Thank you. So to keep us on time let me give you a brief overview of what I’m going to be speaking about today. And basically what we’re going to spend some time doing first is defining what stress is in IBD and specifically from three perspectives that I thought would be most clinically useful for you.

The psychological manifestations to mainly depression and anxiety. Pain and specifically thinking about functional abdominal pain and sleep disturbance which I hope by the end of this talk if you weren’t thinking about assessing and treating your patients you will after today. And then we’re going to move on to – in these different categories of stress, what kind of empirically supported treatment options are there, psychotherapies, hypnosis, exercise and sleep regimes and last but not least psychopharm or none of the above.

So what is stress? I love that cartoon because I just think that a picture speaks a thousand words. But basically stress is any acute threat to homeostasis of an organism and it can be either a real or physical event or a perceived psychological. So both of these types of events can induce the organism to have a cascade of chemical and hormonal reactions that really are meant to enhance survival.

Now our stress mechanisms in our body were really designed to handle acute stress. They don’t do so well however when acute stresses are severe or when they become chronic. And some of the types of stresses that we think about when we evaluate patients, GI patients for stress, biological
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stresses, any kind of disease process is going to be a stress for the brain, infection, surgery, both the
preop anxiety and sort of postop issues, environmental stresses, life stressors have been well studied,
trauma, either from childhood or actually an acute trauma in adulthood and psychological stressors,
anxiety and depression.

So let’s talk about anxiety and depression in IBD. When we look at the studies overall and this is
over decades of research the rates of anxiety and depression both are in the 25 to 40 percent
prevalence rate. Why such a huge range? There’s a number of factors and fortunately or
unfortunately the range comes from sort of methodological differences across the study. So the
biggest reason for that range is that there’s such – a sort of difference across studies of how anxiety
and depression are defined. Some studies look at symptoms, others look at DSM-IV diagnoses. So
again, and then with that then is different populations, subpopulation studies, I think the biggest
difference certainly in inflammatory bowel disease is the acuity, duration of diagnosis, chronicity
and course of the IBD and then also colitis and Crohn’s disease both have slightly different rates of
depression and anxiety and then last but not least whether you’re looking at the patient at an active
or inactive disease state. Even with all that being said though, 25 to 40 percent is a big chunk of
patients that it really is worth thinking about screening for anxiety and depression aggressively in
these patients because it is treatable.

So let’s focus now a little bit on depression and what does the literature support about the
association of depression and IBD. First of all, depression has been shown to influence IBD relapse
so there’s shorter remission period in depressed cohorts versus non-depressed cohorts relative to the IBD. It can aggravate current inflammation, it’s been related to reduce health-related quality of life and it actually has been shown across several studies to impact how well a biological treatment affects IBD activity. In the case of Infliximab the depressed cohort did not have as high a remission rate as the non-depressed cohort.

Now IBD can also influence, sort of etiologically, depression. Cytokines, the complex inflammatory proteins release from the GI tract during inflammation are known to affect the brain both by direct and indirect mechanisms. Steroids that we use to treat acute flares we know can cause a depression and the depressive subtype cause is different from the cytokine type. When you have depression induced by steroids you get more irritability, you get a lot of sleep deprivation and you get a lot of cognitive disfunction.

And then last but not least we’re just starting to appreciate that some of our immunomodulators in a certain subset of vulnerable patients, can also have depressogenic effects. And ___ has a couple of case reports out associating it with depression.

So when we look across the studies there has been somewhat of a controversy in the GI literature about the relationship between these psychological factors and IBD severity and course. So if we do a quick summary of that literature I think we can pretty definitively say that depressive severity is significantly related to IBD severity so activity at that time point, that cross sectional look. And that
actually psychological stress has also been shown to impact intestinal permeability, increasing the permeability.

The patients perceived negative stigma of having IBD has been significantly associated with IBD activity. Social isolation has been linked to IBD course and the one area however that we really have not convincingly proven in the literature is that depression or forms of psychological stress impact IBD course. Now being a clinician in this field I cannot myself decide if that’s because we haven’t designed the correct study yet over a long enough period with a large enough cohorts. Or if in fact the psychological state more impacts what’s going on with the disease here and now. I think that’s some of the exciting research that’s on the horizon.

You have this in your handouts but this is just the literature that supports the pros and cons of those associations. Now it is important to say statistically an association is just that, two things are linked and just a reminder that that does not imply causality. We like to think about causality but that’s a whole other set of experiments that it takes to prove that and so right now we just know that they’re linked.

