

Mindset Health's Claire Davidson in conversation with Dr. Simone Peters about gut-directed hypnotherapy, the gut-brain axis, and diagnosing IBS

00:00:00 Dr. Simone Peters: The brain-gut axis and of course gut-directed hypnotherapy. So when we talk about hypnotherapy that is gut-directed if you like, what we're talking about is using hypnotherapy to treat disorders of gut-brain interaction. And obviously, there's lots of different disorders that fall under this sort of subheading, but the focus again of today's presentation is going to be on those disorders that are related to bowel function. And when we think about bowel disorders, again, there's lots of things that fall under this. There's lots of subcategories that fall under this heading, including irritable bowel syndrome, functional constipation, functional diarrhea, functional abdominal bloating and/or distension, unspecified functional bowel disorder, and of course, opioid-induced constipation. And again, in the interest of time, we're only going to focus on irritable bowel syndrome today. So it's probably no surprise that irritable bowel syndrome is really the most common functional gastrointestinal disorder and it has a worldwide prevalence of around 11%. Of course, there are wide variations between countries, and when we talk about countries like the US, the UK, and Australia, we're probably actually sitting somewhere up at about 15 to 20% prevalence rates. It's more common in women by a ratio of about two to one, and certainly, younger people are more likely to be affected than those who are older than age 50. That said, in clinic, we are seeing more and more patients present who are in fact older than age 50. So it's not as though the condition only affects those whom are younger. It has, as you would expect, a very considerable impact on quality of life. And it costs the healthcare system billions of dollars per year and not only in terms of direct costs through presentations to tertiary settings, or specialist centers, but also indirect costs through absenteeism from the workplace, or certainly reduced productivity at work. And interestingly about 40% of those patients who have been diagnosed with irritable bowel syndrome, they have been diagnosed for quite an extended period of time. By that we mean really more than sort of 10 years. And even though they've had this formal diagnosis of irritable bowel syndrome for a long time, quite a large percentage, 60%, report ongoing symptoms. And I guess there's probably these statistics, I think, tell us that we're probably not really doing enough for these patients in terms of finding adequate ways of managing these symptoms.

So when we talk about symptoms, the symptoms that patients need to present within order to fulfill the criteria for having irritable bowel syndrome is a recurrent abdominal pain and usually this is in association with changes in the stool consistency. And when we mean changes in stool consistency, we mean diarrhea, constipation, or in fact a combination of the two. Now, while patients need to have abdominal pain, which is associated with changes in their stool consistency in order to meet the diagnostic criteria for irritable bowel, when we see patients clinically they typically don't present with only abdominal pain and issues with their stool consistency. They often also present with symptoms of bloating, and/or distension, and there's a clear distinction between the two. So when we talk about bloating, we're talking about the feeling of fullness. So for example, if I gave somebody a really big meal and they ate it and they felt full and uncomfortable, we would use the word bloating to describe that feeling. However, if somebody were to actually find that their gut would seemingly visibly distended, so you can actually see a visible difference in the circumference of the gut, then we would call that distension. And of course, it's possible for patients to have bloating in the absence of distension. Wind, or for those in America I think you call wind gas, and of course, nausea.

00:04:27 Dr. Simone Peters: So, we use special charts like this, which is called the Bristol Stool Form Scale, to assess what patients mean in terms of the form of the stool if you like. And if we look up the top here at this sort of, this type one type two form stool, if patients present to us and they report that this is the type of stool that they pass the majority of the time, these patients would fall into the category of being constipated. Similarly, if patients present and they describe to us that they're passing a type six type seven bowel movement most of the time, we would think that these patients would fall into the category of having diarrhea-predominant irritable bowel syndrome. And, of course, quote-unquote, normal bowel movements sort of fall into this range of being a type three, type four bowel movement. I think one really important point here from a clinical perspective, is that in fact, we are sure that when we communicate with patients that we are talking about the same thing, and it's not uncommon, in fact for patients to present a clinic and say that they have really terrible diarrhea, say for example, but then to tell me that they pass a type four bowel movement. And this is obviously not only we see this all the time in clinic, but there's also been some work that's been published in this area now, which actually tells us that what patients report in terms of the consistency of their stool is not necessarily what they're passing. So when a patient obviously has gut symptoms, what they do is most typically what they do is they present to some sort of a health care provider. Now often in Australia, that is their GP or the gastroenterologist and in doing so, the first aim, I guess, of that patient reaching out,

is to ensure that there's nothing going on in terms of those gut symptoms that is in any way alarming in the context of there being any inflammation or any ulceration or any other nasties that we need to be concerned about. And so often the healthcare provider will order a series of different investigations to ensure that that is not the case. This can include, but is of course not limited to, blood tests and of course, you know, we're looking for just the overall ensuring the overall state of the individual in terms of their overall health is within normal ranges. But also that they're nutritionally, their diet is nutritionally adequate, and nutritional profile is within the range of normal. That Celiac disease is excluded and, of course, we need to ensure that patients are consuming adequate amounts of gluten in their diet in order for us to be able to do this. And as you can imagine this is, you know, obviously very important given that irritable bowel syndrome and Celiac disease often present in the same way.

