Bipolar disorder is probably gaining more, more recognition in the public’s eye in the general population because we have media, we have journalists who are very interested in presenting information about mood disorders, the range of mood disorders and really promoting information knowledge in an unbiased way, really trying to reduce the stigma of mental illness by improving our communication about major disorders effect, that can affect 1 to 4% of our population. Bipolar disorder type I, I guess we call it the more severe form of bipolar disorder affects 1.3% of the population. The spectrum illnesses related to bipolar disorder can affect 4 to 6% of the population, and the defining characteristic of bipolar illness is the fact that if a person has had a lifetime episode of one or more manic or hypomaniac episodes, but frequently the patients will present to us in our clinics with various forms of depression, often they are severe depressions, unremitting depressions, atypical symptoms are common and when we carefully interview our patients they will describe their first episode of depression often times in childhood, their first episode of hypomania or mania in their late adolescence and the episodes of depression and hypomania are not treated, not recognized for probably 7 to 10 years before a person finally reaches a clinician who makes the appropriate diagnosis and will introduce some treatment options.

And how do we characterize – how do we distinguish mania, hypomania from depression? Well, hypomania is, is described as a distinct period of having abnormal persistently elevated euphoric expansive irritable mood that lasts for 4 days or more and up to one week or more. In fact patients with severe mania can have days and days, weeks of elevated mood and it’s really quite uncharacteristic, it’s really sort of over the top, high irrita – high levels of irritability, elation, feeling really on top of the world. Patients will often describe three or more additional symptoms that
include having grandiose ideas, feeling sort of outrageously powerful, not needing to sleep, rather
activated, overly agitated. This need for sleep is quite apparent, patients will go from not – from
needing 7 to 8 hours of sleep, 9 hours of sleep in order to feel well down to 2 to 3 hours and really
not even able to fall asleep, not needing to sleep and able to just sort of run, run, run. Patients will
describe flightive ideas really reflected by creative ideas, increased levels of sort of productivity that
could be gained during these time periods, but it may become overwhelming for some folks.

What happens that people will describe poor concentration, they are distracted, drawn to relevant
stimuli and it becomes really hard to finish the multiple projects that they may begin. Often times it
can cause damaging consequences, patients will report excessive involvement in pleasurable
activities, excessive gambling. We’ve had a number of patients reporting increased spending, almost
to the point where they reach bankruptcy, foolish investments, dangerous driving, fighting with cops
and really out of character of their usual self. And on top of that a patient will report multiple
episodes of depression. Depression is characterized by two weeks or more of having either a low
mood, sustained low mood or feeling just this lack of enjoyment, lack of taking pleasure in their past
activities, in their work, in their hobbies, enjoyment in their time with their families. People will
notice significant weight loss, but more commonly patients who have bipolar disorder will report
increased appetite, weight gain, feelings of really being slowed down. On the other at other times
they will notice restlessness and agitation. This loss of energy, feeling incredibly amotivated,
worthlessness, lots of self-doubt, lots of self-criticism, poor concentration to the point where patients
with severe depressions will report frequently morbid thoughts, recurrent thoughts of death,
eventually planning they may even report plans to take their life.
Now we’ve been talking about seasonal affective disorder a fair bit this afternoon, but really I want to make sure that providers understand that when we communicate to the health insurance plans about why we need to justify a light therapy box for seasonal affective disorder we really need to be explicit in letters that we send to the prior authorization health plans that these are patients who are suffering severe recurrent episodes of major depression. They may have unipolar disorders or they may have bipolar disorders but it’s very important to specify this when we communicate it to, when we communicate it in the prescription that we write for these patients and when we write our letters or prior authorization to seek approval for coverage of a light therapy box. And it’s defined – seasonal patterns of depression are really defined by having two or more episodes of depression that onset in the fall or winter and spontaneously remit in the spring for two or more years in a row. And SAD is quite common, we have to remember that SAD can actually affect 1 to 4% of patients in the community, but among the patients that we treat for depression or bipolar disorder it can be 10 to 20% of patients who will have SAD who come to us with major mood disorders who may benefit from a light box.