What are some of the work that we are doing here and also at Boston Children’s Hospital, we run a two site study where we’re screening kids with IBD for depression and then providing treatment for kids who have clinically significant depression. So we see 665 kids, 9 to 17 and we use a childhood depressive inventory, it’s about a 5 minute process right during the medical appointment with their
GI doc. What we found, we replicated it several times is 25 to 26 percent of these kids when they’re screened for depression at that time point have clinically significant depression. Why? Why it is so important is both when I started the program at Boston Children’s and then now here, about one percent of those kids had been previously identified for their depression prior to us setting up this screening process. So of that depressed cohort, when you look at who’s making up this depressed cohort - 52 percent male. That’s really interesting because if you took non-IBD cohort in this age range it would be a 2 to 1 female to male preponderance for depression. Forty-two percent have active IBD, so active IBD is not alone explaining these rates of depression. And with some overlap with that group, 46 percent are on steroids. Now what is also interesting is that when we looked into the difference factors, that within IBD severity, that could account for predicting the depression, low albumin and increased abdominal pain were the two most robust predictors. And with abdominal pain interestingly they’re both clinician report on exam as well as the child self perceived pain.

So why do we really want to pause for a moment and think about functional pain and IBD? Well first of all right here at Presbyterian Hospital, Dr. Binion and his colleague Dr. Mourabet actually just completed a study that looked at some of the rates of – I’m going to back up, observed the rates, they actually looked at patients who were admitted for IBD admission in 1998 and 2008 and they took the codes that were used for billing. So these were not interviews, they weren’t based on questionnaires, just the billing codes that physicians used on patients. And what they found and the light is actually, the light column is depression and the darker column is pain and in that decade we
had much higher rates of billing for depression and pain. Now that’s interesting, we can’t talk about rates or prevalence because is that better educated physicians, is that more awareness or are the rates going up. I would actually argue that it’s a combination of both but when you look at the literature up to 80 percent of adults with inactive IBD defined by lab values and severity measures continue to have impairing functional pain.

In youth when we looked at our patients, 37 percent with inactive IBD continue to have pain. And why this is important, I mean it’s important from a treatment perspective but for the medical dollars it’s extremely important. So when we look over and over at the 20 percent of IBD patients who account for 80 percent of the medical costs for treating IBD, chronic pain and depression are key factors.

Now let’s move to sleep information. So there’s many studies in animal knowledge and in humans that sleep and the immune system are integrally related especially when you have chronic inflammation, it disrupts sleep at a physiological level, both the circadian cycle which is one aspect of sleep and the REM, non-REM component or the sleep cycle architecture. And both of those need to be acting appropriately for you to get a restful uninterrupted night of sleep that is then going to help you with your daytime functioning.

Specifically in IBD there are some small studies out there and one larger one supporting sleep disturbances in both adults with IBD and in our cohorts when we looked – using just a quick, again
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another 5 minute screen, questionnaire, self-report questionnaire it’s called the PSIQI, it’s the Pittsburgh Sleep Index Quality Index. We found that 42 percent of kids with self-reporting significant sleep disturbance. And again this is taking all comers, all IBD comers.

So moving on to steroids now because we’re going to get back to the sleep and the treatment section of the talk, there’s several levels that steroids can affect and impact mood in IBD. First off, the HPA axis as we know is our endogenous regulator of our cortisol which is released during stress response and we know in adults without IBD that this is significantly impacted during depression. We also know not just in IBD but across other disorders that the steroids we prescribe in, again, a subset of vulnerable patients, cause mood and cognitive symptoms. In our study with the kids we’ve shown it over and over, that the kids on steroids have a higher risk and more severe depression than the kids off steroids even after we control for IBD activity. And one of my colleagues in Boston is studying the cognitive effect of high dose steroids, 20 to 40 mg equivalence of Prednisone for a 1 week period can cause changes in attention and short term memory. Luckily the most recent research is showing that these are at least in children reversible effects. So when the kids come off the steroids these kind of things normalize. But if you think of your adults and your adults are trying to remain productive in the work environment, a lot of what my team does at the Coping Center, at the VIP center, what we will be doing is actually helping these folks get the kind of school excuses, work excuses so that they can actually remain optimally functional and this is – I mean it really does cause an inattentive-attention deficit disorder ____ clinical picture even though of course they don’t meet the criteria because it was induced by steroids.
So hopefully, I mean I’m trying to oversimplify to make this clinically useful but there’s a lot going on and there’s a lot left to tease out in patients with IBD in terms of how the disease itself, the steroid treatment and then sort of their psychological perceptions are interacting to influence both the brain and the gut.