It's very possible that they also do a stool, collect some stool from a patient and they will use that stool to ensure that there are no parasites or bacterial infections, no indications of inflammation in the stool and then often they will do things like colonoscopy, gastroscopy, if in fact that there, you know, there appears to be a need to do so. And, you know, it's a bit of a double-edged sword, of course, you know, in an ideal world, we want all those results, all of the results of those investigations to come back and show that there's nothing wrong. But in doing that, what it means is that, you know, there's no obvious reason as to why these patients are having these symptoms. But I think this is when it becomes really important that we apply the diagnostic criteria for irritable bowel syndrome. And in fact, if we've ruled out all of the nasties, and patients actually meet these following criteria, which has been identified by the Rome Foundation, then it's a really clear diagnosis of irritable bowel is made. And in order to meet this criteria, patients need to have recurrent abdominal pain. They need to have had this pain on average, at least one day per week in the last three months, and it needs to be associated with two or more of the following. This pain needs to be related to defecation. So either they have pain prior to defecation or after. It needs to be associated with a change in the frequency of the stool. So an increase or a reduction in the frequency and of course associated with a change in the form or the appearance of the stool. Therefore, you know, the patient becomes more constipated or has diarrhea. And they need to fulfill this criteria for a period of time, for three months, and they need to have had these symptoms for at least six months prior to diagnosis. And if patients meet this criteria for having irritable bowel syndrome, then it's really important that their health care provider provides a very clear, very concise, and very reassuring diagnosis. Because we know that in those patients who receive a very firm diagnosis of irritable bowel syndrome, then they are less likely to seek health care in the future in the context of, you know, overutilizing healthcare services, more likely to attend or to receive treatment for their symptoms, and are certainly more likely to respond to those treatment strategies.

00:09:57 Dr. Simone Peters: So when we think about what causes irritable bowel, there's probably lots of different factors that all contribute to the condition itself. Of course, intestinal motility is one issue. This is the time it takes from when somebody eats something to when they pass that same thing at the other end, and obviously, we know that in some people with irritable bowel this can be altered. Visceral sensitivity or what we call hypersensitivity relates to this over-sensitivity of the nerves that lie in the gut and probably about 70% of patients who present with irritable bowel have some degree of visceral hypersensitivity. The microbiota or our microbiome has been suggested to have an impact on both physical symptoms in patients who have irritable bowel, but there's also emerging evidence to suggest that what types of bacterial species we have in our gut can also impact our mood. And we're going to talk a little bit later on about the impact of patient's psychological state in conditions like your irritable bowel syndrome, and while this is a very, very interesting area, I've not sort of delved too far into this in today's presentation in the interest of time. Gut permeability, immune activation, genetics, and also brain-gut interactions are all thought to play a role. So in terms of treatment, unfortunately, there is no cure for irritable bowel and so essentially what we're trying to do is we're trying to manage these symptoms in the best way that we can. Historically treatment has focused on medication. So whether this be prescription or over the counter medications, but unfortunately, most of these medications have led to benefits of less than half in these patients, less than half of these patients that we treat report benefits, and if they do report benefits and the therapy gain over placebo is very small, only about sort of seven to 14%. And I guess because of this, because of the poor response rates to medication, but perhaps not only this, perhaps also because, in terms of using medication, we have no one drug that fixes all symptoms. And as we've sort of discussed most patients with irritable bowel present with a combination of lots of different symptoms. And so I guess what happens if we go down the pharmaceutical path is that we end up using lots of different types of medication in order to treat each individual symptom, of course, which all come with their own individual side effect profiles.

So what we've seen, perhaps in recent years, is actually that patients are really sort of sought alternative options and these predominantly have included dietary modification, and also behavioral therapies. And I think a really key point is that integrated care is becoming the rule, not the exception. So 10 years ago, you know, it was very unusual that we would have these centers that focus predominantly on you know, the management of symptoms in patients who present with irritable bowel. These patients were presenting to individual practitioners. But in fact, what we find now, and certainly here in Australia and over the world, is that integrated care is becoming much more common in the context that patients present, for

example, to a tertiary setting, and they have a team of people that are looking after them. So they have a gastroenterologist, they have a functional GI nurse, they have a pelvic floor physiotherapist, a dietician, a psychologist, a hypnotherapist, a combination of people that are all working together for the management of these symptoms in these patients. And this is, I guess, just a pictorial representation of what we just discussed. So this idea of integrated care, the gastro, the psychologist, the dietitian, of course, it goes beyond this, you know, like I just mentioned to you, the pelvic floor physiotherapist and so on.

00:14:00 Dr. Simone Peters: But I guess if we talk about medications first, there's some like that certainly are very useful in, you know, a certain number of patients who present with irritable bowel. Of course, laxative therapy is one and it would come as no surprise that we often use laxatives in patients who present with constipation-predominant irritable bowel. This can include **osmotic[?]** or stimulant laxatives, and obviously is usually managed by the patient's healthcare provider, their GP, their gastroenterologist, or so on. Anti-diarrheal agents are used for those patients who often present with loose or very urgent bowel movements and again they can be used as preventatives, but also in more of a sort of a curative setting. Antispasmodics, antidepressants, in fact, we often use antidepressants in very low doses as a way of reducing visceral hypersensitivity. And again, we talked about this idea that visceral hypersensitivity is fairly common, and about 70% of patients who present will have some degree of oversensitive nerves in their gut. Probiotics, prebiotics, antibiotics. Again, these all work on the same premise and that is in some way we are altering the microbiome. And of course, there's evidence to suggest that each of these are useful in their own way, and certainly can not only help to improve symptoms of irritable bowel but on occasion can also -- have been shown to actually contribute to the initiation of the problem to begin with. For example, a patient who goes overseas and, you know, eats something a little bit funny, they end up with post-infectious IBS, we treat them with antibiotics and, you know, probably through the treatment of antibiotics we've contributed to the perhaps the overall problem.

