more normative social drinkers. And in each of these groups we had two cohorts, half had depressive disorder in the past year and half did not. So how did we gather the data? With a little background, the data were collected over the course of one year from October, 2020 to October, 2021. If we go back, there were a lot of pandemic restrictions in place back then. So this not only delayed the initiation of the study, but it also imposed restrictions in terms of face masks, distancing and complexities and getting breathalyzer tests and so forth.

(03:06):

So we decided to double down on our smartphone method of collecting data. My colleague Dr. Dan Friedberg and I developed this method back in 2017 and we went ahead and used it in this study. So the method is to gather data using user-friendly one-minute short prompt surveys that an individual can complete on their own smartphone before they engage in drinking. And then they get frequent repeated prompts during the first three hours of a typical alcohol drinking episode in their natural environment.

(03:39):

So they are trained on our app. We have an orientation session, and once they've gone through that. We look at a timeline follow-back calendar, so we know when they often drink or drink excessively, then it's up to them to initiate an episode. So once they've activated the app, they take a picture of their beverage, we do this as a validity check that they are drinking alcohol, and then the app will send them seven more prompts at various short intervals over the next three hours. They will answer survey items briefly about what type of drink they're having, the size, context, and location and their subjective effects. And those include things like how stimulated, sedated, how do you feel the effects of the beverage and do you like or want it?

(04:20):

In this study, we wanted to really focus in on this allostasis model. So we added in negative affect for the first time. This was the average of asking them the prompts for how sad you feel, how anxious and how stressed. And we also for the first time added in a comparison non-alcohol drinking episode, liking this to a laboratory study where you might have a placebo session, although there are differences in the natural environment. So we wanted to make sure that the responses that we see in an alcohol episode were not merely a response bias or a general mood effect that people feel anyways. What did we find?

(04:54):

Well, we found that our participants who had alcohol use disorder drank a lot of alcohol as we would've expected. They averaged between eight and nine drinks over those first three hours. And those estimated breath alcohol concentrations were about 0.12 gram per deciliter. That's about one and a half times the legal limit for driving. Those who did not have alcohol use disorder as we would've expected had more moderate drinking. They had a few drinks and their estimated breath alcohol was about 0.4, so that would be the equivalent to two or three drinks in that ballpark. The people in our study who had alcohol use disorder and major depression experienced a very pronounced increase in alcohol's positive effects. That's stimulation. The hedonic reward, the liking item, and the motivational reward, wanting. These effects were similar to their counterparts who have AUD but do not have depression. So they looked just like their cohorts who do not have depression.

(05:50):

So we call this a high sensitivity to alcohol's pleasurable effects that emerged early in the episode. It happened within the first half hour to hour. We didn't see these effects in the non-alcohol episode. And these heightened positive effects were maintained throughout much of the three-hour episode. So the control group, those people without alcohol use disorder, again, who had moderate drinking during their episode with or without depression, they did show some modest increases in stimulation and liking, but they did not show increases in wanting, and these levels were nowhere near the magnitude of what we found in the people with alcohol use disorder again, with or without depression.

(06:28):

So finally I wanted to point out alcohol did indeed reduce the ratings of negative affect. But this reduction was relatively modest and of a much lower magnitude than alcohol's increase in stimulation liking and wanting. And again, these subjective effects persisted for much of the episode in people with alcohol use disorder and with or without depression.

Aaron van Dorn (06:50):

Which would then counter to the allostatic model which would argue that people with alcohol use disorder are drinking to impact the negative affect that they're already feeling whereas what you found is that the people who with alcohol use disorder were having a larger positive affect from the alcohol than people who did not have that alcohol use disorder.

Dr. Andrea King (07:07):

Yes, right. So we see this effective group. People with alcohol use disorder definitely had these higher positive ratings, and then within that group, the cohorts with depression and not depression... According to theory, those with depression are more prone to negative affect. So you would think if there's a subgroup that would really show this shift to drinking to alleviate negative affect, we would see it in them and we didn't. So we saw an overall positive effect in people with AUD and then even those who had depression, we saw this really hedonic pleasurable effect of alcohol.

Aaron van Dorn (07:37):

Your study is the first to take a look at a real-time assessment of positive and negative affects from drinking episodes in people with and without AUD. To be clear, your study was cleared by institutional review boards, but what were the ethical concerns with building a study out of people with a substance abuse disorder, actually indulging?