I was very fortunate to have a very talented fellow here, Christine Kawowsky, look at quality of life in our kids with IBD and we actually also added in from some of the young adult literature to help you think about what are some of the factors that impact patients self-report of quality of life. Depression and anxiety - always at the top of the list. Lack of control something that in psychological terms we call contingency. When you feel that you don’t have control over your disease you’re going to report a lower quality of life. Sleep disturbances, maternal distress and that’s more in the kids of course, poor IBD course, medications especially if you’re on steroids and most of that is related to the side effects that the patients complain about and then the duration of IBD.

In one study in children and what was interesting there was you would think that perhaps that was a negative association and in fact, quite the opposite. These kids were studied over two years and actually the longer they had IBD the more improved quality of life the kids reported. So why that’s important and we don’t know if that’s just a phenomena that would happen in any person who had IBD, you get used to it or possibly the medications are working or is it something to do that children just have sort of a more flexible, less developed self-identity and so they can adjust better. Again,
that needs to be worked out.

So we talked about some of the biological factors related to IBD, I think it’s important when we’re thinking about patients and now the cohort of patients who don’t have active IBD but still have depression. What other factors could be playing a role? Well, we have to think about genetics, that could be a whole talk but certainly in psychiatry, the field of genetics and the mutations that make you more vulnerable to depression affecting chemicals, hormones, peptides in the brain is growing and something that hopefully in about 5 years in psychiatry or pharmacogenomics will help us to identify those patients and actually know which of our medications will best target depression in those folks, we’re not quite there yet.

Social factors, social isolation is huge as a driver of depression. Demographic factors, low socioeconomic class and of course the life style choice that we started the talk with. Psychological factors other than anxiety and depression, I want to pause and talk a moment about illness narrative.

So what is illness narrative? Illness narrative is basically the patient’s perception or how they describe their illness experience. Often very different from what the GI doc tells them about their disease. So all of us when we have things happen to us, weave a story, a story that we fit into sort of the context of our beliefs and how we see the world. And patients with diseases do the same. And this has actually been very well studied mainly in the medical anthropology literature and adjustment to illness over and over is very, very strongly correlated with these perceptions or what we’re calling
We polled this aggressively in our kids with IBD by a set of questions, some examples here, how do you feel about having IBD? How has it changed your body, your life? What control do you think you have over your IBD? And we just let the kid either talk or write or type, most kids now especially the adolescents give you much more useful information if you allow them to text it to you. And so we get that information and we analyze it for themes to get the degree of pessimism or optimism and what we found in the first 50 adolescents that we analyzed is damaged self is by far the absolute number one reported perception of these kids and we define that as either feeling damaged compared to their old self before they had IBD or to other kids their age who don’t have IBD. And this was not correlated with their severity of depression so this is an independent predictor and you’re now looking at its impact on treatment. Feeling lack of control, overall pessimism, I hate this disease, it has ruined my life kind of comments. Shame, especially in regard to bathroom access and ostomy leakage and we were shocked to find out in an obsessive compulsive type of way how much patients with IBD plan their days, avoid activities around having access to bathrooms just to avoid the risk of – and this is even when they’re having completely inactive disease, a symptom free state. And then guilt over being a burden to their caretakers.

Now lets stop and think about the brain for a moment. So how does the depressed adolescent brain cope with IBD? And I’m fortunate enough not just to be able to run clinical trials but to be also doing function imaging of our kids both at baseline and after treatment. So we’re able to answer
some of these questions. Well, first you’re going to be a little bit surprised but our pathway to the brain is going to take us through the pupil. Why the pupil? Well actually the pupil is an inexpensive and very, very accurate way of tell us what the brain is doing because it is so enervated by the cognitive and emotional processes of – centers of our brain and so what happens in the pupil actually is a very good predictor of what you’re going to see in certain brain regions especially cortical and limbic regions of the brain when you do the neuroimaging.

So this looks complicated and I do have a pointer, but it isn’t. So these are four cohorts of kids and really for the purposes of all of you the dark blue lines are the kids that are depressed and have IBD, the rest are normal controls depressed kids that don’t have IBD and nondepressed kids. So what we do is we show these kids an emotionally provocative word here, usually it’s a negative word something like divorce, something like pain and then we just actually measure what their pupil does. So initially this is pupil change, pupil dilate and then they go back and they return to normal. And I want to focus you here, because what we found here and this has been replicated now in other populations but that there’s a diminished late pupil response about 9 to 12 seconds after you show a patient the stimulus of interest if you’re depressed. The magenta is the depressed cohort, the blue line is the depressed with IBD cohort.