Dietary modification is also really common. Dietary fiber is obviously a really key element to ensuring that patients are able to pass a bowel movement effectively with a sense of complete evacuation and certainly no urgency. It's a bit of a fine balance. Obviously, we want to make sure that the people's diets are fibrous but also we want to make sure that they're eating the right type of fiber. So they're not going to eat what we call fermentable fibers, or fibers that are going to make them more bloated or more uncomfortable, or certainly have more pain. And then elimination diets like I said are probably those that are the most commonly applied and of course, these vary. These can be based on IgG-mediated responses, IgE-mediated responses, and what we call naturally occurring food chemicals. So things like **salicylates[?]**, **amiens[?]**, **glutamates[?]** and while there's very limited evidence in the literature to suggest that this style diet is useful in terms of managing symptoms, anecdotally, we do find that it can absolutely be a benefit. And one of the main reasons I suspect that we've not been all that -- we've not been able to sort of quantify I guess, or run trials in this area and in a way that is meaningful, because there's a huge variation in these food chemicals based on the source of these particular foods. Food additives so colours, preservatives, flavour enhancers, gluten. Gluten I think was the flavour of a few years, a few years back, and of course, you know, outside of the realm of Celiac disease. I mean, obviously, we're not talking about Celiac disease at this point in time, but if you had a patient who had Celiac disease, it's a no-brainer. They need to be on a gluten-free diet. But there's also this entity that we call non-Celiac gluten-sensitive patients and, you know, who often described that when they consume gluten they feel worse, and when they go on a gluten-free diet, they feel better. Now there probably are a very small percentage of these patients that have a true gluten sensitivity outside of the realm of Celiac disease. **[inaudible 00:17:55]** also discovered is that gluten doesn't exist in a product on its own. It usually coexists with a particular carbohydrate called **fructan[?]**, and this falls under this sort of FODMAP category. And we know that when we challenge patients with **fructans[?]**, that they almost always respond symptomatically.

So I think out of all of these elimination diets, the low FODMAP diet is most certainly the diet that has the most evidence to support its use in IBS populations. And if we look at dietary FODMAPs, essentially, they are short-chain carbohydrates. They're indigestible, or they're slowly absorbed in the small intestine. And we've grouped them together under this term FODMAPs which stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. Importantly, when we feed patients these foods that contain these FODMAPs, we induce symptoms in them. So we make them feel worse when we give them large loads of these FODMAP-containing foods and then, of course, when we remove these foods from people's diets, we make them feel better. This is not a healthy diet although FODMAP diet is not a diet that we suggest for fun. We suggest it as a clinical tool to manage a clinical problem and of course, that problem in the context of what we're talking about today is irritable bowel syndrome. And so when we use it as a way of managing symptoms associated with irritable bowel syndrome, we do this under three sort of phases. So we restrict these foods from people's diets, we then do that. Typically we try and do that over a very short period of time, so a four to six week time period, then we reintroduce as many of these FODMAPs back into the diet as absolutely possible. Of course without making people's symptoms worse, and then comes this idea of personalization. So finding this sort of sweet spot between the reintroduction of these foods, but of course, like I said, without making the problem or the symptoms worse.

00:19:57 Dr. Simone Peters: In terms of behavioral therapies. We use behavioral therapies to manage symptoms through the manipulation of inflammation that takes place from the top to the bottom. So the central nervous system or the brain and the enteric nervous system which is known as the gut, and of course this link is referred to as the brain-gut axis. Interestingly, often I think we forget but this communication takes place in both health and disease and I think, you know, give credit where credit is due. We as humans, for a long time, have suspected what I think science is only discovering in recent years and that is that we use our gut to give us an idea of how we feel overall and in fact, we use language associated with the gut in everyday life. Examples, you know, we're pooing our pants with fear or we can't get our arses into gear if we don't complete a job. We get butterflies in our tummy when we fall in love. Now we know it's clearly a two-way street. So the gut influences the brain but the brain of course also influences the gut. So if we talk about how the gut influences the brain, there's lots of things that happen at the gut level or the enteric nervous system that can contribute to overall gastrointestinal function. Motility, secretion, blood flow. We also know that the way that this information travels from the gut to the brain is via the vagus nerve and this is the nerve that runs up through the diaphragm between the lungs and the heart, along the esophagus through the neck, and into the brain. It also, of course, works the other way around as well and while what's going on in the gut is regulated predominantly by the enteric nervous system, it does require very close coordination and communication between the mind and of course the gut. The brain likes to be involved. And of course, because the brain likes to be involved, it can impose direct patterns of response and it can obviously modulate transmission of different signals and these changes can be triggered by lots of different things, of course, which does include our cognitive state or how we feel on an emotional basis. And this can be in the context of environmental stresses, and certainly during strong emotions. There has also been research to suggest that patients who have irritable bowel syndrome actually have a reduced thickness of what we call the prefrontal cortex. And what has been suggested this -- this indicates or what we think we can ascertain from this is that this means that our patients who present with irritable bowel are not that great at ignoring the sensations arising from their gut. So they become very hyper-vigilant to what's happening. And of course, the more hyper-vigilant they become, the more likely it is that they are to experience visceral hypersensitivity, the more attention I give these symptoms, and of course, the more severe the symptoms then seem.

We also know that irritable bowel is characterized by physical symptoms. We -- I mean, we've talked about that in-depth already. But we also know that patients who present with irritable bowel have really above average rates of anxiety and depressive disorders. And if we look at this across the literature, and of course, there's, you know, this variation depending on what study you read, but we're talking probably about 40 to 60% of patients who have irritable bowel will have some sort of psychological comorbidity. We know that stress is one of the most important things that's discussed between the brain and the gut and, of course, when the brain sees a problem, it wants to solve it. And so in doing so, it borrows energy from the gut, and in borrowing energy from the gut, what happens is that blood flow is reduced. So if we consider that, you know, the blood should have about a third -- the gut rather should have about a third of our body's blood supply at any one given time, you can imagine that if a patient's sitting in a heightened sympathetic state for an extended period of time because of stress, then, in fact, there is going to be reduced digestive function. Now, that's not a problem, of course, in the long term, but in the short term, it probably means that this patient is going to experience an increase in symptoms. So I guess the big question is, you know, is it the chicken or is it the egg? And I think this is something that we talk about all the time. And there was this particular study that was done quite some time ago now, but I think it's still a relatively interesting study in the context that essentially what these researchers did was they followed patients over a 12-year period, and when they enrolled these patients, they enrolled them into one of two groups. Either these patients had irritable bowel syndrome, but they did not have psychological comorbidities, or they actually presented with anxiety and/or depression in the absence of any gut symptoms. And like I said, they followed these patients over a 12-year time period and at the end of the study, what they identified was that those patients at baseline who presented with irritable bowel syndrome, and no psychological comorbidities had developed either anxiety or depression. And those patients who presented with anxiety and/or depression had developed irritable bowel. So I think what this tells us is that these two systems are so incredibly linked, perhaps more linked than what we ever give them credit for.