And what we’ve been talking about in the past two talks is that bipolar disorder, depression in women and depression during pregnancy or postpartum and patients who have seasonal affective disorder share common traits, share common symptoms. And these symptoms are called atypical symptoms of depression that we can inquire about with our patients and actually track during their time that we are seeking to monitor treatment response. So patients will report the sluggishness, the increased appetite, the carb cravings, the weight gain, needing to sleep too much, daytime sleepiness,
the problems with late bedtime and waking at noon time. During episodes of the depression these are symptoms that are really quite heightened but after they begin treatment and find an appropriate treatment and start to respond we will notice that these depression symptoms will gradually improve and disappear.

So when we are treating patients with SAD we really have to observe for the possibility that they might have bipolar illness. And important features of their depressive illness that might signal having a bipolar illness versus a simple seasonable affective disorder, versus a seasonal affective disorder are the following: patients who report psychotic symptoms, so we really need to be inquiring about strange ideas, delusional beliefs, beliefs of persecution, paranoid thoughts. We need to be trying to understand could the patients be having somatic delusions about certain physical symptoms that they are experiencing, exploring for auditory or vision hallucinations along with their depressive symptoms are really important to inquire about when we assess our patients at baseline and at repeated time points when we provide follow-up evaluations.

This experience of let in paralysis, patients who report an abrupt onset and remission of their depressive episodes, whether they are seasonal or nonseasonal could actually signal bipolar disorder. This could actually indicate that patients are cycling possibly rapidly cycling from episodes of depression to euthymia within you know weeks at a time. And I have actually evaluated patients for my study on bipolar disorder, and within a timeframe of 3 to 4 weeks a patient has – presented with severe depression with a SIAT score of 35+, which is very severe, within 4 weeks later her mood had improved to a euthymic level with very minimal changes to their medications, so we have to be
very careful about identifying bipolar disorder in patients who report having seasonal depression and but also have abrupt onset and remission of their illness.

Important to also inquire about family history of bipolar disorder, I think most clinicians are very aware of the importance of asking this question, new clinicians really need to be wary of sort of identifying additional family member, first degree, second degree relatives who have bipolar disorder may actually suggest an increased risk in the patient who is in our office for having bipolar disorder. And also in patients report they have repeatedly seen their doctor, who tried various treatments, tried various antidepressants, none of them worked. You know of course patients need to be titrated up to the appropriate dose of response, but often times patients who have received adequate treatment trials at the appropriate dose for at least 6 to 8 weeks time frame are patients who report what we call the poop out effect, where the depression treatment works for a while and then it suddenly stops working. We really need to increase our suspicion for patients who might have bipolar disorder and maybe they were sort of – the diagnosis was missed a the first go-around.

So the public impact of having bipolar illness is considerable. It can impact the general population in our community substantially. Patients who have bipolar disorder can suffer recurrent episodes 35% of the time and recurrent manic episodes in 14% of patients. And the consequences of unremitting depression can be pretty substantial, people suffer from poor quality of life, may report increased physical symptoms and increased need to see doctors. There is a really impressively high risk in their lifetime for having any kind of suicidal ideation and having repeated suicidal ideations will definitely increase a person’s risk for a suicide attempt. And also functioning becomes very
difficult so patients may miss work or they may not be able to perform at the level they really desire. Overall it prolongs suffering and it may even increase the lag time before we provide proper treatment.

Others have asked me well what about the relationship between seasonality and suicide? And in general I think the consensus is that there is likely more of a heightened risk for suicide in the spring or in the fall, and it really is related to the transition into spring and the transition into fall. There have been recent studies on suicide rates in Greenland, which is sort of very close to the North Pole, high rates of suicide, increasing rates so it may be also changes in the community, increased levels of violent deaths related to suicides and it’s important to recognize the patients who complete suicide are more likely than not to have a psychiatric diagnosis, they may be having problems with alcohol abuse or dependence and suffering from depression. So it’s very important to screen for suicidal ideation in our patients who we are treating in the office.