Dr. Andrea King (07:52):

This is a really good question. The study was approved by our IRB and ethical concerns were lessened by the fact that we were examining their behavior, their natural behavior in their own real-life environment. We didn't impose anything in these individuals. So everyone is an alcohol drinker on a weekly basis. Either those with or without alcohol use disorder. They're already engaging in drinking behaviors and we feel like the best way to really understand them is to assess this behavior in real time rather than getting surveys after the fact retrospective surveys, or there are some limitations to the laboratory environment, which can be somewhat sterile. Our instructions to our participants using this real-time monitoring was that they shouldn't change their behaviors or deviate from their normal behaviors. While in the study, compensation for doing the study wasn't dependent on any drinking of a specific amount, there was no coercion.

(08:40):

And third, we offered to reimburse individuals for any ride-shares that they may have needed during or after the events for any safety reasons. So the only thing we really did ask of them was that they refrain from smoking cigarettes or using recreational drugs or eating very large meals during those first three hours of their episodes. And that the episode should not be something that's out of the ordinary for them, things like a wedding reception or New Year's Eve. So we wanted them to be very typical and we really encountered no problems. I would like to point out that while the people with alcohol use disorder really drank a significant amount, as I mentioned, between eight and nine drinks in just a few hours, they're responding to the prompts on the smartphone app was similar about 90%, between 88

and 90% as the participants in the control group, those who don't have AUD. So we found that people with alcohol use disorder can respond to these prompts reliably.

Aaron van Dorn (09:34):

Were there any limitations on the natural environment we were talking about? Were people allowed to drink in bar rooms or was it something they were confined to their home and doing it by themselves?

Dr. Andrea King (09:42):

Yeah. Great question. Again, these were during October, 2020 to 2021, so I don't have the exact percent at my fingertips, but we have a variety of context. I think we did see maybe a little more drinking in the home or someone else's home than if it wasn't that year of getting through the pandemic. But we also had environments in bars and restaurants and other outside locations. So we asked that. And in all of our statistical analyses, we actually co-varied for those environments. We do know that being in a bar environment and other research might increase and augment positive effects, but we measured that and controlled for it and once we controlled for it didn't affect these responses.

Aaron van Dorn (10:20):

Sure. Drinking with friends obviously might have a different impact than drinking at home by yourself.

Dr. Andrea King (10:23):

Right. And again, some people were at home, but they were interacting with others because they might've been on a Zoom call or a FaceTime so things changed in these environments during this period and then as we go forward.

Aaron van Dorn (10:34):

Sure. I think we all remember COVID Zoom calls and such.

Dr. Andrea King (10:36):

Oh boy, yeah.

Aaron van Dorn (10:38):

Your findings indicate that participants with AUD, with and without comorbid depressive disorder received a positive alcohol response, including stimulation, liking and wanting. And that these effects were maintained for much of the heavy drinking session, whereas participants without AUD, while also with or without comorbid depression. While they also initially received positive effect from the alcohol, those effects faded much more quickly. What does this indicate about the validity of the allostatic model of addiction?

Dr. Andrea King (11:00):

Yeah. Well, you're right that the study findings did not support in the sample the shift from that first reward surfeit stage to the second stage of reward deficit as described in the allostasis model of addiction. While the theory per se doesn't mention comorbid conditions because it's largely based on animal models. Major depressive disorder is very relevant because it's one of the most prevalent disorders in AUD. Up to maybe a third or half of people with AUD have a depressive disorder. And

ostensibly we thought those who have a co-occurring depressive disorder would be the subgroup most likely to engage in excessive drinking to relieve negative affect and not reward.

(11:37):

So the findings may suggest some revision or rethinking of the allostasis model could be wanted such that the first reward-sensitive stage that's purported to fade, maybe it doesn't fade and it persists for many. And perhaps the second stage is better characterized by continuation of reward sensitivity coupled with increases in negative affect and unpleasant effects accompanying withdrawal. And this may make the disorder more complicated as it progresses. The underlying response to alcohol may take on a more positive reinforcement phenomenon for a longer period of time in the development of addiction and maintenance than people originally thought. Maybe this fits the conundrum of why some people engage in very excessive drinking despite having consequences mounting a problem drinking.