00:25:45 Dr. Simone Peters: And I guess that leads us to why we feel behavioral therapies are really useful in this subset of patients. And when we talk about behavioral therapies we're talking about, of course, gut-directed hypnotherapy, but not only gut-directed hypnotherapy. Other therapies that can be really useful include cognitive behavioral therapy, mindfulness-based stress reduction, relaxation training, psychoeducation, and biofeedback. I guess one of the main things is, you know, you're sitting there, you've got a patient in front of you. You think that this patient is going to benefit from a behavioral therapy, but you want to know whether they're the right kind of candidate. And I guess this sort of table here gives you some indication as to whether this particular patient is likely to respond to behavioral therapy. Typically, these patients who are good candidates for behavioral therapy have been given a firm diagnosis of irritable bowel syndrome. And this gets

me back right to the beginning of the presentation when we talked about the importance of a firm diagnosis of their condition. They understand that it's real, they understand that it can possibly be caused by dysregulation between what's going on in the brain and the gut, and they can identify that the symptoms that they have a really big impact on them from a functioning perspective, or from a quality of life perspective. They believe that they have some sort of control over these symptoms and they want to take some responsibility for the management of the symptoms. They can identify that these symptoms are exacerbated by how they feel psychologically, whether that be in response to stress, or whether they can identify that at times when they feel more anxious that their tummy symptoms tend to worsen, and that these patients are also prepared to put in the time and the effort that it takes to engage with behavioral therapies. Understanding that, you know, it's not going to be an instantaneous or a quick fix. Patients who perhaps are not the best patients in terms of response to behavioral therapy are those that do not accept their diagnosis of irritable bowel. And often these are the patients that have not either had that firm conversation with their healthcare provider almost back at day dot or, in fact, they may very well have, but they're still fixated on this idea of there being a quote-unquote, problem. They talk about their symptoms, but without sort of being able to recognize that these symptoms have any impact on them or their ability to cope. They often can have other really significant psychosocial stressors and sometimes in this context, other therapies are perhaps more appropriate, including medications or pharmaceuticals. Sometimes these patients are just not able to commit. They're not able to commit financially, they're not able to commit timewise to, you know, the realities that behavioral therapies do take time and they do take a level of commitment and there are obviously a subset of patients who are not prepared or not willing to put their time and effort in.

00:29:03 Dr. Simone Peters: So I guess now we need to talk a little bit about hypnotherapy and gut-directed specifically hypnotherapy. So gut-directed hypnotherapy involves an introduction, and we give suggestions for imaginative experiences at this time. We then use a hypnotic induction and the aim of the induction, of course, is to get the patient to enter into what we call an altered consciousness or a trance base stage, and then once they're in this altered state of consciousness, we want to try and give suggestions. And it's the suggestions that make something hypnotherapy and, of course, in these patients who present with irritable bowel syndrome, of course, the suggestions are going to be for the control and normalization of gut function. And we can use really nice metaphors to help to bring about this change. This differs from all the other forms of psychological treatment or behavioral therapies where the therapy is provided to the patient in a conscious state. So when we talk about suggestions, the key thing is that we're providing these suggestions when the patient is in this sort of subconscious or trance-like state and we want the suggestions to be highly repetitive. So for example, for improvements in pain and bloating, we'd be telling the patient that there'll be no more pain, no more bloating, no more discomfort, and of course, this suggestion would be made repetitively throughout the hypnotherapy session. Improvements in bowel habits. So bowel habits will continue to improve day by day, week by week, month by month, and of course, the improvements will happen over time. So you'll again continue to get better and better and better.

And when I say we use metaphors, there's some, I guess there as an industry, we love and these are really solidly evidence-based these metaphors, and were originally described by Peter Whorwell, who's kind of the pioneer I guess of gut-directed hypnotherapy over in the UK. And examples of this include the flow of a river. So a patient imagines the gastrointestinal tract is a representation -- a river rather is a representation of the flow of the gastrointestinal tract and, of course, the patient manages or changes the flow of the river according to what's needed. So for example, in somebody who has constipation-predominant irritable bowel, it may very well be that they need to increase the flow of their river. Hand warmth. So you know, that's pretty common sense. Essentially what we do is we get patients to place their hands on their abdominal region and then when they do that the sensation of warmth in their hands will travel from the hands and into the gastrointestinal tract, and then, of course, that feeling of warmth brings the feelings of calmness and control. Medicine is another really common one. We get patients to imagine that they are going to a lovely old pharmacy, that they swallow down this particular medicine that has been made specifically for them, and that when they swallow down this medicine, they imagine that this medicine provides protection against the symptoms that they present with.

So, I guess what we really want to know is how useful hypnotherapy is in patients with irritable bowel and there's been a number of randomized control trials that have done. There's been a number of comparative studies that have been done and also some uncontrolled trials as well. When we look at RCTs the very first one was done by Peter Whorwell's group in 1984. And like I mentioned to you before, this was the gentleman who kind of put gut-directed hypnotherapy on the map and continues to be really heavily involved in research in this space right up to today. And of course, I guess the main thing that we're interested in is that the outcome of this particular trial show that hypnotherapy was superior to better control which was in this case psychotherapy. Move forward to 1988, and again, a greater number of sessions, 12 sessions in this example, but against hypnotherapy, superior to the control as well as in 2002 in 2006. So we're starting to see sort of large numbers in terms of sample size at this point. In 2011 we saw a sample size of 90 patients and again, hypnotherapy superior to control. We have had one study where we've not been able to identify a benefit to hypnotherapy above and beyond that of the

control. But studies since this time, one in 2013 and again, one in 2017, with quite a substantial sample size, show that hypnotherapy was superior to control. Interestingly, the response rates do vary and they vary amongst these studies quite considerably, anywhere between 25 and 75%. And we suspect that the main reason for this is the patients are they're actually being included into these studies, and I think certainly earlier studies, what typically tended to happen is that we included patients onto studies using hypnotherapy if they were unresponsive to other treatments. So these are kind of the most tricky patients to treat, if you like, as opposed to sort of other studies that have been done in more recent years whereby we've actually used patients who have been naive to any other forms of treatment.