What we are recognizing now is that patients with bipolar disorder often have cyclic mood changes. This can be reported in the form of having seasonal depression with the onset in the fall and resolving in the springtime. This may be reported in the form of patients who have rapid cycles. They can shift in their mood episodes and alternate in polarity four or more times across the year. More severe forms of rapid cycling can be described as ultradian cycling in which the cycles of depression and mania or hypomania can actually happen within 24 hours. And this actually fits the criteria for a mixed episode. We have questions about well are patients who go through perimenopause or go through the menstrual cycles at risk for depression at certain times across the
menses cycle or in relationship to perimenopause? We really don’t have enough information on the perimenopausal patients but what we are starting to understand is that among patients that have menstrual cycle related symptoms the symptoms may actually disappear and really sort of quiet down when patients are properly treated with appropriate mood stabilizers.

So with bipolar disorder, unipolar depression what we are noticing is that often times with mood disorders patients can be susceptible to mood changes related to sleep deprivation, jet lag, shift work, which provokes a disruption in circadian rhythms. On the other hand, patients may also potentially have or be at risk for having disrupted circadian rhythms. For example patients may report difficulty with falling asleep, variable sleep patterns and efficiency low levels of activity even when their mood states are quite fine.

But what we are understanding now in our research on circadian rhythms and also on light therapy is that light synchronizes the circadian rhythms, the ambient light, the light that’s in the environment hits the retina, the back of the eye and this sends a signal to the brain, to the center of the brain to deeper regions in the brain, specifically the suprachiasmatic nuclei, which is an area of the brain that performs a function to synchronize the brain and body’s circadian rhythms. So the ambient light, the lights within the environment is a Zeitgeber, it’s a really primary synchronizer that can regulate circadian rhythms and shift our circadian rhythms earlier or later depending on when the light is exposed to the organism. Other synchronizers which we might have talked about can also regulate body rhythms and this includes exercise which can regulate muscle, rhythms in the muscle, meals, which can affect rhythms in the liver and the liver function and even our work and school schedule.
So synchronized rhythms is – having synchronized rhythms is critical for general health, for maintaining alertness and allowing us to be able to perform cognitively and experience healthy mood states. So we need synchrony between the different body clocks, but we also need synchrony between our body and brain clocks and the day/night cycles. So when there is dyssynchrony that happens from either being required to work shift work chronically, or if we suffer from acute jet lag this can impair our alertness levels, it can worsen our sleep, it can affect our work performance and it may even increase our risk for health outcomes, and could increase our risk for obesity, diabetes and even for cancer.

So what kind of level of light do we need to synchronize our rhythms? The minimal level of light that’s required to synchronize our brain and body’s rhythms is about 1,000 lux, and this is equivalent to the light that is emitted, that – this is equivalent to the amount of sunlight that comes across the horizon at daybreak. Now even in sunny climates we, because we live in sort of a built environment few people might receive sufficient light in their environment to entrain or synchronize the internal clock, but we may be suffering from sort of a lack of sufficient environmental or ambient light input to provide strong signals to allow us to experience synchronized circadian rhythms between our brain and our body. And we do need robust rhythms in order to regulate our sleep/wake patterns and it may actually have effects on our mood. So there are patients, we talked about the morningness, eveningness factor related to, to sleep and being able to experience restful sleep, and what happens is when night owls – night owls basically are describing a group of patients who prefer the evening versus the morning, so they may have a later bedtime and a later wake time, and they may perform more effectively in the afternoon, evening hours. So the problem, or the potential social problem
with night owls is that they may have circadian rhythms that may not fit with certain jobs or schedules that they are required to do. And this is perhaps a form of social jet lag that can prove a stress on our rhythms.

And so what are the effects of light on the body and the brain from the human circadian, from the human point of view? As the primary synchronizer ambient light may exert important effects on cognitive brain function, emotion processing, specifically may have effects on serotonin neurotransmission and we have sort of you know every time we open up a journal we are coming across really intriguing research that is exploring aspects of the circadian rhythm and some interesting work that’s coming from Belgium has examined exposure to blue versus green light which can modulate the brain’s response to emotional stimuli that’s provided in the form of noises or sounds. And what it’s done is that we’ve – people are discovering that in humans the activation - that there is increased activation in the temporal cortex, in the hippocampus in response to blue versus green light, increased functional connections in the temporal – between the functional – between the temporal cortex, the amygdala and the hypothalamus in response to blue versus green light when patients are responding to emotional stimuli.