(12:21):

Related to this, I would like to mention that people might look at the findings and say, "Well, we know people who have addiction show tolerance to alcohol." But we like to point out it's not overall tolerance to all alcohol effects, but it's really tolerance to sedation. So we found people with AUD had very excessive drinking, but their levels of sedation from alcohol did increase, but it was on par with people without alcohol use disorder who only had a couple of drinks. So we think this is evidence that they are showing less sedation, these sluggish effects of alcohol. We sometimes use an analogy of a car and the brake pedal as sedation.

(12:56):

So if you have faulty brakes and you don't feel those internal cues of being sedated, that may make you more likely to go on and engage in excessive drinking. And then couple that with what we're showing is a ramped up accelerator pedal with this rapid pronounced stimulatory and pleasurable effects of alcohol, that fuels wanting more alcohol, losing control and engaging in alcohol misuse. So we see this despite people having mounting consequences. So I don't know if this challenges the validity or it says with more data and more evidence we might want to refine models more.

Aaron van Dorn (13:29):

Could it also indicate that people who are susceptible to AUD or have AUD might be more susceptible to the pleasurable effects of alcohol more so than people who don't have AUD or drinking issues?

Dr. Andrea King (13:39):

Exactly. You really hit the nail on the head. We have other research where we looked at young adults who did not have AUD, and then we followed them for 10 years and we re-challenged them with alcohol for 10 years. And we found that initially they had a higher pleasurable stimulation liking, wanting response to alcohol than people who were light drinkers. And then over the course of 10 years, we found that these effects increased and were potentiated for stimulation and wanting with liking remaining high in those who developed AUD over the course of 10 years. So we do see in a longitudinal study some of this evidence. People who were light drinkers just really showed this lower pleasurable effect initially. And then that continued on throughout the 10 years. People who then faded away and matured out of excessive drinking started showing less stimulation over time. So these changes may be a footprint to how you respond to alcohol or for some people they may be malleable depending on some of the behaviors you engage in.

Aaron van Dorn (14:32):

You've already mentioned that your study took a naturalistic approach to the study of alcohol use, and I was wondering how does that compare with the typical gold standard of laboratory studies where you have someone in a controlled environment? What are the limitations to both of these approaches?

Dr. Andrea King (14:45):

Yeah. Great. So I'm a person who's been doing laboratory challenge for, I don't know, 20, 25 years, 30 years. So I know this paradigm very well. I've done it most of my career. It started in the 1940s, took really effect in 1960s. We were examining people entering treatment and looking at their responses to alcohol. These were people who had addiction. But we had a real hiatus for a couple of decades with the advent of IRBs and considering ethical considerations, especially of measuring alcohol responses in people who have alcohol use disorder. So NIAAA, the Institute of Alcohol Abuse and Alcoholism set for standards for ethical administration of alcohol and said, "We can give alcohol to people who do have an alcohol use disorder under certain conditions." So we have seen more research looking at laboratory paradigms, but still not a lot looking at people who have alcohol use disorder. And I could only count on one hand how many had alcohol use disorder and might have a comorbid disorder. And usually those give modest doses in the laboratory.

(15:44):

So I'll pivot now to the last decade or so with technological advances. We have led to a lot of more studies looking at what we call ecological momentary assessment or EMA. And these can gauge behaviors in someone's real natural environment, which really has some nice positives. In the approach that Dr. Friedberg and I have taken we've looked at high resolution EMA, which specifically targets heavy drinking episodes and people who are excessive drinkers. Now, some of the limitations are self-evident that we can't really give people amount of alcohol. So the type of alcohol, they may choose the drinking pace, that's not controlled. There may be less internal validity because there could be confounds. We talked a few minutes ago about the context. Those could differ, although we can try to control for them statistically. And we can make some instructions to them, but we're not in that environment to make sure that they're not smoking or using drugs. Even though we ask them to do that. We can gauge if they really are drinking by having them take that picture.

(16:40):

In other research we've had people wear a wearable biosensor, alcohol biosensor and it measures transdermal alcohol. And we found really good concurrence between their self-report and this maybe less intrusive type of method. We can't really do breathalyzers in the natural fields because people would have to stop drinking for 15 minutes, rinse their mouths with water, and what we've done is just altered what we're trying to study, which is natural drinking behavior. So we can't really do certain things that we can do in the laboratory. When it's talking about the pros though, some of them really are important to note with this ecological momentary assessment that the data collection is less labor-intensive and it's less costly financially. So we can acquire more data in a shorter period of time.