00:34:33 Dr. Simone Peters: So in terms of comparative studies hypnotherapy is compared to biofeedback, education intervention, and more recently, the low FODMAP diet. The low FODMAP diet comparative study was a study that I ran with Monash University as part of my Ph.D., and I thought I'd just run this, run you through this very quickly, but essentially, we included patients who were naive to both dietary and psychological therapies. So of course, it would just be impossible to do this kind of study today. But essentially, we randomize these patients to receive one of three treatments. They received the gut-directed hypnotherapy on its own, the low FODMAP diet on its own, or in fact, a combination of the two. Those who received the hypnotherapy underwent six weeks of hypnotherapy. So they came in and met with the hypnotherapist weekly, and I had a session of course, and I was then asked to listen to a hypnotherapy recording each day in between their sessions. Those patients who were randomized to the low FODMAP diet came in at week one at baseline or week one. They were taught obviously the principals of a low FODMAP diet. They were encouraged to follow a low FODMAP diet over the next six weeks, and telephone contact was made each week to ensure compliance. And then of course those in the combination therapy received exactly that. A combination of both the hypnotherapy and the low FODMAP diet.

We had a small, I guess, numbers one would argue but the study was adequately powered and there were no differences in terms of the baseline demographics with regard to gender, age, or IBS subtype. The importance of this slide is really just to know that these patients were notably symptomatic. These patients were what we would expect for those who present with irritable bowel at initial consultation and this is based on what we call our visual analog scale. So essentially a visual analog scale is a 10-centimeter line. One end of that line indicates that patients have no symptoms at all and the other symptoms are the most severe they could possibly be, and patients are asked to indicate on that line where their symptoms fit over a period of time. And in this study, it was over sort of the previous seven days, and then they're given a millimeter score. So a millimeter score of, you know, between 60 and 70 is a considerable score.

So in terms of the primary endpoint, we looked at overall gastrointestinal symptoms. So you can see here on the y-axis is a visual representation of the visual analog scale, which I just described, and across the x-axis is the time points. So you can see at baseline there was no difference between the three groups in terms of their symptoms, and they were all notably symptomatic. You can then see that there was a significant improvement from baseline to week six, but that there was no difference between these three groups. So all three groups improve really significantly but there was no difference between the three groups. And when we say they improve significantly, they improve significantly not only from a statistical perspective but also from a clinical perspective. So any change in 20 millimeters we will consider to be clinically relevant and at this point at that sort of six weeks and certainly six-month time point they're fitting within what we consider to be a normative range. So then from six weeks to six months, you can see that they've maintained those improvements and that those -- again, even though it looks as though there's a little bit of a divergence there at six months, statistically there's no difference in terms of those three groups with regard to response. So all patients responded to the initial treatment, and then they maintained those improvements at six months. And I think this is really, really important, especially from a hypnotherapy perspective, because what it tells us is that if patients are maintaining these improvements, that this is not just a placebo response.

In terms of secondary endpoints, and this isn't the easiest slide to read so I apologize, but we looked at abdominal pain, we looked at bloating, we looked at wind satisfaction with stool consistency and nausea. And you can see that in all other than nausea, there was a significant reduction from baseline to week six, which was maintained at six months. When I say that there was no significant improvement in nausea these patients weren't particularly nauseous to begin with, and where that was seen in terms of their baseline levels was again what we would consider to be of a normal healthy population. So it's nice to know that people responded, but I guess what we also want to know is how many people responded. So when we look at percentage of response, we see that about 62% of people responded to this as a treatment in terms of the hypnotherapy at week six, and similar figures shown for the low FODMAP diet and those who received the two, and then, of course, these improvements were maintained six months. In the hypnotherapy, there was a slight further improvement of those in the low FODMAP diet and a bit of a reduction actually in those who receive the combined treatment. I was on the study so I guess I'm privileged to know that we had a few fairly complex patients present who just all happened to be randomized to the combined treatment and, you know, this is why you do clinical trials. The reality is that these things can

have an impact on the results but we weren't probably all that surprised by that finding. And of course, we did see that some patients worsened in terms of their symptoms and again, this wasn't beyond the realm of what we would expect.

So in terms of conclusions, what we know is that hypnotherapy is really very effective, similar in terms of rates of efficacy and percentage of response to that of a low FODMAP diet and that there seems to be no benefit to patients doing the two things at the same time. I think a notion that as well is when we say there's no benefit to patients doing both things at the same time, the reality is that, you know, most patients are doing more than one thing at the same time in a clinical setting. And there's obviously no problem with that. And we say no additive effects were observed but by the time we got to that six-week or that six-month time point, patients fell within what we'd consider to be normal ranges of symptoms. So you can't really be better than better, so to speak. There's also been some uncontrolled trials that have been done. There was an audit with a really substantial number of patients who was done by the group in the UK, and these showed, this particular audit showed that 76% of patients had a very significant reduction in their IBS symptoms and this was based on the IBS-SSS questionnaire. And this was after 12 sessions of hypnotherapy. You notice that there seems to be this theme of, you know, different numbers of sessions and I think certainly the group in the UK initially were providing 12 sessions of hypnotherapy with their patients, but there has been work that's been done now by the same group that shows that actually six sessions are adequate. And then if patients haven't responded by that six-week time point, they're probably -- they are unlikely to respond beyond that. So there seems to be no clinical benefit of going beyond six sessions. And again, there's been some sort of long-term work that's been done, which is shown that patients who respond to treatment maintain these improvements. And this has been assessed right up to five years post-treatment, which again confirms that this is not just a placebo response.