And the intriguing piece to light therapy is that it may not only just effect the circadian timing system is that it may also effect neurotransmitters that are intimately involved in regulating mood. The serotonergic pathways from the mid-brain, raphe nucleus which are important for regulating mood, sleep and appetite also provide non-photic or non-light input to the suprachiasmatic nuclei and this may impact our circadian rhythms. But we are still not really sure how this may relate to
antidepressant effects of light therapy, but we do know that seasonal symptoms can improve with serotonergic drugs like Lithium or Fluoxetine, depleting Serotonin by depleting Tryptophan, which is a precursor of Serotonin can actually reverse antidepressant effects of light therapy and optimal response to light therapy has been associated with certain genetic variants of the Serotonin transporter gene and so this sort of provides more evidence that light can actually have effects on not only the circadian rhythms but also on brain chemicals that are important for mood, mood disorders.

And we have talked extensively about what is bright light therapy, but just as an overview, well just to review again the established form of bright light therapy that is most – that is indicated for the use of treatment of – that is indicated for the treatment of seasonal effective disorder is broad spectrum white light. So it’s not necessarily full spectrum, it’s actually a broad spectrum white light that provides about 6 to 10,000 lux of light UV filtered. The main indication or as we had discussed, it’s mainly indicated for seasonal depressions and may be effective for nonseasonal depressions and it may be effective for circadian dyssynchronous problems related to phase delayed sleep disorder, shift work, jet lag.

And as we had talked about the dosing and the duration – dosing is likely related to first of all the duration, so most patients we would advise that they begin with 30 minutes a day of light therapy. This can be titrated gradually by 7 to 15 minutes increment to a target dose of 45 to 60 minutes per day. And the time of day again it’s usually introduced first thing in the morning within the first 5 to 10 minutes upon wakening and individualized based on the person’s response to the MEQ questionnaire.
The patient should be seated at a comfortable distance, about 12 to 14 inches away and the box should be actually situated a little above, probably about 6 to 12 inches above the surface where the person is seated at, and the box should be tilted downwards and illuminate the surface in front of the person. The person’s face should be exposed to the box which measures usually about 18 inches to 24 inches with – in length and patients really need to make sure that they keep their eyes open. So appropriate activities as Dr. Wisner was saying, patients who have really gained the most benefit have discovered that the light therapy can be incorporated into their daily activity and used sort of at a time to incorporate their other psychotherapy skills, for example people will use their workbook, their anxiety phobia workbook, they will practice journaling their sleep, their activity levels, they will take that time to read and perform tasks that are enjoyable to them. And in that way they really can sort(196,724),(814,786) of bring in their cognitive behavioral therapy skills and sort of merge that with their light therapy and gain additional benefit. And we actually did see a patient who was able to incorporate a little bit of an exercise regimen to their light therapy and gain benefit from the treatment. It was a little bit murky about what actually helped in their treatment response, whether it was the regular exercise or the light therapy that induced her response.

But important side effects to discuss with our patients include the potential that they will experience increased irritability, headaches, eye strain, nausea is a commonly reported symptoms, agitation, insomnia if it’s used too late at night and hypomania. Now some of the side effects can be titrated, so what we do is if patients are noticing increased side effects even when they begin light therapy at 30 minutes a day is that they can back off on the dose and bring it back by 7 to 15 minutes. And some
patients may benefit from beginning their titration at 15 minutes daily. It is important though to continue to titrate the dose likely on a weekly basis to the treatment dose of response because we really don’t want to stop until the patient has experienced a full treatment response.

