TALK FOR ASBA CONFERENCE May 2014:

Circadian Rhythm Sleep Disorders

I. Introduction [title slide]

A. Hello

Hi. I'm Peter Mansbach, and I'm president of Circadian Sleep Disorders Network. I'm really glad for this opportunity to talk about circadian rhythm sleep disorders, including diagnosis and treatment.

B. Disclaimer [Overview slide]

[**Overview slide**] Let me start by saying I am not a medical doctor. I am here to raise awareness about Circadian Rhythm Sleep Disorders on behalf of those who suffer from these often debilitating disorders. I myself have Delayed Sleep Phase Disorder.

C. Why should you care?

It is estimated that half a million American adults have Delayed Sleep Phase Disorder, and another 90,000 have Non-24-Hour Sleep-Wake Disorder. These are vastly underdiagnosed, in part because people are unaware of these disorders, and because their severity and resistance to treatment is not widely understood.

D. Emphasis

In this talk I would like to particularly emphasize the need to take into account the patient's natural circadian cycle when evaluating patients in a sleep study.

II. Circadian Rhythm Sleep Disorders

Let me start with some background. Many of you already know this.

A. What are circadian rhythms? [Circadian Rhythms slide]

1. General

Circadian means "approximately a day". Circadian rhythms are processes which cycle daily. They are produced internally in all living things.

They are also referred to as *the body clock*.

2. In Humans

Humans have internal cycles lasting on average about 24 hours and 10 minutes, though the length varies from person to person. (Early experiments seemed to show a cycle of about 25 hours, and this still gets quoted, but it is now known to be incorrect. It arose because those experiments allowed light exposure in the evening.) While these internal rhythms are approximately 24 hours, they are adjusted daily by

external factors, called *zeitgebers,* especially sunlight or other bright lights. This synchronizing with the 24 hour day/night cycle is called *entrainment*.

The most noticeable feature of circadian rhythms is the sleep/wake cycle. But there are other circadian rhythms including swings in many hormones throughout the day, the body temperature cycle, appetite and the times of best alertness. Ideally these rhythms are in sync with each other and with the light-dark cycle in nature. Most folks are awake during daylight hours and sleep during darkness.

3. Suprachiasmatic nucleus

The master clock in the body is a small part of the brain called the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN keeps the clocks within organs and individual cells in the body in sync.

4. ipRGC cells

The master clock normally gets adjusted every day when a person is exposed to light. The receptors in the eye most effective in doing this are not the rods and cones we learned about in school, that give us vision. They are cells called ipRGC cells (intrinsically photosensitive retinal ganglion cells), which are not involved in vision, and were discovered not so long ago.

B. What are circadian rhythm sleep disorders? [Circadian Rhythm Sleep Disorders slide]

1. Definition

A Circadian Rhythm Sleep Disorder is an abnormality of the body's internal clock, in which a person is unable to fall asleep at a normal evening bedtime, although he is able to sleep reasonably well at other times dictated by his internal rhythm.

2. Description

The person cannot fall asleep when desired, so he complains of insomnia. He has trouble waking up when desired, so he complains of excessive sleepiness. It takes some insight to make the connection that the problem may be with the timing of sleep rather than the sleep itself.

3. Inflexibility

One factor common to these disorders is inflexibility: even when physically tired or sleep deprived, sufferers cannot make up for lost sleep outside of their hard-wired sleep times. This factor is generally misunderstood by people who do not suffer from these disorders, leading to a conclusion that we are just lazy or that we haven't tried hard enough to live on society's schedule.

Some people are flexible and can adjust to sleeping on practically any schedule. Still, they may prefer to wake up early (we call them "larks") or stay up late ("night owls"). But other people cannot adjust, and forcing themselves to be awake at the wrong time for their body can make them ill. They have a Circadian Rhythm Sleep Disorder.

4. Coordination with other circadian rhythms

In addition to the sleep/wake cycle, the internal coordination of the various other rhythms may also be faulty. For example, some hormones may be on a different daily cycle than others, and this lack of coordination between systems may produce other symptoms in addition to the sleep disorder. This is believed to be the cause of the discomfort of jet lag.