00:42:10 Dr. Simone Peters: In terms of mechanisms of action, we are able to very nicely look at changes associated with various things post hypnotherapy. So for example, changes in gut motility, visceral sensitivity, immunological effects, central processing, and we've shown obviously that after hypnotherapy, were able to normalize central processing patterns. But interestingly, we're not sure exactly how we're managing to do this and so while we can measure change, I think a lot still needs to be done in the realm of understanding the mechanisms of action. Practical considerations. I think the first relates to safety. Hypnotherapy is really exceptionally safe. There are only very rare circumstances where we don't think that it is useful or should be, in fact, used in any way, shape, or form, and this is usually associated for those patients who are already in some sort of altered state of consciousness. For example, patients who experience psychosis. There are no known side effects to hypnotherapy, which is again really reassuring. We understand that there's no issues in terms of hypnotic susceptibility. Everybody can be hypnotized and if we consider that daydreaming is hypnosis, I'm yet to meet anybody that doesn't experience daydreaming. We can use these very fancy scales to determine the level of depth of hypnosis that somebody is likely to experience and, of course, we know that as individuals, some people are more hypnotizable than others, but what we also know is that the depth of hypnotic state does not correlate with the outcome of the therapy. Which is again really reassuring and, of course, especially given that only 15% of the population get to that really, really deep level like what we see on the TV and the movies, hypnotherapy is really, in the clinical setting, is really quite different to what we've been exposed to in terms of entertainment purposes.

Unfortunately, we're not able to predict who is more likely or less likely to respond to hypnotherapy and while there have been some studies that have shown that, you know, there might be a particular predictor of response in that setting. If we look at our combination in the literature, there really is no predictors of response in terms of age, gender, duration of symptoms. So it doesn't seem to matter if you've had irritable bowel for a very short period of time or a very long period of time. What type of symptoms you have in terms of your bowel habits subtype, your personality, or your imaginative ability. So in terms of applying hypnotherapy, the rates of response of hypnotherapy are at least as good, if not better, than most of the pharmacological treatment options that are available. We know that response to hypnotherapy is similar to the gold-standard dietary approach in IBS so a low FODMAP diet, and therefore we think that it should be offered fairly early in the management of irritable bowel and not necessarily saved for those patients who have very complex psychological comorbidities. Although those are unresponsive to other treatments. These are sort of your **heart sync[?]** patients and, of course, you know, if we can -- the earlier we can get on top of people's symptoms, the more likely it is that they're going to respond to treatment. There are some limitations I guess to using hypnotherapy. The first relates to cost. It's very expensive for patients to undergo a course of gut-directed hypnosis, and unfortunately, the reason that it's probably so expensive is because there's just very, very few trained professionals that are working in this space. So what that means is that there's very long waiting lists in a private setting and in a public setting while we can counteract for cost in that context, the waitlist is so very long, and certainly here in Australia, we're talking about sort of 18 to 24 months.

And so I guess at Nerva what we started to try and think about also or certainly what we tried to overcome this problem, I guess, in the context of being able to make hypnotherapy available to people on a much larger scale while trying to minimize the costs associated with it. And, I guess, this is where we sort of started to come up with this idea of providing this program

of hypnotherapy. This program that we know works in terms of clinical trials. That we know works in terms of clinical settings, but through a program that is easily accessible. And so Nerva was born and certainly, patients are able to access hypnotherapy recordings through this particular program. Lots of different information that we've seen is being really useful in terms of managing symptoms and responding to treatment. And I thought I would -- Obviously, this is delivered over a six-week time period which is again, supported by the literature. So I thought I'd just take you through what patients receive when they go through the Nerva program. So essentially they receive hypnotherapy recordings and you can see here like I mentioned to you before, these metaphors that are really commonly used for this idea of the medicine and the river, the comforting hands, and of course, some others as well are provided to patients to listen to on a daily basis. These repeat over time and this repetition is really important from the perspective of these suggestions for change or suggestions for the control and normalization of gut function to take place. It's got a really great interface in the context that it's easy to navigate, and that the hypnotherapy recordings go for about a 10 to 15-minute time period. So not overly time-consuming. And again, this is based on what we've done in clinical trial settings and certainly what we do in clinical practice. But also in conjunction with providing the hypnotherapy what we've aimed to do is to give patients lots of information that they should have received but perhaps haven't. So information about what irritable bowel syndrome means in the context of the symptoms, how it's diagnosed, what can trigger these symptoms, how we treat irritable bowel syndrome. So lots of these things that I've talked to you about today. Including dietary therapies, what the place is for dietary therapies in the context of managing symptoms, and also psychological therapies. This is provided to participants in week one.

In week two, we talk a little bit more about hypnotherapy. So what got directed hypnotherapy is. Answering some of these questions I guess that most people have around hypnotizability. What -- How hypnotherapy works in terms of mechanisms, who's likely to respond. So this again, this idea of predictors of response and what the advantages of hypnotherapy are compared, perhaps, to the alternatives. In week three, we start to talk a little bit about the gut-brain axis and we've discussed this in detail today. So the link between the two, the impact that our psychological state certainly have on the functioning of the gut-brain axis, certainly in the context of the physiological function of the gut. Hypervigilance we know that patients with IBS are certainly very hypervigilant to the symptoms that they experience and then teaching things that we apply in clinical practice all the time. So cognitive diffusion, ways of getting patients to practice diffusion, trying to minimize this sort of catastrophic thinking, being realistic. So making sure patients know when to seek help if needed. We also talk about more gut-related -- the gut-related side of things. So we talk about motility, we talked about sensitivity and we talked about the low FODMAP diet, of course, and how this has an impact on the microbiome. And of course, the importance of liberalizing the diet where possible in order to ensure that your patients haven't really diverse microbiome and obviously the impacts of this has not only from a physical perspective but also from a psychological perspective. And then in week six, really trying to ensure that people are aware of what is normal. And I, you know, I think we sort of often gloss over this as being not all that important, but I guess the reality is that in a clinical setting I spend quite a vast majority of my day talking about what is normal because these patients, this subset of patients, are often catastrophizing, are certainly very concerned with what they believe is normal. So obviously making sure that they know what their stools should look like. They know how much bloating fits in the range of normal, how much wind is okay, and certainly where to go if they need help.