And why this is important is we know that this far out, this is the cortex, the prefrontal cortex that is driving this response. And if you don’t believe me you will after our neuroimaging data and why this is important is it was the first study out there and we had just, I’m getting this published now so
it will be out in about 3 months – that kids with IBD and the depression does share common 
neuroanatomical characteristics kids who don’t have IBD. So it’s a very real phenomena in the 
brain.

Now I’m going to go on because this isn’t a scientific talk but you might have noticed that the kids 
with IBD have a more robust autonomic dilation here of their pupils and interestingly this is actually 
having IBD. This is a nondepressed IBD cohort and we don’t know what that means yet but we do 
know from the literature that the autonomic nervous system especially with chronic IBD can be 
impacted and obviously the pupil is highly autonomic nervous system driven.

Alright, so the neuroimaging very quickly, now I’m not going to focus on the dorsal lateral 
prefrontal cortex because I just told you that we see changes, suppression of the metabolism in that 
brain region related to the ____ of severity. I’m going to instead focus on the inferior frontal cortex, 
this area right here. This is an area of the brain that has been linked to semantic processing so the 
meaning of words. So again what we are doing is we’re showing kids negative words again and then 
we’re looking at their brain region and we’re looking at it in the time frame again correlating it with 
the pupil response that is taking in the information and what we found is that when we show kids 
IBD specific negative words like diarrhea compared to general negative words like divorce, that this 
brain center lights up significantly more. So these kids who have IBD and naturally we looked at 
this compared to normal controls, the normal control brains, look down here you can see the IBD 
words. So these words have a meaning to these kids.
Now what else is very interesting, you know, we looked at this peak change and we looked at the correlation between IBD severity and change in brain metabolism, the sicker you are with your IBD the less your brain reacts to negative words. Wow. Have any of you ever sat with an adolescent who’s having active disease and the degree of denial – oh, I’m fine. I want to go to my football game. Oh, I’m fine, I’m not going to take those steroids. This could be one sort of neuroanatomical basis for understanding how their brains are really sort of playing that trick on them.

Alright, so now enough of the science and now we’re going to go back to the practical aspects of the talk and talk about psychiatric treatment strategies for stress and IBD. So this is a review of many, many studies, some better done than others and really wanting to give you the take home messages, that cognitive behavioral therapy or CBT as we refer to it in our field has the most empirical support for depression and anxiety in adults with IBD. And mainly related to treating psychosocial aspects so anxiety, depression, quality of life, coping with the disease, less robust findings for its direct apparent impact on the IBD course or severity.

There are a few studies showing psychodynamic therapy and some relaxation therapy impacting decreased hospital stays and less number of sick days from work, self-management training and education programs have been somewhat less studied but what is out there seems promising at least in terms of helping patients cope and improve their self perceived quality of life. And as I mentioned across these studies so regardless of the psychotherapy modality less support that we can
get directly impact IBD course.

So what is cognitive behavior therapy since this is a gastrointestinal audience? So basically its designed to teach coping strategies, to help patients alter their behavior and their thinking when its productive to functioning. It helps them interrupt negative cycles of thinking. In our adolescents we use the blue chart, blaming yourself, looking for the negative, unhappy guessing and negative exaggeration, four most common negative distortion strategies used by patients who are depressed. And we try to teach kids to catch those automatic thoughts and then to replace negative thoughts with more positive or at least neutral thoughts. Because that impacts how you feel in that moment. And it also teaches problem solving techniques. So deciding what you can and can’t control in your life and changing your behavior, is it something that you can control and changing your thinking about it like if you - like having IBD, you can’t change that so how can we teach you to become less distressed by it.

We took the CBT in our kids with IBD and we’ve now modified it to create an adult CBT manual and we basically added in specific areas that we need to target that we think are particularly problematic for patients with IBD and depression. So obviously the illness narrative is something we really focus on, we incorporate a lot of education about depression and IBD. We use a lot of hypnosis, medical hypnosis is having a whole growth of evidence for supporting physiological changes, brain changes and so we are using that to impact abdominal pain and immune functioning in these patients.
And then I think last but not least we’re actually making this a viable option by providing many of
the sessions by phone to these patients. We have the CBT manual that we can work with that
connects therapists and patients and we also, when we do offer face to face we actually offer it
together with the medical visits.

This is just an example of – and again we talked about the negative stigma in these patients. I can’t
tell you how much stress we alleviate just by explaining a model like this to our patient, oh, no,
we’re not giving you the psychiatric diagnosis of depression, it’s actually that your brain is yet
another organ that your IBD is impacting. And so we’re going to work on mitigating the effects of
IBD or steroids on your brain.