C. CRSD Subtypes [Subtypes slide]

The *International Classification of Sleep Disorders Revised* (ICSD-R) lists 6 subtypes of circadian rhythm sleep disorder: (ICD-10-CM diagnostic codes)

- Delayed Sleep-Phase Syndrome (G47.21)
- Non-24-Hour Sleep-Wake Disorder (G47.24)
- Advanced Sleep-Phase Syndrome (G47.22)
- Irregular Sleep-Wake Pattern (G47.23)
- Shift Work Sleep Disorder (G47.26)
- Jet Lag Syndrome (no longer listed)

[omit] Note that "Jet Lag Syndrome" and "Shift Work Disorder" refer to disorders (severe cases) of jet lag or shift work, not to all instances of these. Newer classifications omit jet lag disorder, since it is temporary.

We'll focus mainly on Delayed Sleep-Phase Syndrome and Non-24-Hour Sleep-Wake Disorder.

D. DSPS

1. ICSD-R Definition [slide] [omit]

[omit] The ICSD-R lists these factors for diagnosing DSPS

- Sleep-onset and wake times that are intractably later than desired
- Actual sleep-onset times at nearly the same daily clock hour
- Little or no reported difficulty in maintaining sleep once sleep has begun
- Extreme difficulty awakening at the desired time in the morning, and
- A relatively severe to absolute inability to advance the sleep phase to earlier hours by enforcing conventional sleep and wake times.

2. Definition [slide]

Delayed Sleep-Phase Syndrome (or Delayed Sleep-Phase Disorder as it's now called) is a disorder in which a person's sleep occurs much later than desired. He finds it difficult to impossible to fall asleep until very late at night, and therefore difficult to wake up until very late in the morning or even afternoon.

3. Example [Normal and Delayed Sleep Phases slide diagram]

For example, a normal sleeper (green line) may sleep from 11pm to 7am. Someone whose sleep is delayed six hours (as an example – red line) would be sleeping from 5am to 1pm. This makes it

impossible to hold a typical 9 to 5 job. If the person tried to hold the job anyway, but still couldn't fall asleep till 5am, he would quickly become severely sleep deprived.

4. TWO factors [slide]

Why not just go to bed earlier? There are TWO factors involved in DSPS, something people often overlook: one is that the body's clock is shifted later in the day; the other is that the person is unable to shift it earlier. He either cannot sleep at an earlier time at all, or his sleep at the earlier time is not restorative.

It's similar with shift work: some shift workers can adjust to working at night and sleeping during the day. Some have difficulty. Some cannot adjust at all.

5. Hard to understand

This is REALLY HARD for a person with normal sleep to understand. They can fall asleep when they are tired. They get tired when they're supposed to. They may have trouble getting up on time, or they may feel tired during the day, but then they can get to sleep earlier the next night. We can't.

It is really difficult for most people to understand what we're up against. Even if the DSPS person forces himself to get up early, and then goes to bed early, he cannot sleep. It's like he's on "internal caffeine".

6. Biological markers [Biological markers slide]

There are a number of biological markers that can be measured, that cycle with the circadian rhythm. So we can objectively measure the timing of a person's circadian rhythm, and confirm that there really is something physical going on with these disorders.

Melatonin is a hormone produced by the body, which is intimately involved with sleep. Its level normally rises about two hours before bedtime (called Dim Light Melatonin Onset, or DLMO), is high during the night, and falls toward morning. In people with DSPS, melatonin secretion is delayed, or in some cases non-existent.

Core body temperature normally is high during the day, drops around bedtime, reaches a minimum [*nadir]* a few hours before awakening, and then rises again. Core body temperature is also delayed in people with DSPS.

Cortisol also follows a circadian rhythm, as do several other hormones.

7. Incidence (how many affected) [slide]

How many people have DSPS (and are not just evening types by preference)? Based on a Norwegian study, 0.17% of ADULTS have this disorder. That's well over 1 in 1000 (closer to 3 in 2000); over half a million American adults. About 3 times as many people as have narcolepsy, which I've shown for comparison! (But we need more data.)