(17:23):

So in the lab testing, we can only really study local participants. They have to be on site for many hours and we have to provide transportation. We can test one person. On a day we might spend five or six hours of a research assistance time to test them. So this is really important. In this present study sample this was a national sample because we recruited through social media and other advertisements across the country. So two thirds of our participants weren't even living in the Chicago area. And that's really different when we do a lab study. Both of them might be due to the Hawthorne effect, which is a phenomenon in psychology that says maybe your behavior changes because you know you're being studied. But we feel like that can happen in the natural environment. We hope the one-minute pings are

short enough where they're engaging in their normal environment because we're not putting too much burden on them. In the laboratory they're also being monitored so I think those things are similar in these environments. I think they could be complimentary approaches to really study.

Aaron van Dorn (18:18):

Alcohol use disorder is a major health issue in the United States and around the world. And understanding AUD and its impacts is a major area of concern for public health. Are there immediate clinical implications for your research?

Dr. Andrea King (18:27):

Yes. I think there are. Even among patients, there's this assumption that alcohol use disorder must reflect. In parts some attempt to cope, use alcohol to deal with trauma or negative emotional states such as depression or anxiety. And our data here show that even in those people with addiction and depression, they're experiencing positive like effects of alcohol. In other words, it's not just relief of negative affect that is characterizing their drinking experiences. This message is really not conveyed to them and not really encouraged in any part of treatment. So my colleague, Dr. Friedberg and I, we're clinical psychologists and we often include these concepts in our therapy with patients with alcohol use disorder. We don't rely solely on the folklore of the self-medication hypothesis or that they are in the dark side of addiction. But we really talk about them to be more aware of the sensations that alcohol produces and we incorporate this into treatment for drinking reductions or abstinence goals.

(19:21):

We hope this can reduce the stigma when discussing alcohol that we don't know why they have this response to alcohol, but it really does put them on a different playing field than people who are social drinkers, normative drinkers who can have a drink or two and just leave it. There are maybe clinical implications in terms of development of new pharmacological agents or repurposing existing agents that may interact with brain receptors and key reward areas. So if we can decrease activity of the reward system that's hyper aroused in such individuals, maybe we can reduce the excessive pleasure. So again, we didn't do imaging, but there could be aspects of modulation of dopamine signaling, brain regions like nucleus accumbens or hypothalamus or insula. So maybe more development of medications targeting this could be important implications of these findings.

Aaron van Dorn (20:09):

What's next for your research?

Dr. Andrea King (20:11):

Oh boy. Several things. We are continuing to chart the course of examining alcohol responses across the lifespan. We just completed data collection in an older sample of adults ages 40 to 65. This is very rare in the field. And these are people who either have or don't have alcohol use disorder. So we think that this might be even another or deeper test of the allostasis model of addiction in that the persons who are older at these ages have had alcohol use disorder for many decades. They usually have had alcohol use disorder since their 20s and now they're in their 50 and 60s. So unlike these younger samples in their 20s and 30s. We are going to examine the responses. We just finished testing in two blinded laboratory sessions, one with alcohol versus placebo challenge. And then we also added onto this study using the same method of high resolution EMA. So we are going to then after this look at their responses to alcohol and non-alcohol episodes in their natural environment. So we hope to examine these in the near future.

(21:10):

We also, in terms of the lifespan, are going to go to really younger ages. So one limitation of lab studies is that we cannot give alcohol challenge to a person under the age of 21 in the United States. But we can do this with our high resolution EMA because they are adults at age 18, they can consent to being in a study. So our goal is to extrapolate our findings and enroll a sample of the youngest adult drinkers ages 18 or 19 who are starting drinking careers. We would measure the responses in alcohol and non-alcohol episodes and then we will assess theories of the risk for initiation of heavy drinking or AUD. Some theories talk about low level of responses to alcohol. Will we see a low level response? And then if we follow them for two years on drinking behaviors, will that predict? Or will we find findings more like the differentiator model, which says they're more sensitive to those stimulatory and positive effects and they're less sensitive to the negative or sluggish effects. So we'll be testing those models of the initial responses to alcohol.