Retinal toxicity is not – has proven not to be associated with ongoing use of light therapy, however, there is this potential hazard to the retina with excessive exposure to blue light. And this could result in age related, an increased risk for age related macular degeneration from long term exposure to the 4 and 500 nanometer wavelength, which is sort of excessive exposure to blue light. So we really want to make sure the patients are not using exclusively blue light all the time. We don’t have enough safety data to endorse that quite yet, and there are certain patients who have macular degeneration who also have skin diseases that sensitize them to light, such as porphyria, lupus, chronic actinic dermatitis or solar urticaria which is a high reaction to sunlight. These are patients who may need special monitoring if they are going to begin light therapy. There are certain medications that could increase photosensitizing effects and this, they include Chlorpromazine, which are older antipsychotics, the antimalarial drugs which are used for the treatment of rheumatoid arthritis, melatonin and St. John’s Wart.

And so I’ve had some questions related to how do we check for eye safety, and again I really encourage you to go to the back of the CET textbook, to the cryotherapeutics textbook where they actually give you the password to log onto to cet.org and there you can open up a range of assessment tools including the eye safety checklist if you are uncertain about whether or not this person should be starting on light therapy because of past eye diseases. I’ve had questions about
whether or not patients who have had cataract surgery would be appropriate for light therapy, in fact having cataracts would probably reduce the likelihood that a person will experience a treatment response to light and it would be – they may gain full advantage of the light therapy by having you know been treated for their cataracts.

So what – so there are many advantages to light therapy and the advantages include the fact that there are – there are few major side effects. We avoid drug-drug interactions, and the treatment is relatively affordable. And the light dose can even be titrated, not only against side effects but also against emergent hypomania. And I’ll talk about that in a little bit later.

But I really wanted to make sure that we get the information across to providers and also to health plan folks that there are really important cost comparisons to look at that could justify the use of a light box versus choosing an antidepressant. And in reviewing sort of what are the costs, what are the 30 day costs for these antidepressants what we – what we can conclude is that the light box is probably as affordable as a generic antidepressant like Sertraline or Fluoxetine and may be even a little bit more affordable if a person is required to use it on a daily basis throughout the year. So the cost for generics range from about $40 to $60 per month, and light boxes if we include shipment costs and replacement bulbs probably will range from $20 to $40 per month. So there is really good justification based on treatment indication and also on a cost comparison basis.

And how can we use the light therapy? Well mainly we’ve been talking about using the light therapy as a monotherapy type treatment but really the treatments can be combined with medications
to boost the effect. Clearly there is no evidence that the combination treatment has adverse outcomes or but the add on treatment may not provide additional benefit above and beyond monotherapy, however there are certain patients if we do need to individualize treatment it may be – it may be an option to add on light therapy in patients who are on existing antidepressant treatments.

And just moving along, so what we are discovering is that patients are – there is groups of patients that may be excellent responders to light therapy, they could have major depression or they could have bipolar disorder. And the response rates to patients who have seasonal affective disorder and underlying bipolar or unipolar illnesses are pretty similar. So the response rates are about 50% in bipolar patients who have SAD and about 67% in patients who have unipolar SAD. Now when we looked at season, nonseasonal depression in patients who have bipolar disorder these are groups of patients that actually may have increased response rates compared to patients who have unipolar depression that’s nonseasonal.

And what we did was in our preliminary study to look at light therapy for women with bipolar depression we took a treatment design that was not really an open label study even though I think some of our critics described it as an open label study. This is a study that took place a few years ago and it’s really what we call a dose ranging preliminary efficacy and safety study to look at preliminary efficacy, tolerability safety and to determine the ideal dose for patients who have bipolar disorder. The reason why we can’t really call it an open trial is that the patients who came into this study were blinded to the hypothesis and also the clinicians who performed the mood ratings for depression and also for emergent mania with the mania rating scale were also blinded to the
hypothesis. The patients were randomized, well the patients began with a dim red light use of the light box which was a dim red light for 2 weeks, and this was followed by advancement to an active bright white light for 2 weeks at the lowest dose for 50 minutes every day. And we advanced and titrated the dose by 50 minutes each week to the – to the dose of response. The max dose was 60 minutes a day, and we started with morning light because morning light was indicated for seasonal affective disorder, and this is the form of light treatment, the timing that we initiated in the patients who had bipolar depression.