But most go undiagnosed.

It's much more common in teens. Estimates of perhaps 7 – 10% of teens are common. That's around 2,000,000 Americans. But most of them grow out of it in their 20s.

8. My junior year, my diagnosis

Let me tell you about some of my own experiences.

[**Snooze Alarm slide**] In college I had trouble getting up on time for class. My roommate junior year threatened to go to the dean because I kept snoozing my alarm, seven, eight, nine times, he said. I was unaware that I was even doing that.

But who knew about sleep disorders? A lot of people complained about hating to get up in the morning. So I just forced myself to do so. I was young.

That year I had to take the earliest class of my college career. [**Sleeping in Hallway slide**] I had an hour between classes, and I was so tired that I would lie down in the corridor outside the next classroom and nap. If you're tired enough it doesn't matter how weird you look.

I also started having migraines during that class, but didn't make the connection with the early rise time.

I wouldn't be diagnosed until 16 years later.

[**Sleep Study slide**] Even that was a stroke of luck. Back then, there weren't any sleep labs in the Washington DC area, where I lived. So I was referred to Montefiore hospital's sleep lab in New York. Quite by chance, at that time a research team there was first elucidating DSPS. Their paper wouldn't be published for another year. But they recognized the disorder in me immediately.

Since then I've lived on my natural schedule. But I did lose my physics job, and my career in research, because of my hours. Fortunately I could find contract work in computer programming, which I could do on a later schedule. My sleep time now is roughly 3 am to noon.

While I was living on society's schedule I had two episodes of major depression, and was always a bit down [dysthymia]. Since I've lived on my body's preferred schedule, I've had no more episodes of depression, and a pretty normal mood.

9. Other stories

I read letters from our members with DSPS. Here are some quotes:

[**Member Quote slide**] "For decades I worked day jobs after sleeping 3:30 to 7:30 a.m., catching up on weekends.... That worked while I was young and resilient. Next step was adding a "nap" 5 to 10 p.m. Wreaks havoc with the social life, but it kept me my job for years.

"If you can't be normal, you're not good enough. You learn to apologize, make excuses, tell lies. No one understands. "

[**Member Quote slide**] Another member writes: "I just can't help thinking that I'd have no problem being awake and alert if I were to simply follow my own natural sleep cycle. The only problems I would face are unemployment and nearly no social life."

10. Other people

Summarizing many of the stories I've heard:

- So many bright people with career aspirations that were stopped in their tracks by their sleep disorders;
- people unable to get suitable accommodations at work;
- people who went for years being repeatedly misdiagnosed, and often given medications, with side effects, for conditions they didn't have;
- So many unwarranted referrals to mental health professionals, and mental health professionals who then treat it as a psychiatric disorder;
- So much misunderstanding by society, even by the patients' own families.

We're often told we could get up early if we wanted to. We show the doctors articles on the web, research articles in the journals, but *sometimes they refuse even to look at them*. They just refer us to the psychiatrists.

E. Others (ASPS, ISWD, shift work disorder) [Circadian Sleep Disorders diagram slide]

Advanced Sleep-Phase Syndrome (ASPS) (purple line) is the opposite of Delayed Sleep-Phase Syndrome: people fall asleep early in the evening, and wake up very early in the morning, perhaps 4am. It is much rarer than DSPS, according to the Norwegian study. People who suffer from it get up early, get to work on time, and don't generally need to sleep until after normal work hours. So their lives are not disrupted as much, compared with DSPS or Non-24 people.

I don't know much about Irregular Sleep-Wake Disorder. It is very rare. It occurs mostly in people with severe brain dysfunction.

F. Non-24 [~17 mins to here]

1. Definition [slide definition of Non-24]

Non-24-hour Sleep-Wake Disorder (Non-24 for short) is a disorder in which an individual falls asleep later and later each day, eventually rotating all the way around the clock. Generally the delay in sighted patients is about an hour or two each day, corresponding to a "day" that's 25 - 26 hours long; but it can be much longer. In blind patients the delay is usually less. In either case, their body's preferred sleep times progress all the way around the clock.