(22:07):

And then finally, I'd be remiss in saying we're trying to incorporate some of this research into adding personalized alcohol response feedback as part of brief intervention. So we did a study about 10 years ago where we did a lab challenge in young adults who engage in weekly binge-drinking. We gave them feedback from a lab session of this is how you respond to alcohol. And then we followed them for six months and those who got that extra personal feedback showed a 50% reduction in binge-drinking six months later. So what we're going to do now is pilot this. We're going to say what the smartphone assessment method, can we also see these kind reductions if people know you have this response phenotype and that may put you at risk and here are some techniques through brief intervention to change your drinking. So we have many things going on to continue this line of research.

Aaron van Dorn (22:53):

Well Dr. King, thank you for taking the time to speak to us today.

Dr. Andrea King (22:55):

Thank you.

Aaron van Dorn (22:56):

Up next Dr. Ned Kalin. Dr. Kalin, welcome back to AJP Audio for February, 2025.

Dr. Ned Kalin (23:01):

Thank you, Aaron. It's a pleasure to be with you.

Aaron van Dorn (23:03):

Earlier in this episode I spoke with Dr. Andrea King about a real-time assessment of positive and negative alcohol effects on individuals with and without alcohol use disorder and with and without major depressive disorder. What can you tell us about the paper?

Dr. Ned Kalin (23:14):

Aaron this is a very interesting paper and a unique study because what the investigators did was to actually use an alcohol challenge. And during that challenge study, the emotional and affect of changes that the individuals had when they were actually consuming alcohol, and compare their responses to another situation where the individuals were consuming a non-alcoholic drink. What they looked at was

basically individuals that had alcohol use disorder with depression, and also individuals that had use disorder that didn't have depression. And they also look at the complementary individuals that had depression without alcohol use disorder. The whole idea here is to understand whether the emotional and affect of change is associated with consuming alcohol are different between individuals that have comorbid depression versus those that have alcohol use disorder without comorbid depression. And the reason for wanting to understand this is that there may be different emotional drivers or motivators to consume alcohol that may differ for individuals that have depression as compared to those that don't.

(24:19):

So for example, one might think that the reason that people that have depression that end up overusing alcohol might be because it reduces their negative feelings or their depressed feelings. And that might be a more prominent effect in depressed individuals than individuals that aren't depressed to develop alcohol use disorders. For example you might think that those individuals might get more of a positive buzz out of the alcohol instead of a reduction, necessarily negative emotions. So anyway, that was the motivation for the study. As I mentioned, it's a really creative and unique design because of this administration of alcohol and then actually measuring the emotional response in real time.

(25:00):

What the investigators found was a little bit surprising. They found that it didn't really matter if you were depressed or not as far as overall your general emotional response when you're consuming alcohol. Individuals with depression and alcohol use disorder had a reduction in negative feelings, but also a bigger increase in positive feelings. And that was basically the same pattern that was seen in individuals that had alcohol use disorder who were not depressed. Generally a increase in positive feelings and a smaller decrease in negative feelings. So I think one of the surprising things here was that it didn't seem to matter whether you're depressed or not as far as what you emotionally experienced and got out of a consuming alcohol if you had alcohol use disorder.

(25:43):

Now the editorial by Dr. Markus Heilig from Linköping University in Sweden, it's really worth reading this because he points out that these findings are not entirely consistent with the theory which was considered called the allostatic theory of substance abuse, where one tries to use alcohol to adaptively regulate one's emotions. And in that case you might expect that depressed individuals would have a greater reduction in negative emotions and affect with the consumption of alcohol. And he points out that this still could be true in larger studies or in different populations. Nonetheless, it's a really interesting finding and an interesting study.

Aaron van Dorn (26:21):

The rest of the February issue is also taking a close look at subjects around addiction. Next up, we have a review from Brand and colleagues looking at behavioral addictions.

Dr. Ned Kalin (26:29):

This is an important contribution. I think we're all aware of this in psychiatry, but just in general in our society, that one doesn't have to be consuming an illicit substance to have an addiction. And there are many things that we can behaviorally addicted to. The internet is certainly one of the more prominent examples. Gaming on the internet, for example, engaging in sexual behavior that's compulsive, compulsive buying behavior, a whole host of things. And I think access to the internet and social media provides the opportunity to facilitate some of these addictive-like behaviors in individuals that are more vulnerable to this. So this review really gets into this in-depth in relation to behavioral and addictions.

Talks about their importance, what the signs and symptoms are, and also how they're frequently comorbid with a variety of other psychiatric problems. And also how they can be treated effectively with cognitive behavioral therapy. So an important addition to the issue complementing the addictive behaviors and problems that are associated with illicit drug use or alcohol use or smoking for example, and now getting into behavioral addictions.