When we looked at our CBT protocol delivered over a 3 month period in our kids with IBD and
compared it just to kids getting medical treatment, we saw significant decreases in depression, we
improved brain functioning, improved quality of life, we showed that the kids can have more
optimistic illness narrative after 3 months, decreased medical utilization which was huge, just after
the 3 months of treatment - and that we actually looked one year post treatment to track that – and
improved abdominal pain and fatigue. And that graph there basically is showing you, the red is the
CBT group, the orange the treatment as usual, medical treatment as usual group. And that’s the
percent change of those symptoms, anhedonia, sleep, fatigue, poor appetite, pain, we specifically
focused on symptoms that we thought well if there’s something that the medical treatment of IBD
was going to impact, it would be those kind of neurovegetative symptoms.

And, in fact, if you got CBT those symptoms improve more and more rapidly than just with medical treatment. So, again, all of our evidence is showing that even if you think all of the depression, anxiety is related directly to the IBD, treatment is worth it.

Very, very quickly because I’ve got the 2 minute warning and we don’t have commercial breaks here for TV stations, so the brain imaging here is also supporting, here we’re showing the dorsal lateral prefrontal cortex, the aqua is basically these kids brains before they were depressed with – or before they received treatment, depressed, goes offline, after treatment it comes back online. Let’s go to the area of the brain that processes self referential memories, the sub geniculate anterior cingulate cortex, again goes offline when you’re depressed and comes back online when you’ve got the CBT treatment and the degree to which we bring this back online so to speak and improve metabolism in this brain region correlates with the degree to which the illness scenario is improved from pessimistic to optimistic. So, again, we really work hard to correlate our behavioral findings with the neuroanatomical underpinnings.

Hypnotherapy, I already alluded to, there’s a growing number of studies showing that there’s significant impact here not just on psychological phenomena but actually IBD-related inflammation, specific cytokines and actually decreased rectal blood flow. So, again, these are small studies, they need to be replicated but all of our clinicians and all of our Coping Centers here at Presby are
certified as medical hypnotists.

Exercise and IBD. Again we don’t think about exercise as a psychosocial intervention but a psychiatrist, you think about it as a behavioral activation paradigm. And again, growing literature for exercise. The important and actually in a non-IBD patient it’s one of the most potent antidepressants out there, so again, moderate, not exhaustive but much better for coping than a sedentary lifestyle.

Behavioral treatments for insomnia. There are strategies that you can suggest to the patients for insomnia, the basically behavioral strategies, the educational strategies, you have these in your handouts but even just these simple recommendations to patients can significantly improve sleep disturbance even if the sleep disturbance is driven by IBD physiological process.

There’s a growing literature on pharmacotherapy of sleep. Now this would be a wonderful reason for referral to somewhere like the VIP center because this now gets more complicated, you need to monitor the side effects of some of these medications, the effect of these medications on – or interactions with the IBD medications. But there are medications that both can improve sleep, quality, decrease the number of awakenings at night and address daytime sleepiness.

And then there is a very small literature supporting the use of antidepressants in IBD and again you have these in your handouts. Bupropion has the most studied and actually has been also shown to
have some impact on improving bone density and actually in improving IBD course. We don’t know if that’s a direct or an indirect effect via treating the depression. And some of the SSRIs, serotonin reuptake inhibitors also have support.

A lot of times when we don’t have response from our antidepressants which is often the case, it’s just important to remember that there’s a whole host of factors that could account for this. Non-adherence being the number one that we certainly probe both in our adults and in adolescents. Then undiagnosed bipolarity so manic depression, that’s different, you’re not using the right class of antidepressants, we now have about 7 or 8 different classes of antidepressants. Other behaviors, a lot of our adolescents self-medicate their IBD with marijuana, IBD activity interfering with absorptions and then the medication interactions.

So in closing when we approach patients with IBD we really are thinking about a biopsychosocial model, biological factors that we’ve covered, psychological factors that we covered and that we target with mainly psychotherapy and hypnosis and then very importantly the social factors.

And then in ending, so the VIP center that you heard alluded to will be operational in January and what we really are aiming to do with our adults with IBD is to integrate behavioral health into medical care and in doing so already reducing the stigma of getting this kind of help. Selling it as something that is imperative for you to do well with your IBD whether you’re medically or surgically getting the intervention. And it’s going to facilitate our screening in identifying the folks
who need these kind of services in sort of a personalized medicine and medical home model kind of way.

And this is just, I’m going to end here and we’re going to implementing this first with patients with IBD then expanding to pancreatic disorder and eventually as we grow we’re going to have this available actually for all GI patients across all disorders in the Center. And as you can see, some of the things that I’ve been talking about are exactly going to be what we’re going to target and then you see a column of some of the treatment options. Thank you.