It's also known as Free-Running Disorder, and hypernychthemeral syndrome.

2. Example [Non-24-Hour Sleep-Wake Disorder slide diagram]

For example, let's suppose our subject goes to sleep today when she is tired at midnight and sleeps till 8am, and is fine. Tomorrow, she may not be tired enough to fall asleep until 2 in the morning, and so she'd need to sleep till 10. The next day she can't fall asleep till 4am, and she sleeps till noon. So it progresses: a few days later she'll be going to sleep at noon, and some days after that, at 6pm. Her sleep progresses all the way around the clock, back to where it started, and keeps going like that.

3. In blind people

It is estimated that over half of all totally blind individuals suffer from non-24. That's about 90,000 Americans. This is not surprising, given that sighted people synchronize their slightly longer circadian rhythms to the 24 hour day through light exposure, and the totally blind aren't getting that light exposure through vision (rods and cones). Some do respond to light exposure via ipRGC cells, which are separate from vision; others do not.

4. In sighted people

In sighted individuals non-24 is believed to be rare, but that is not known for certain. What is known is that it is rarely diagnosed. Yet I know of over 60 sighted individuals with non-24. The causes in sighted patients, in contrast to blind patients, are likely to be similar to the causes of DSPS, which I'll discuss in a moment.

5. Incidence (how many affected) [slide]

I've added a line for non-24 to the bottom of the previous incidence slide. You can see it is much rarer than DSPS.

6. Living with Non-24 [slide]

Some non-24 folks, especially those unaware of the condition, force themselves to live on a 24 hour schedule. When their body's preferred sleep time coincides with the earth's night, they sleep well and feel fine during the day. When their body's preferred sleep time falls during the daytime, they sleep poorly and suffer excessive daytime sleepiness. This makes their problem look like periods of insomnia, with some good nights clustered together in between. So it is difficult to recognize the non-24 as such, and as a result non-24 is almost certainly underdiagnosed.

Other people "go with the flow", and sleep and wake as their body dictates. They are sometimes in sync with the day/night cycle, but their sleep progresses around the clock, later and later each day. They find it impossible to hold any conventional job, and difficult to have a social life.

For some, the delay is regular. For example, they may shift an hour later each day. But for others the delay varies, up to several hours, and they cannot predict their schedule at all. So it becomes difficult to schedule any appointments in advance

7. Personal Stories

I read letters from our members with Non-24, and it breaks my heart to hear their struggles. Many of these folks cannot find a job, and have no money. Here are some quotes from different people:

[**Member Quote slide**] “Ever since I became Non-24, I constantly have to beg people to change their schedules, or try to be pleasing and unobtrusive while I quietly ask if they have another time available. It's affected my relationships with all: family, who don't believe in it; friends, who can never find a slot to talk to me, let alone get together, and, have finally stopped trying; doctors, next to impossible to schedule…. When I can't meet the world’s demands, I am deemed selfish or weak or lazy or depressed.... I could be fine with me. But the world is not fine with me, and that makes me not fine.

I feel so isolated; I'm desperate for social contact.”

[**Member Quote slide**] Another member writes: "What is hardest is explaining non-24 to new acquaintances, for example someone you might meet at a party. It tends to derail the whole social process. The inability to remain employed has an even more profound effect on my social life. It's not something people accept when you look healthy."

G. Causes [Possible Causes slide]

What are the underlying causes of these disorders? I believe there are several different abnormalities that can cause both DSPS, and sighted Non-24. These may include:

- long intrinsic circadian period
- lack of sensitivity to light
- over-sensitivity to light
- lack of melatonin production
- long elimination time of melatonin
- deficiencies in the light-sensitive ipRGC cells of the retina
- long time from core temperature minimum to wake up time
- differences in tolerance to phase mismatch, etc.

I don’t have time to go into the details of how these causes can give rise to the symptoms.