Aaron van Dorn (27:36):

An important thing to consider especially since every sports game you see these days is wall-to-wall gambling ads.

Dr. Ned Kalin (27:40):

Absolutely. And I think the gambling business has really figured out how to hook people with the very rapid feedback about opportunities to gamble in the next event that's occurring. And also priming individuals who haven't started yet by giving them bonuses or money to get going, that seems to be free and so on. So I think we all as a society need to be very wary of the growing behavioral addictions, almost probably from the standpoint of epidemic proportions.

Aaron van Dorn (28:12):

Next we have a paper from Conway and colleagues looking at the association between tobacco product use and mental health and substance use problems in adolescents in the US.

Dr. Ned Kalin (28:20):

This is also a really interesting study and important in its own right. This study looks at the association between tobacco use with other mental health problems and with other substance use problems in adolescents, which is well known to be highly associated with each other. What's different about this study is that they really try to pin down the time course or the temporal relation between the use of tobacco and the development of mental health symptoms or vice versa mental health systems that might proceed and perhaps contribute to the use of tobacco. And what's particularly germane about this is that this is in an adolescent population, which of course is a population at risk and where these habits in cigarette smoking and tobacco addiction gets seeded and started that can have a lifelong course if not interrupted or dealt with.

(29:15):

So this is a study that enrolled a large group of subjects. It was 32,000 roughly adults and approximately 14,000 adolescents. They were followed over about a five or six year period. They were queried from the standpoint of their use of tobacco products, including cigarettes being the most common, and also the development of internalizing and externalizing psychiatric symptoms. Overall in this group, 13% of the individuals in the sample were found to have internalizing problems, and roughly 12% were found to have externalizing problems. And 68% of the sample, which is incredibly high, was found to actually be using tobacco at some point during this period of time. So very high.

(30:02):

Now what the amount of use in each individual is a different issue, but this was at least some use across over 2/3 of the sample. And they found that there were numerous effects that went in both directions. That is from use of tobacco to development of mental health symptoms as well as mental health symptoms followed by the use of tobacco. And they also found some interesting differences in males and females, which may be important from a clinical standpoint. So just to give you some examples,

they found that cigarette smoking was associated with a later development of internalizing problems. But this was pretty selective to female adolescents. In individuals that were somewhat older in the 18 to 24-year-old range, cigarette smoking was associated with a later development of internalizing problems in both males and females. So it looked to be selective earlier on and then both males and females a bit later on. And then in the older age group, 25 years of age or older, females were found to both have an increase in internalizing and externalizing symptoms, and males were found to be selectively having an increase in externalizing problems.

(31:08):

So there are these different age by sex relationships that are somewhat complicated. But the bottom line here is that smoking behavior in adolescents is associated with a later development of externalizing and internalizing problems. And they also found associations in the other direction as well, such that internalizing problems and externalizing problems were associated with later tobacco product use in adolescent females. And interestingly enough, this association was only there for externalizing problems preceding tobacco use in adolescent males. So some complex interactions. But bottom line is that using tobacco in adolescence increases risk for later development of psychiatric problems and also having internalizing and externalizing problems in adolescence also increases one's risk or the association of developing tobacco use later on. So important bi-directional interactions and important to keep in mind when we're treating our patients from the standpoint of both of these factors interacting over age and also some differences related to sex.

Aaron van Dorn (32:15):

Another thing for clinicians to keep in mind.

Dr. Ned Kalin (32:17):

Definitely.

Aaron van Dorn (32:17):

Kypriotakis and colleagues looked at the safety and effectiveness of smoking cessation treatments in people with major depressive disorder. What did they find?

Dr. Ned Kalin (32:24):

So we have really helpful FDA approved treatments for treating smoking cessation or helping people with smoking cessation. And the currently available treatments that are approved are nicotine replacement and various preparations, varenicline as a medication and also bupropion. What these investigators wanted to do was to study whether or not these treatments were effective, but even more importantly, safe in individuals that had depression who were undergoing treatment for smoking or smoking cessation. Now, this may sound like an obvious thing, but it's not so obvious. And there have been reports actually of some of these medications making individuals worse... Of depression symptoms and other emotional types of symptoms.