00:51:06 Dr. Simone Peters: So, it's all very well, I guess, to put this information into an app and while we, you know, have the best intention in the context of putting information in has been supported by clinical trials and that we use in a clinical setting. It's, I think, really also very important to analyze the data that's coming out of Nerva to make sure that we're doing what we say we're doing, and really reassuringly we know that app users report improving having improvement in their symptoms by the end of the program. And we've been really careful to ensure that we're using scales that are interpretable in comparison to the literature and so we've used this sort of visual analogue scale that I've talked to you about already today. We've also collected quite a large number of patient responses in between June 2019 and April 2020. And again, this was used -- This was assessed using the visual analog scale, which I might point out, is validated as part of the IBS-SSS, and without giving too much away, again, we've shown that you know, patients that have responded really beautifully. And for those of you who are interested, this will be presented as an oral presentation at Digestive Diseases Week. Virtually I'm afraid, so I don't get to go to America this year in May. And also knowing that we have some randomized control trials coming soon as well. So I think the main thing is, you know, watch this space. We know that Nerva is working really well and we just need to, obviously, be sure that it continues to work brilliantly in the future. And I think that if we can get some RCT data behind us, that will be really fabulous.

Thank you! Any questions?

00:52:55 Claire Davidson: Thank you, Simone. We do have a few questions. I will try to get to everyone's. If I can't get to your questions I will respond to them via email after this, but we'll try to get through all of them. So first one: patients often

ask what they can do in addition to the low FODMAP diet. Would you still recommend adding gut-directed hypnotherapy to the low FODMAP diet protocol even if there were no overall additive effects?

00:51:06 Dr. Simone Peters: Yes. So I think this is a really key point. So in the study, I showed that, we showed that there was no benefit to combining the two treatments. But when we say there was no benefit by the time patients had responded to the therapy, at the six-week time point and then again at the six-month time point, their -- symptoms that they reported were within normal ranges. So like I said during the presentation, you can't be better than better. But that said in clinical practice, the vast majority of patients that we see are doing a combination of a low FODMAP diet and hypnotherapy. In fact, it's not uncommon that patients actually have probably gone too far with the diet in the context that either they are over restricting their diet, or they're followed a low FODMAP diet for an extended period of time and they've not gone through the reintroduction process. And sometimes using something like hypnotherapy can be a really useful bridge to get better control of their symptoms while working with them to actually start the reintroduction process from a FODMAP perspective.

00:54:30 Claire Davidson: Great. Can you please provide a greater explanation of the altered state of hypnosis and how it is achieved in a session?

00:54:39 Dr. Simone Peters: So essentially, the best way of describing hypnotherapy is being a bit like meditation with suggestion. So the idea is that a patient goes into a relaxed state and then in that relaxed state, the subconscious part of the mind is more open to the suggestions that we give. And of course, the suggestions that we give are targeted towards the symptoms that the patient presents with. So this idea of control and normalization of gut function. I guess in terms of depth of hypnotic state, as I mentioned before, the depths doesn't seem to correlate with the outcome. So as long as patients feel comfortable and they feel relaxed, we're confident enough that we're making that direct suggestion with the subconscious part of the mind, and that patients will respond.

00:55:29 Claire Davidson: Great. Sort of along the same lines of that, does hypnotherapy need to deliver specific imagery based on IBS subtype?

00:55:39 Dr. Simone Peters: I think, not necessarily in the context that -- I mean, you can use wording that is appropriate for somebody who presented with diarrhea and/or constipation. So for example, you will see improvements in your bowel function. You will see these improvements day by day, week by week, and month by month. I guess if you're in a clinical setting and you can manipulate the script, so then it is, you know, specific to the symptom that the patient presents with, then you have the ability to do that. In terms of in clinical trials, everything is per protocol. So everything is the same, obviously, for every single patient. And obviously, there's huge variation in terms of the symptoms that these patients present with. And it's certainly in a clinical trial setting where everything is kept the same in terms of, you know, improvements in bowel symptoms. Say, for example, we say 75% of improvement. So I don't think it necessarily means to be overly specific.

00:56:42 Claire Davidson: Okay. This is from a dietitian who works mainly with eating disorder patients. Has gut-directed hypnotherapy been studied in this population?

00:56:51 Dr. Simone Peters: No, I'm afraid not.

00:56:55 Claire Davidson: Okay. I think this question is in reference to your study, Simone. When symptoms were still low at six months, were participants still actively doing the hypnotherapy, or have they stopped after six weeks? Then the relief lasted up to six months?

00:57:13 Dr. Simone Peters: Yes, good question. We actually didn't ask patients this in any formal way. We do know that at the end of six weeks, patients were told that if they enjoyed listening to the hypnotherapy, they certainly could continue to do so. But if they were sick of it, they never had to listen to another recording again. So, you know, I guess they had the

opportunity to decide whether they continue to listen to it or not. So in the trial, it's probably difficult to ascertain. In clinical practice, we often encourage patients to try and stop listening to things at a point, but it's usually not immediately after they've finished sessions together. And often this is because they're doing other things at the same time. So for example, they've been doing the hypnotherapy while liberalizing their diet. And so it may very well be that at the end of the six weeks of the hypnotherapy, their symptoms are beautifully controlled, but they're continuing to work with their dietician to liberalize their diet. And so for example, we'd get them to continue to listen to the recording while they were going through that process, but then sort of encouraging them to sort of, to reduce the amount of times that they listen, I guess, in the longer term once they've gone through that process. There's no real indication that people need to continue on with these strategies forever in order to maintain these improvements.