It’s my belief that both DSPS and Non-24 have similar underlying causes. They may differ in the degree of various factors, and how they interact, with the result that DSPS people can entrain to a 24 hour day (though not at the usual time), and non-24 people cannot. I know of several people who used to have DSPS, but are now Non-24.

1. Age effect

I would note that, anecdotally at least, younger people seem better able to maintain a required schedule despite their circadian disorder. As they get older, they may no longer be able to do that. So that may be what drives them to see a sleep specialist.

III. Diagnosis [diagnosis slide 1]

How are these disorders diagnosed?

A. Patient reporting and sleep log

Some patients will come in with a history of unusual sleep hours. Some may already have kept a sleep log, and may even have charted their sleep times graphically if they've read about circadian disorders on the web. This is most valuable if the patients have been able to sleep on their body's preferred schedule. If they are forcing themselves to get up for a daytime job, it may be less informative.

[**Sleep Chart – DSPS Patient slide**] Here's an example of a sleep chart. It's a form that's been used by some sleep doctors. Here the time of day is marked across the top, from 6pm one day to 6pm the next. Successive days are shown one below the next. Sleep periods are marked in dark gray. I've added an indication of normal sleep hours (11pm to 7am) in light blue, but this would not normally be shown. This is two weeks' worth of my own sleep, that I recently recorded, so it's for a typical (though relatively mild) DSPS person. You can easily see the delayed sleep pattern. The chart shows a few naps as well.

[**Sleep Chart – Non-24 Patient slide**] This chart was recorded by one of our Non-24 members. The first few days seem quite irregular, but starting around the 4th day there's a clear progression around the clock. Remember that some of the sleep periods wrap around from one day to the next.

B. Actigraph [actigraph slide]

Many doctors, if they suspect a circadian disorder, will ask their patients to wear an actigraph to monitor their actual sleep and wake times. An actigraph is a motion sensing device that is worn like a wristwatch. Again, this is most illuminating if the patient is sleeping on his own schedule.

This slide is the actigraph recording of another member with Non-24. The white areas are the sleep times. The dark marks represent activity.

C. Polysomnogram – timing! [diagnosis slide 2]

Many sleep doctors require a polysomnogram (PSG) (overnight sleep study), at least to rule out other sleep issues such as sleep apnea or restless legs. But the sleep study is most revealing when it occurs when the patient can actually sleep, and sleep normally. Many of our members complain that their PSG was administered from 11pm to 5am, and they were unable to sleep at all during that time.

I myself went for a re-evaluation 15 years after my original diagnosis. The doctor ordered a PSG, which was conducted from midnight to 5am. The doctor concluded that my problem was that I wasn't getting any deep sleep, and wanted to treat me accordingly. Not only were the hours unsuitable for my DSPS, there were other extenuating factors such as a full-blown migraine headache. But the doctor insisted that "the lab measurements never lie". A little humility, please? There is still so much we do not understand about sleep. Please, LISTEN TO WHAT THE PATIENT SAYS.

With Non-24 people the situation is even more complicated. Many Non-24s can't predict their sleep times more than a few days in advance, but have to schedule the PSG weeks ahead. They don't know what to do, and often report that the sleep doctor didn't even want to hear about the problem.

D. Misinterpreted MSLT - DSPS misdiagnosed as narcolepsy?

Some doctors will hear the complaint of daytime sleepiness, and refer the patient to get an MSLT, a Multiple Sleep Latency Test, to test for narcolepsy.

Dr Mignot and others have noted that workers on a night shift may test positive on an MSLT, even though they test normal when working on a daytime schedule. This is because their internal circadian rhythms are out of sync with respect to the hours they're trying to sleep. One might expect, therefore, that someone with DSPS forcing himself to live on a daytime schedule might also test positive on an MSLT, since his rhythms are similarly out of sync. [and see http://www.ncbi.nlm.nih.gov/pubmed/14592363: Clinical caveat: prior sleep deprivation can affect the MSLT for days. Janjua T, et al.]

