AJP Audio – Gal Arad – May 2023

Aaron van Dorn (00:07):

Welcome to AJP Audio for May 2023. I'm Aaron van Dorn. Ms. Gal Arad, a researcher at the School of Psychological Sciences at Tel Aviv University in Tel Aviv, Israel joins us to discuss a non-pharmacological intervention for the treatment of social anxiety disorder in comparison to standard care. Afterwards, we'll once again be joined by the *Journal* Editor-in-Chief, Dr. Ned Kalin, to discuss the rest of the May issue. Ms. Arad, social anxiety disorder affects between four to 12% of the population and shows only moderate response to current frontline treatments, selective serotonin uptake inhibitors and cognitive behavioral therapy, with around half of patients prescribe these treatments continuing to show symptoms. Your study looked at a new non-pharmacological treatment called Gaze-Contingent Music Reward Therapy. What does that consist of?

Ms. Arad (00:48):

Gaze-Contingent Music Reward Therapy, or GC-MART for short, is based on finding that compared to non-anxious people, people with social anxiety tend to turn more attention to it and to dwell longer on socially threatening stimuli. These can be negative or uninterested facial expressions in an audience while speaking publicly or even a hint of disapproving expression in a social gathering. This attentional tendency is implicated in the maintenance of social anxiety and therefore it's the target of GC-MART. We used eye tracking technology to reduce this tendency apply musical feedback.

(01:28):

In each session of GC-MART patients first select music that they enjoy listening to, and then they're instructed to gaze freely as they like at matrix's of faces with either disgusted or neutral expressions while their gaze is continuously trapped. As long as they're looking at neutral facial expressions, the music they chose keeps playing. But whenever their gaze turns to threat related faces, the music stops. This feedback is meant to adjust gaze patterns, to be more like those of non-anxious individuals, and eventually to reduce symptoms. Previous clinical trials have shown that this type of treatment is quite effective when compared to tight controls in the past.

Aaron van Dorn (02:11):

Your studies split patients between three arms, GC-MART, which you just described, SSRIs and an active waiting list control. What were your results?

Ms. Arad (02:19):

Most importantly, we found that both GC-MART and SSRI were both more effective than wait list control in reducing social anxiety symptoms and that no significant differences were noted in the efficacy of these two active treatments. This result was found both when symptoms were assessed using a clinical interview and when patients self-reported on symptoms. What we also found was that GC-MART was acceptable and made as much sense to patients as the pharmacological option. This suggests that GC-MART, which is a relatively new, low cost and accessible treatment, is comparable to SSRI, which is a well-founded and effective treatment for social anxiety. I'll add that importantly, when it came to depressive symptoms which are highly comorbid social anxiety, we found that SSRI was significantly more effective than wait list control, whereas GC-MART didn't show such an effect. So although no significant differences were noted between GC-MART and SSRI in reducing depressive symptoms, it does seem that for social anxiety with comorbid depression, SSRIs may be more effective, which is not surprising as it replicates findings from separate previous trials and SSRI and GC-MART separate.

Aaron van Dorn (03:36):

Patients in the GC-MART arm showed significant reductions in the dwell time on threatening faces. What does this result suggest?

Ms. Arad (03:42):

Essentially, indicated effective target engagement with our treatment protocol. What it means is that we were able to alter gaze patterns using the musical feedback that we provided. What strengthens this finding is that this reduction in dwell time on threat was observed only in the GC-MART group and not in the SSRI or wait list controls, which implies this is indeed the result of the applied feedback in the treatment sessions.

Aaron van Dorn (04:09):

What were the limitations of your study?

Ms. Arad (04:10):

There were four limitations to consider. So first we used wait list as our control group, and this could be considered a weak control. It doesn't count for potential placebo effects. However, response rates in this study were high and comparable to previous published trials, which indicates that clinical improvement was most likely not fully due to nonspecific treatment effects. Second, although no significant differences were found between the GC-MART and SSRI groups and social anxiety symptoms, the current study wasn't a non-inferiority trial, so such difference can't be ruled out entirely. Third, long-term effects weren't measured, so the last measurement was taken one week post-treatment. Future studies could assess longer term effects of both treatments, especially as SSRIs are commonly recommended for at least a year while GC-MART is a short acute treatment plan. And lastly, a limitation of this study is that for both treatments, clinical effects were limited with average LSA scores remaining in the clinical range post-treatment. While this is consistent with the results previous trials in social anxiety, it does imply that there is still more work ahead of us in improving treatment efficacy.