Intriguingly after we finished seeing the first 4 patients across the 6 week – across this 8 week protocol we discovered that we were inducing mixed episodes and emergent mania and hypomania in 3 out of the 4 patients who were involved in this dose ranging study. Two of the patients actually developed full response to morning light, and so because of this rapid onset of emergent mania and also the high adverse, high rate of adverse effects in these patients we really had to sort of temporarily stop the protocol and take a look at what was going on. And we’ve tried to evaluate what were the possible factors that could be causing the mania or hypomania.

We had ensured that the patients – we tried to ensure that the patients would have the lowest risk by only bringing in patients who were treated on mood stabilizers before they were allowed to enter, enroll in the study. We examined the light box and we were wondering whether or not the intensity was too high because we were giving patients about 7 to 10,000 lux boxes. And we sort of tried to figure out well could we adjust the distance from the box? Could we reduce the intensity of the box? Or is there another factor that we should be examining?
And the other factor that we, we thought about is adjusting the timing of the light therapy. Now the timing of the light therapy was – was based on – was chosen based on how we usually treat SAD patients. And timing it in the morning may be advantageous to cause changes and phase shifts in the circadian rhythms, but it may not even – may not be so advantageous if we are exploiting the light therapy as a form of depression treatment because it affects the neurotransmitter systems or other systems that we’re not yet familiar with. So we decided to consider morning versus midday versus evening light. And the preliminary data that had been published by other groups including Ellen Liebenluft had looked at evening data, evening light which proved to be pretty minimal in its effect, midday light that seemed to provide a fairly robust effect without any adverse consequences, and morning light which seemed to prove to be quite effective also. Now Ellen Liebenluft had chosen a group of patients that were extremely challenging to treat, she had chosen to study patients in an open setting, patients who had rapid cycling or mixed episodes, and so our patients were selected to only have major depression, major depressive episodes of bipolar disorder so we changed the protocol. And we decided to implement midday light for the remaining patients in the study and we found that 44% were actually full responders, and full response is determined as a 50% or more reduction in their mood ratings, 22% were partial responders but eventually if we were able to move them to the higher dose above and beyond the 60 minute mark we were able to induce response in some of the other patients. And by moving another patient from midday light back to morning light we were able to elicit response in this patient at the max dose of 60.
So what we discovered is in addition to this is that patients usually begin to experience an onset of antidepressant response within the first 2 weeks of light therapy, and full response by 6 to 8 weeks. And so this, this information really was able to allow us to help patients understand what to expect from their treatment, so really when we are educating patients about how to use the light box we really want to understand how long do we have to wait before we can see a response, and how – at what point in time do we need to think about additional treatment options.

And this preliminary study was not only helpful in providing information to our patients on how you know light therapy could be useful for patients with bipolar depression but it really did inform the use of light therapy for patients of bipolar disorder and the design of a future study. And so our current study based on the preliminary efficacy study is a randomized control trial. And we already have a good idea of why light therapy may be effective for patients of bipolar disorder and we also need to justify to funding agencies and also to ourselves what are the major knowledge gaps about bipolar treatments. Essentially it is still very important to pursue treatments for bipolar depression mainly because the current drug studies although they have uncovered promising agents for mania there are really still few options for bipolar depression. The other problem is that the mood stabilizer treatments often induce undesirable comorbid disorders. It’s really important to inform patients that when they are about to start on certain atypical drugs or medical – or anticonvulsant drugs some of these drugs could increase risk for diabetes, obesity, glucose intolerance, hyperlipidemia, and these can result in longer term consequences such a diabetes mellitus type II, cardiovascular diseases and early death.
So still we have just a handful of agent medications that are effective for the treatment of bipolar depression. The response rates, you know they are not fantastic, they are about 36 to 50% response when patients are prescribed monotherapy mood stabilizers. When patients are prescribed mood stabilizers plus antidepressants there really is not much more gained by that, still the response rates are in 33% range.

And not only do we have problems with the metabolic effects, when we do add on antidepressant medication therapy there is also the concern about switching into mania or hypomania, and the culprit drugs are in this order: Venlafaxine or Effexor, which is a serotonin norepinephrine reuptake inhibitor; Sertraline which is a serotonin reuptake inhibitor and Bupropion, which may be the antidepressant that’s less likely to cause flips into mania or mixed episode. The other problems with adding an antidepressant to the treatment mix is that it could cause rapid cycling or could make the cycling worse, it could result in mixed symptoms and refractory illness.