Furthermore, for someone with DSPS forcing himself to live on a daytime schedule, the earlier part of the MSLT would be performed during the patient's internal night, his body's sleep time. So the MSLT would be measuring his sleep propensity during his sleep time, not during his wake time. Probably not what's intended.

Most doctors are now aware of narcolepsy, and many sleep doctors are able to recognize it. But so many are still unaware of DSPS, or think it occurs only in teens; unaware of non-24, or think it occurs only in blind folks. So they send the patient for an MSLT, get the positive result, and diagnose narcolepsy.

It seems possible that at least some people diagnosed with narcolepsy without cataplexy may in fact have Delayed Sleep Phase Disorder as their primary disorder. Certainly the daytime sleepiness is similar, if the DSPS patient is not sleeping on his own schedule.

E. Biological Markers?

I mentioned earlier that melatonin and core body temperature follow a daily rhythm.

1. CBT phase shift [CBT Rhythm slide]

This chart shows core body temperature, but what I say applies to other cycles as well. I've shown a normal temperature cycle in green. The blue area represents sleep time on a normal sleep schedule. As you can see, core body temperature is quite low during this period.

In red I've shown the same temperature cycle shifted 6 hours later in time. This is what one would expect to see for a DSPS patient. But imagine the DSPS person trying to sleep during the normal sleep time (blue area): his body temperature is still high, his body is running full steam.

2. Why Not Use as a Diagnostic Tool?

Why Not Use Biological Markers as a Diagnostic Tool?

One reason is expense: whichever marker is being measured, has to be measured frequently over a 24 hour period. In the case of saliva melatonin the patient needs to provide saliva samples over many hours, and each sample has to be analyzed. Nevertheless, this test has been done in some cases.

Another reason is that it's easy to confound the results. Melatonin levels are affected by light exposure and activity, and even by food. Accessible body temperature such as oral measurement is affected by eating as well as activity. It really requires a standardized laboratory environment to get meaningful results.

IV. Treatment [treatments slide 1] [~32 mins to here?]

How are DSPS and Non-24 treated?

A. Sleep Hygiene

As with all sleep problems, the first step is to assure that the patient understands and follows recommended sleep hygiene [**sleep hygiene slide**]: Most of you have seen this, so I won't read it.

For people with DSPS or Non-24 this is generally not sufficient to normalize their schedule.

B. Sleeping pills (no help) [treatments slide 2]

Sleeping pills are often prescribed by GPs, but they are of little help. They may make you unconscious, but don't alter your circadian rhythm, and the resulting sleep is often not restorative.

C. Chronotherapy (risky)

Since most people with DSPS find it difficult to move their schedule earlier, the original treatment, called chronotherapy, had patients moving their schedule later instead, an hour later each day all the way around the clock until they reached their desired wake up time. Then they were supposed to stabilize. Even when successful, this treatment had a high rate of relapse and had to be repeated frequently. But for some patients, their sleep times kept progressing and wouldn't stabilize: their DSPS had become Non-24, a much more disruptive disorder. So this could be a risky treatment. [Oren DA and Wehr, TA, Hypernyctohemeral Syndrome after Chronotherapy for Delayed Sleep Phase Syndrome, (1992), http://www.nejm.org/doi/full/10.1056/NEJM199212103272417]

D. Light Therapy [Light Therapy slide 1]

1. Standard Procedure

The most common treatment for circadian rhythm disorders is light exposure. It has been shown for normal sleepers that light in the morning advances the rhythm (makes it earlier), whereas light in the evening delays it. So for both DSPS and Non-24, the light must be used in the morning. (We'll see in a moment why that has to be the patient's internal morning!) And the light has to be bright. The common recommendation is 10,000 lux for at least half an hour. That's very bright: typical room lighting in a home runs between 50 and 100 lux. Sunlight is great of course, and there are a number of light boxes now made for this purpose as well.