Aaron van Dorn (05:25):

Are there any immediate clinical implications for your findings?

Ms. Arad (05:27):

Given that up to 50% of patients with social anxiety remain symptomatic following a full course of treatment and that relapse rates are quite high, having new effective treatment options for the disorder is important. This study indicates that GC-MART, which is a short, low cost and minimally demanding treatment option, is a viable alternative for treating social anxiety disorder. As eye tracking technology is becoming more and more affordable and accessible, this is pretty exciting news for the field.

Aaron van Dorn (05:57):

What's next for your research?

Ms. Arad (05:58):

We're continuing to explore the clinical effects and underlying mechanisms of GC-MART with the hope that such knowledge could be used to enhance treatment efficacy. For example, we're working on a study exploring the possibility of GC-MART may affect basic attentional controlled capacities, in addition

to specific threat related attention patterns. In addition, in this present study, we actually collected pre and post-treatment MRI data that shed light on common and specific neural processes, underlying GC-MART and SSRI treatment.

Aaron van Dorn (06:32):

Ms. Arad, thank you for taking the to speak with us today.

Ms. Arad (06:35):

Thank you. Thanks a lot.

Aaron van Dorn (06:37):

Up next, Dr. Ned Kalin. Hi Dr. Kalin and welcome once again to AJP Audio.

Dr. Ned Kalin (06:41):

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

Aaron van Dorn (06:43):

The May issue of AJP focuses on treatment issues. Earlier I spoke with Ms. Gal Arad about the use of a digital intervention of the treatment of social anxiety disorder. What can you tell us about it and how it fits into the May issue?

Dr. Ned Kalin (06:55):

Well, this issue is devoted to either presenting new treatments or thinking about how we can enhance current treatments for various psychiatric disorders. This particular paper, as you mentioned, is focused on social anxiety disorder and uses a really interesting intervention, which is basically attempting to modify one's bias towards threatening stimuli or in this particular case for social anxiety patients, towards threatening faces. The intervention that is being explored here is training individuals to not attend preferentially to threatening faces, which is a particularly relevant stimulus for people that have social anxiety disorder. So in this study there were three groups. One group got this training that was eye tracking based attention bias modification, 10 sessions over a 12 week. Another group got standard SSRI treatment with escitalopram up to 20 milligrams. Turns out that the average maximum dose over this period of time was only 11 to 12 milligrams, which is important to keep in mind.

(07:57):

Then finally, there was a third comparison group that was a wait list comparison group that were told that they would later get the attention bias modification training. The findings were interesting. The findings basically showed that the attention training, bias training, was as effective as the SSRIs. So it was sort of a non-inferiority trial, but both treatments, active treatments were significantly better than the wait list, which you would expect. It turned out that the SSRI treatment group did better from the standpoint of if they had comorbid depression symptoms, they tended to get better, whereas this was not the case in the eye tracking based attention modification group. Interesting finding, a new approach to treating social anxiety, one that does not use pharmacotherapy. One thing to keep in mind in this study is that the average dose of escitalopram was only 11.6 milligrams per day. We tend to think of therapeutic doses more in the 20 milligram range. One of the issues and interpretation would be to keep in mind that this arm of the study had a lower dose of medication than you might want to use clinically.

Aaron van Dorn (09:02):

Next up, we have a study looked at the treatment of trichotillomania and skin picking disorder from Grant and colleagues.