So in this study the main aim is to understand and compare the response to light therapy versus a comparator in depressed adults who are men and women who are between the age of 75, 18 to 75 who have bipolar or one or two disorders. And the primary aims are to examine the change in depression levels after 6 weeks of treatment with light therapy versus our comparator, to examine the proportion of patients that experience response or remission and the time to response and relapse. And it’s very important to not only examine who are responders which we define as a 50% improvement in depression scores without any emergence of mania or hypomania, but it’s also to really see if the treatment is effective to get rid of most of the symptoms. We really – our main
treatment aims are to get patients back to their usual level of functioning as defined by remission, so very low levels of depression, no mania or hypomania and a return to their original level of function. And we really should not be stopping our goal, our treatment goals just at the response definition, really we want to see patients get fully better so that they can return to their original work and hobbies and enjoyment of life.

Now the other things that we want to examine in the study are what are some important predictors of treatment, and Nomni and others have focused their important research on examining genetic predictors related to – that could be related to treatment response but we are still sort of like a little bit in the ice age when it comes to bipolar disorders and we are still trying to understand what are the circadian rhythm disturbances in bipolar disorder and what could the light therapy be doing in terms of effecting the brain’s response, what could the light be doing in terms of changing how circadian rhythms timing – the circadian rhythm timing in patients who have bipolar depression if at all, how the light might be changing patients activity levels and also their social rhythm patterns. So there are still much investigation to be done.

And in this protocol and I think I’ll probably just stop here, really what we are going to do is take the information that we gain from the preliminary trial and have patients agree to be randomized to the active versus the comparator treatment across 6 weeks with careful follow-up. We will help patients discover whether or not the light therapy is an effective treatment for them and this is information that can be used in the future in order to guide their – the patient and their clinician’s decisions on
whether or not to use light therapy or whether or not there are other options that may be feasible for them.

Now we have talked a little bit about safety assessment, important factors to consider when we are treating patients with light therapy or even with medications is to be able to identify when patients are not only improving but definitely when they are worsening. The use of light therapy can elicit a range of treatment responses and in the CT.org, the textbook that we have disseminated there are some important assessment tools that you might include in your practice, the use of the high C is definitely important for assessing the emergency of mania or hypomania, but also critically assessing for safety risks. So asking about suicidal ideation, inquiring about the level of depression and also incorporating a system so that patients can access the clinician or the prescriber so that the – if there are emerging symptoms that happen rapidly the patients will be able to reach a clinician and speak with a clinician on how to adjust the dose because most of the emergent responses can respond, can improve with rapid adjustments to the light dose. For example we can eliminate hypomania by reducing the duration of the box, we can actually incorporate additional treatments to improve sleep, we can adjust the antimanic dose and these are treatments that – these are adjustments in our treatment that can be used effectively to stop the emergency of hypomania or mania and to address severe depressions that may be sort of breaking through before the patient can fully respond to their treatment.
So what I’d like to do is see if people have questions for me. I know that there were some questions related to melatonin at some point. But I really wanted to just address the clinical questions first and we have 5 minutes left so I’ll just leave this open to questions.

In regards to the trial, how (inaudible).

So your question is how do we run the trial to ensure that they are using the box? That’s a really good question, that’s a question that we ask, yes that we are face – you know at many different levels of scrutiny from our research committee level to grant reviewers. And we actually can incorporate measuring devices that measure the patient’s use of the light box. We can actually go to extremes and we have even contemplated video recording, like actually inserting a little video monitor into the box to observe people’s use of the light box. But that sort of was a little bit overboard. We could infringe on privacy, so we held back from that. So but we do actually have a device that will measure their use of the box, and they – our decision to whether or not keep the patient in the study after they completed the first 6 weeks, which is the acute phase, which is the time frame where we are most interesting in measuring treatment response we do make decisions on whether or not to continue patients based on their adherence to treatment. And that’s one of the measurements that we use.