2. Phase response curve [PRC slide]

Treatment using light is based on the *Phase Response Curve* (PRC). This curve shows how much the circadian clock shifts in response to light exposure at different times of the day. I've shown a sample PRC, and marked some points on it just to explain what it means. The red dot, for example, tells us is

that, if that patient is exposed to bright light on awakening (about 10 hours after DLMO), his circadian cycle will shift about 15 minutes earlier. The green dot shows that exposure to the same light an hour before bedtime can shift the cycle two hours later.

Various studies have determined PRCs. The actual values depend on the light intensity, duration, color, and prior exposure. But they are qualitatively similar: light exposure early in the day advances the clock (moves it earlier), but light exposure late in the day delays it. During the night the effect changes from a delay early in the night, to an advance toward morning. The change occurs around the time of core body temperature minimum.

Note that most of these studies were done on people with normal circadian rhythm.

3. Individual Variability [Scatter in PRC data slide]

I also want to emphasize the individual variability. For example, the red dot in the previous slide and this one is the result of curve fitting primarily to data from four individuals, shown inside the green oval. One of them showed a delay of about half an hour, one had no change, and two showed advances of about an hour. That's what gave rise to the average 15 minute advance. So please, don't expect your patient's response to lie right on the curve!

4. Timing Issue when starting therapy [Light Therapy slide 2]

So there's an often overlooked wrinkle in prescribing light therapy: the patient's clock may initially be considerably delayed. Even if he is forcing himself up at 7am to get to his job, his internal time may have his body thinking that "night" is from 5am to 1pm, with a temperature minimum at say 10am. But if the patient is told to use the lights immediately on arising, he is being told to use the lights BEFORE his temperature minimum, when they will cause his schedule to be delayed further. Not what we want.

There is little data on how to proceed. Some doctors and many of our members believe it is necessary to determine one's natural wake up time, and to start by using the lights at that time. One can then move the lights earlier, perhaps by 15 minutes every few days, until reaching the desired wake up time. It may also be necessary to avoid light exposure before one's current temperature minimum, if one is getting up then for work.

For non-24, of course, one can simply wait until the patient's internal schedule comes around and coincides with the desired schedule, and then start the treatment to keep it from shifting further.

Light treatment cannot start independently of the patient's current internal schedule.

5. How Fast to Shift

How Fast to Shift ? There seems to be a lot of variation in how fast patients are told to shift their schedule. Some of our members were told to shift immediately to their desired wake up time. Others were told to shift half an hour a day. Many of us believe from personal experience that shifting may occur more slowly, and there is some research that supports that. [Akash, M, Soma, H, Yamamoto, T, et al, Noninvasive method for assessing the human circadian clock using hair follicle cells, http://www.pnas.org/content/107/35/15643.full]

6. Success Rate

Some people are helped by light therapy. Others, not so much. One study documents success rates of 42% for DSPS patients, 32% for Non-24. Obviously this depends on the details of the intervention. I'll talk more about this later. [Yamadera H, Takahashi K, Okawa M, A multicenter study of sleep-wake rhythm disorders: therapeutic effects of vitamin B12, bright light therapy, chronotherapy and hypnotics, (1996), http://www.ncbi.nlm.nih.gov/pubmed/9201777]

E. Light Restriction ("Dark Therapy") [treatments slide 3]

Recent research indicates that even low levels of light in the evening can delay the clock. In other words, it takes a really bright light in the morning to advance the clock, but only moderate light in the evening to delay it. Blue light has a particularly strong effect. It is thought that the bluish light from TV, computers, and phones may be delaying the rhythms even of normal sleepers.

So some patients are now trying to restrict light in the evening, including using blue-blocking glasses, and have reported some success with shifting their schedule this way. But there are no standards yet regarding how much light is tolerable, how early the restriction should start, and whether light without blue content is ok to use during dark time.

F. Melatonin

Melatonin is also used to treat circadian rhythm disorders.

1. Phase Response Curve [Phase Response Curve for Melatonin slide]

Researchers have developed a Phase Response Curve for melatonin (heavy curve on the slide). Qualitatively it is the opposite of the PRC for light: melatonin in the morning delays the body clock, in the evening it advances it (makes it earlier).