Dr. Ned Kalin (09:07):

So again, another interesting study examining a new treatment. In this particular case, the study was focused on using the NMDA antagonist memantine, which is used for the treatment of memory impairment in Alzheimer's disease. Memantine is interesting because one of the mechanisms that's hypothesized to be associated with these habit related types of pathophysiologies is alterations in the glutamatergic system. So in this particular study, the investigators had 100 participants. They were randomized to either receive either memantine 10 milligrams a day for one week and then increase to 20 milligrams per day or placebo over an eight-week period. Important to keep in mind that the patients included in the study either had trichotillomania or had skin picking disorder and so they were clumped together. Some might argue that the group should be separate, but I think there's a good rationale for putting them together.

(10:06):

Both are these pathophysiological alterations associated with habitual self-directed behaviors. The primary outcome measure was a change in the NIMH symptom scale that was focused on trichotillomania. Basically what they found was a fairly strong effect of the active treatment memantine. 60% reduction in the clinical global index improvement scale in the memantine group as compared to an 8.3% improvement in the placebo group. The scale that was specifically used for trichotillomania that was developed also showed significant reductions in the treatment group. So a fairly strong effect with a new treatment holding interesting promise for folks that suffer from these difficult to treat disorders.

Aaron van Dorn (10:54):

Reddy and colleagues look at our novel treatment for schizophrenia that combines two different treatments. What did they find?

Dr. Ned Kalin (10:59):

So this was a study that is particularly focused on negative symptoms of schizophrenia and more specifically, even the motivational components of the negative symptoms. It's believed that the negative symptoms and the motivational components that is reduced motivation or a decreased drive are really very much linked to the functional disabilities that patients suffering with schizophrenia have. This is a psychotherapy based intervention in individuals that received either 12 weeks of the intervention, which was a combination of both motivational interviewing and cognitive behavioral therapy. The individuals were also followed for another 12 weeks. So the study lasted for a total of 24 weeks. The focus again, and the primary outcomes were symptoms related to decreased motivation, decreased pleasure, and that core of symptoms that gets at some of the negative symptoms of schizophrenia. The combination of motivational interviewing and CBT is rather unique.

(12:01):

The idea here was that the motivational interviewing along with the CBT would not only target the symptoms that are associated with amotivation, but also would enhance the likelihood of adherence by increasing the motivation of the patients. What the investigators found was in fact that the combination of motivational interviewing and CBT had a more prominent effect than mindfulness treatment alone on these measures and that this was obvious at 12 weeks when the effect was most prominent. The

downside of this is that when the investigators looked out to an additional 12 weeks, the differences between the two treatments were less prominent. So it doesn't look like it's particularly a long-lasting effect. Also, another concern was that when the investigators looked at functioning in the community, there was really not an increase in functioning after these treatments. So while there was a change in the symptoms and based on the rating scales, this really did not translate to major changes in functional capacity for these patients.

(13:06):

Now, despite that, it's a really interesting approach and holds promise and probably is an important step to build on in thinking about how to further enhance this combination treatment and hopefully have this translated to better functional outcomes.

Aaron van Dorn (13:21):

Continuing with the focus on schizophrenia, Taipale and colleagues looked at a burden of polypharmacy versus monotherapy and a cohort of patients with schizophrenia.

Dr. Ned Kalin (13:28):

This is a really interesting study. It's performed in a large sample, over 61,000 individuals from Finland. These are all the individuals, at least supposed to be all the individuals that were hospitalized for schizophrenia between 1972 and 2014. So a very, very large cohort. The analysis followed individuals or their data over a period of roughly eight to nine years. The question that was asked was, when you look at these individuals when they were on one antipsychotic medicine versus more than one antipsychotic medicine versus not being any on any medication, how did they do from the standpoint of significant medical complications or medical issues? The outcome measure that was used there was hospitalizations that were non-psychiatric and they could be medical hospitalizations or they could be for cardiovascular related problems. Somewhat contrary to what we might expect in this particular case, individuals that were taking more than one drug or that had polypharmacy in a sense with the antipsychotics, actually did better from the standpoint of non-psychiatric hospitalizations.