(33:12):

So what these researchers did is that they used individuals that were smoking that were undergoing treatment for smoking cessation, some of which in this case about 450 that also had current active major depression. They had a larger group that were not actively depressed but actually had a history of depression. This was about 2,000 individuals and they had about 4,000 individuals that they followed that had no psychiatric symptoms or no disorders, and also were undergoing smoking cessation. And

then these different groups were randomly assigned to 12 weeks of treatment with either varenicline, bupropion or nicotine replacement or placebo. So basically these four treatments were distributed over these different groups. Another question was asked whether there were different outcomes both from the standpoint of efficacy and also importantly from the standpoint of safety. Bottom line here is that they did not find any significant differences in adverse psychiatric effects across these different groups with these different treatments.

(34:15):

So the primary safety outcome measures in this case that they used were increases in anxiety, depression, anger, suicidal feelings, homicidal ideation and psychotic symptoms. And these did not differ across these groups. So whether you were depressed or not didn't seem to matter, and it didn't seem to matter which treatment you had in relation to whether you were depressed or not. So that's really good news. So it gives us data now to feel comfortable using these treatments to reduce smoking use and to promote smoking cessation individuals that are depressed and who have these problems.

(34:48):

The other interesting thing they found was that varenicline actually outperformed the other treatments for individuals that were depressed and undergoing smoking cessation. Roughly the odds ratio for the comparison between varenicline and bupropion or varenicline and nicotine replacement were between two or three times more likely to get better from the standpoint of treatment if you're depressed with varenicline. It was even greater for nicotine replacement. The odds ratio here was roughly six-fold. This is important clinically, and it really does suggest, although again it's one study, it does suggest that in individuals that are depressed and also want to stop smoking that varenicline may be a more reasonable treatment option from the standpoint of better efficacy and no increase that's obvious in relation to side effects.

Aaron van Dorn (35:42):

Kuhn and colleagues looked at heroin vulnerability and resilience in rats. What can you tell us about it.

Dr. Ned Kalin (35:46):

Now, why in the world would we want to put a rat study in The American Journal of Psychiatry? And I'm asking that rhetorically, but the reason is because we learn a lot from preclinical studies, and particularly animal model studies. Animal models are absolutely critical for us to understand more about what causes the problems we treat or what are the secret ingredients for the treatments that we use that really make them effective. In our clinical research, it's very difficult to ask questions about causality. We ask questions about associations.

(36:23):

So for example, in the study that we talked about in relation to the use of tobacco in adolescents and the development of mental health symptoms, we could show in that study, for example, the investigators showed that tobacco use in adolescents preceded the onset of, for example, internalizing and externalizing symptoms. But that doesn't really tell us that tobacco use is causing the development of those symptoms. It just tell us that there's an association over time. It might be for example that individuals that tend to use tobacco as adolescents also have a greater tendency for a variety of reasons to develop psychiatric problems. And it may not have anything to do with tobacco actually causing the increase in the psychiatric problems. The animal models allow us to ask that question.

(37:08):

In this case, the investigators are very interested in overuse of opiates and more specifically heroin abuse. Yes they've developed a very strong and robust animal model in rodents that have allowed them over the years to ask all kinds of questions about why do some rodents get hooked on heroin and others don't, even if they all have complete access, ad-lib access to the drug. And what this study does is this study actually takes a huge sample size. In this case it's 900 rodents or rats, both males or females. And does all kinds of different phenotyping tests. Not just how much does the animal self-administer the drug. How much does the animal like the drug and need the drug? But also how anxious is the animal under other conditions? How sensitive is the animal to reward? How sensitive is the animal to pain? A whole variety of behavioral parameters.

(38:04):

And what they did is they took all of these parameters and more or less put them in a statistical mixer and came up with different groups of animals based on these different phenotypic characteristics. And based on all of this phenotyping, they could very reliably develop subgroups of animals, some of which were highly sensitive to the effects of heroin and developed big time heroin addictions. And other animals that were relatively resistant and resilient regardless of the access to the heroin. And by so doing, they've now developed a model that allows us to think about how we can look at humans and really begin to think about all the heterogeneity in the different factors and symptoms and comorbidities that people who abuse opiates in this case have and how to subgroup individuals with the hope that we can get more specific personalized treatments.