00:58:34 Claire Davidson: There's a question about anxiety and if there have been -- if changes have been shown in anxiety after doing a course of gut-directed therapy?

00:58:46 Dr. Simone Peters: Yes. So in the interest of time, I didn't talk about psychological outcomes today. But you're absolutely right. So I think in the very -- vast majority of trials, we have included some sort of psychological outcomes, and patients have responded beautifully from a psychological perspective in conjunction with, you know, this physical change. So we see improvements in anxiety, we see improvements in depression, we see improvements in terms of quality of life. And again, these improvements are maintained long term. So in the trial where we compare the efficacy of a low FODMAP diet with hypnotherapy, we showed that while there was no difference in terms of rates of improvement from in terms of physical symptoms after hypnotherapy. What we did actually show that was there was a superior effective hypnotherapy in terms of the psychological outcomes. So there were no changes in psychological outcomes after following a low FODMAP diet say for example, but we did see improvements in levels of anxiety. So levels of what we call state anxiety and trait anxiety. So short term and long term anxiety and also improvements in quality of life.

00:59:55 Claire Davidson: There's a question about gut-directed hypnotherapy and how therapists are trained in it and what the accreditation process is to be able to practice it?

01:00:09 Dr. Simone Peters: Yes so this is -- I think this is probably one of the biggest problems that we have in the context of making this more readily available. There is no standardized training protocol for people to become gut-directed hypnotherapist. Now obviously there's hypnotherapy training, and accreditation to be a hypnotist, but there's nothing in the gut space and so most of us become self-trained. And I guess what you very quickly learn is that there's only very few people that are sort of trained in this kind of approach and so we kind of have all learned from each other over the years. But I'm -- So I'm afraid, you know, there's not really any formal qualifications or formal training that has been accredited to date.

01:01:00 Claire Davidson: Just a couple more questions. We're nearing the end of the list. There's a question about the psychoeducation component of Nerva and whether or not that is part of the program itself, or it's sort of an optional addition to the program?

01:01:19 Dr. Simone Peters: Yes. I mean look, I guess in terms of in clinical trials, you know, there while there is a site who education component, it's not anywhere near as in-depth and what is provided through the Nerva program. And so, I guess to answer that question, patients probably don't need to read through all of the psychoeducation in order to see the benefit. That said, it's certainly not going to do them any harm. So, you know, if the information is there and it's available and it's accurate, I think that it's really important. You know, I can't imagine why patients wouldn't want to read it.

01:01:56 Claire Davidson: Yes. And last question. You mentioned that some patients worsened in your study and that was expected. What is the percentage of patients that worsen when doing gut-directed hypnotherapy or the low FODMAP diet?

01:02:10 Dr. Simone Peters: So it's probably difficult to say, you know, what percentage of patients worsen in a clinical setting because we're not obviously analyzing the data of every single person. But what we do know is that there are a

percentage of patients who do not respond to gut-directed hypnotherapy or do not respond to a low FODMAP diet, or do not respond to pharmaceutical medications, or do not respond to anything. You know the, the reality of any treatment is that there's always going to be a percentage of patients that don't respond. And when we look at gut-directed hypnotherapy, we're talking about 20-25% of people that don't respond. When we look at a low FODMAP diet it's about the same. It's about that sort of 25% mark. When we look at pharmaceutical options, it's usually much higher than that. So, you know, I think we need to be transparent with patients in the context that, you know, when we see patients clinically face-to-face or via zoom, you know, we will always have that discussion in the first session that there, of course, are a percentage of people who do not respond to this. But, you know, I think the reality is that if you could find, for example, if you can find a pharmaceutical, if you can find a drug that had an 80% rate of efficacy, you'd be a very, very rich individual.

[Crosstalk]

01:03:24 Claire Davidson: I lied to you a little, there's one question that came in that's a great question, so I'm going to ask it as well. Can the Nerva app be used exclusively in lieu of gut-directed hypnotherapy with a therapist? Or are they meant to be used in a complementary fashion?

01:03:38 Dr. Simone Peters: Absolutely not, no. The whole idea of Nerva is that people can use it in isolation of any other therapies. So, everything that is in Nerva is what you would expect a patient to -- in terms of the information that is provided, in terms of the hypnotherapy scripts that are used, that is exactly the same as what we would provide to patients in the clinical setting, and is exactly the same as what we've provided to patients in a clinical trial setting. In fact, there's more information in here than what's in the clinical trial setting. So in an ideal world that would do even better.

01:04:11 Claire Davidson: But just to be clear, it can be used alongside other treatments for IBS? It just -

01:04:18 Dr. Simone Peters: It can be used alongside other treatments. It can be used alongside seeing a therapist face-to-face, you know. Actually, I do have a few patients that see me and also do Nerva and I keep telling them, I probably don't need to do both, but for whatever reason, they decided that they want to. But no, absolutely you can use one or the other, or you can use a combination.

01:04:49 Claire Davidson: Great. All right, that sort of wraps up all the nitty-gritty questions for you. Thank you very much for being here and for presenting all this useful information. I think it was wonderful. Just some logistical things. This webinar is recorded. So if you registered via the link, you will get a recording version. So if you missed the beginning, that's okay. There was a few questions through the Q & A about sort of logistical on downloading the app and things like that and if you are one of those practitioners that asked one of those questions, I will follow up via email to you directly. And that should be it. Thank you so much, Simone.

01:05:22 Dr. Simone Peters: Thank you. Thanks for having me. It was a pleasure.

01:05:25 Claire Davidson: Bye now.