(14:39):

This is particularly apparent at the higher doses of medications when they were used. One thing to keep in mind here is that this was within subjects analysis. So this was looking at subjects over time and asking a question about when the subject was taking one medication, one an antipsychotic versus more versus none, what was the likelihood during that period of having a non-psychiatric hospitalization? So somewhat contrary to what you might expect, polypharmacy is not always bad. In particular, in relation to schizophrenia patients, it looks like polypharmacy results in less non-psychiatric hospitalizations. There are a variety of reasons why this might be the case. We have a really nice editorial by Dr. Robert Buchanan and Dr. Julie Krane from the University of Maryland that discuss this issue in general and also think about some of the other factors that might be related to the decreased medical morbidity that was observed in these patients.

Aaron van Dorn (15:36):

And finally, Brant and colleagues looked at the risk of experiencing overdosing in patients undergoing treatment for opioid use disorder.

Dr. Ned Kalin (15:41):

We all are aware of how critical the issue is related to opioid abuse is and the overdose deaths, the cost to society and individuals suffering and families and all that. One statistic that really is striking is that from 2020 to 2021, the CDC estimated that there were over 100,000 drug related overdose deaths in the United States. Of these, roughly 75,000 were attributed to opioid overdoses. What this study did was interestingly looked at the likelihood of overdosing during medication treatment for opioid use disorder. We all know that... And it's intuitive, that by getting treatment you're reducing risk for overdose. But nonetheless, even during treatment, there are a significant number of people that engage in self-harm and overdosing activities. So again, the focus here was to ask, during this period of treatment, what is the likelihood of overdosing and what are some of the factors associated with this?

(16:45):

So this was a large data set that was acquired from three different randomized clinical trials that were performed with the National Institute of Drug Abuse Clinical Trials Network. So the number of individuals in the study was over 2,000 undergoing medication treatment for opioid use disorder or opioid dependence. The three treatments were either methadone, extended release injected naltrexone or a buprenorphine naloxone combination. They assessed the risk of overdose over 24 weeks after the beginning of treatment. What they found was that over this time period, out of the roughly 2,100 individuals that were studied, 39 of the participants had least one overdose, and there was a total of 57 overdosing episodes among those, within those 39 people. Of those overdoses, 28 were due to opioids. Now, they asked the question, "Were any of the treatments associated with significantly more overdoses than the other treatments?"

(17:45):

It turns out interestingly enough that those individuals with the highest level of overdose were in the Naltrexone group. In that group, 5.3% of individuals engaged in an overdose compared to 1.5 and 1.15 in the methadone and buprenorphine groups respectively. The authors speculate about why this is the case and it turns out that the Naltrexone group had more individuals that actually did not even initiate the treatment. Even though they were in treatment, they did not comply with it and did not initiate it. So that was one risk factor which is obvious and was associated more with the Naltrexone group. The other thing that was interesting is that when they looked at benzodiazepine use, they found that those individuals that reported taking benzodiazepines during the 28-day period prior to the study, had roughly a threefold likelihood of overdosing as those compared to those that were not taking benzodiazepines.

(18:40):

Now, why this is the case is not entirely clear. So overall, two risk factors. One is not really beginning or engaging in treatment, sticking with it. The other is if one was taking benzodiazepines prior to the opioid use disorder treatment that was performed. Here, I think the take home message is that even though individuals are undergoing treatment, they may not necessarily be complying with it or even initiating it, and those individuals may be at greater risk for overdosing during this period of time. Also, I think being mindful of the use of benzodiazepines in this population, especially prior to treatment, also looks like it may increase an enhance risk for overdose during treatment.

Aaron van Dorn (19:24):

Dr. Kalin, thank you once again for speaking with us.

Dr. Ned Kalin (19:26):

You're very welcome. Take care.

Aaron van Dorn (19:28):

That's all for this month's AJP Audio, but you can check out other podcasts from the APA. In the April episode of Psychiatric Services from pages to practice, Dr. Dixon and Dr. Berzin are joined by researchers to discuss the effective integrating patient generated digital data into mental health therapy. That and more can be found at psychiatryonline.org/podcasts or wherever you find podcasts.

Speaker 4 (19:48):

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