(38:58):

And in fact, these researchers went on to show that these different subgroups of animals that they identify with all these phenotypic factors and fancy statistical methods, they actually had different patterns of brain activation when they looked at brain activation when the animals were exposed to heroin, which is consistent with the differences in behavior. You would expect to see that resilient animals might have a very different pattern of brain activation than vulnerable animals when exposed to heroin, and that's what they found. So a really important preclinical animal model work that sets the stage for a better understanding of the mechanisms and development of new treatments for substance abuse.

Aaron van Dorn (39:37):

Finally, we have a paper from Grilo and colleagues looking at treatments for binge eating disorder, including cognitive behavioral therapy and an FDA approved medicine.

Dr. Ned Kalin (39:44):

This is another very clinically relevant paper that advances our clinical psychiatric science. It's in a small sample, so I'll start off with saying that it needs to be somewhat cautiously interpreted. But the findings are pretty striking. We've known for a while that lisdexamfetamine, which is a prodrug or dexamphetamine, which is used for ADHD, is also been approved for the treatment of binge eating disorder. And we also know that cognitive behavioral therapy also is an evidence-based treatment that works for binge eating disorder. Now, why binge eating disorder? Binge eating disorder is the most common eating disorder. It's associated with significant psychological distress and it's frequently associated with obesity and increased body mass index. In DSM-5 binge eating disorder is characterized by numerous episodes of binge eating and a true sense of not having control over the excessive eating that is associated with a lot of guilt, marked distress.

(40:46):

But unlike bulimia, this binge eating is not associated with attempts to actually reduce weight gain. So with bulimia, we frequently see purging and vomiting and things like that, laxative use associated with binge eating. This binge eating disorder is not associated with that. What the researchers did is they took these two evidence-based treatments and actually asked the question as to what happens when we combine them. Can we get a better result? Will the treatment be more effective in binge eating disorder patients who also have obesity? And it's important to underscore that these are patients that both have a binge eating disorder and comorbid obesity, which is very common, but not always associated with binge eating disorder. Can we improve outcomes in patients that have binge eating disorder and comorbid obesity if we combine the medication treatment, lisdexamfetamine with CBT. So they had three groups. They had roughly 50 individuals per group, actually 47.

(41:44):

One group got CBT for 12 weeks. Another group got lisdexamfetamine 50 to 70 milligrams per day for 12 weeks. And the final group got CBT combined with lisdexamfetamine for 12 weeks. What they found was, and I think reassuringly, that all three treatments were effective. And it turned out that CBT plus the medication lisdexamfetamine appeared to be the most effective. But when they actually looked at the rating scales, the differences between these treatments did not reach statistical significance. However, when they looked at remission, whether patients were fully well or not, which is a bit of a different measure, they found some pretty dramatic effects. They basically found that the combination treatment, that is, lisdexamfetamine plus CBT had roughly a 70% remission rate, whereas either treatment alone was around 40% or 45%. This is further evidence to support that the combination treatment is the way to go if that's available to patients.

(42:46):

Now, they also looked at weight reduction in these patients because this was, again, a subset that was selected that had obesity as well as binge eating. And what they found here is really an important takeaway. They found that CBT alone was not nearly as effective as the medication lisdexamfetamine. Whether it was administered alone or with CBT. So for example, 53% of the participants that took lisdexamfetamine, again, whether it was or without CBT, had a reduction of 5% of body weight or greater. So that's 50% of patients. And it was only about 4% of patients in the CBT group alone. So clearly the addition of lisdexamfetamine in individuals that have obesity is critical from the standpoint of helping them deal with their weight gain. Again, just to reiterate, the combination with CBT and this medication really appears to be the best clinical approach patients. And this finally, to come back to where I started, the results need to be consciously interpreted because it's a small sample. But if this holds, it really is an important clinical step forward in the treatment of this disorder.

Aaron van Dorn (43:55):

Dr. Kalin, thank you once again for taking the time to speak with us.

Dr. Ned Kalin (43:58):

You're welcome. It's a pleasure, Aaron.

Aaron van Dorn (44:00):

That's all for the February issue of AJP Audio. I hope you'll join us next time when we take another look at some of the best research psychiatry has to offer. In the meantime, be sure to check out the other podcasts the APA has to offer, including Psychiatric Services From Pages to Practice. In their most recent episode, Dr. Dixon and Dr. Berezin talk with Dr. Eunice Wong from RAND, about partnerships between

faith-based communities and mental health service providers. Check that out, and more at psychiatryonline.org or wherever you get podcasts.

(44:25):

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