2. Hypnotic vs Chronobiotic

Melatonin has been used to treat circadian rhythm disorders in two ways, which unfortunately get confused. Some people take it shortly before bedtime, and it helps them fall asleep [hypnotic]. This is indicated by the green dot. Others take it 4 – 6 hours before bedtime. Used in this way, it can help advance their rhythm [chronobiotic]. Red dot. But it can also make them sleepy too early.

3. In the Blind

Melatonin seems especially useful for blind people, since they don't have the option of using bright light in the morning. Several pharmaceutical companies have developed melatonin agonists as an alternative to melatonin itself. A new one has recently received FDA approval.

4. Dosing Issues

There is evidence that the same dose of melatonin, in different individuals, results in as much as 35-fold variation in serum concentration! So the same pill in one person causes blood levels 35 times higher than in another person. Yet some doctors attempt treatment with one dose, and abandon melatonin treatment if that fails. [Aldhous M, Franey C, Wright J, and Arendt J, Plasma concentrations of melatonin in man following oral absorption of different preparations, (1985), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1463812/?page=3; Waldhauser F, Waldhauser M,

Lieberman HR, et al, Bioavailability of oral melatonin in humans, (1984), http://www.ncbi.nlm.nih.gov/pubmed/6493445]

One paper, about a blind patient, documents the failure of a 3mg dose, but success with 0.5mg. The authors conjecture that this may be because too much melatonin remained in his blood by morning, where it again delayed his body clock. [Lewy AJ, Emens JS, Sack RL, Hasler BP, Bernert RA, Low, but not high, doses of melatonin entrained a free-running blind person with a long circadian period, (2002), http://www.ncbi.nlm.nih.gov/pubmed?term=12069043]

We suspect that elimination times may vary among individuals as well.

G. Reasons for Failure [slide]

I have read the personal stories of many people with DSPS or Non-24 who have tried, for long periods of time and at great personal distress, to follow their doctor's treatment prescriptions, but the treatment failed. It failed in that the patients complained of increasing tiredness, decreasing ability to function normally in their lives, even illness. In less severe cases, the reports were of lack of alertness, memory difficulties, or feelings of being dissociated from life.

1. Why do treatments fail?

Why do treatments fail? Many research studies which conclude that the patients have reset their clocks measure DLMO and/or CBT, but don't measure sleep quality, daytime performance, or subjective well-being.

Some patients complain that they still don't feel rested after sleeping on the new schedule after treatment. For this reason they may choose not to continue treatment, so the "low compliance" often cited in the literature may be due to this lack of subjective improvement. To put it bluntly, I don’t care if my DLMO has shifted, if my head is still in a fog all day.

Research on shift work disorder in otherwise normal sleepers is often used as the basis for treating DSPS patients. But some DSPS patients may have underlying impairments, for example insensitivity to the phase resetting effects of light, that make the research results inapplicable.

There are other reasons as well. I don’t have time to go into them.

Most studies of interventions for CRSDs are completed in a matter of weeks, and report on success or failure in shifting the subjects' schedules. But in practical terms, a treatment is successful only if the patient continues to be able to follow the prescribed schedule, over years. This is not always the case.

There are other body rhythms, in addition to DLMO and CBT, including alertness, digestion, cortisol, thyroid, libido, etc. Perhaps they don't all shift in sync - in jet lag, for a related example, it is believed that the various rhythms get out of sync resulting in considerable discomfort to the patient.

There is also evidence that sleep deprivation reduces the effectiveness of light therapy. [Burgess, HJ, Partial sleep deprivation reduces phase advances to light in humans, (2010), http://www.ncbi.nlm.nih.gov/pubmed/21135162]

2. Partial Success?

There can also be partial success to treatment: I've seen anecdotal reports of DSPS people who say they have successfully shifted their schedule an hour or two earlier, but say they cannot maintain a larger shift.

In a similar vein, it has also been suggested that some sighted non-24 people, even if they cannot entrain to a 24-hour schedule with an early wake-up time, might be able to entrain to a 24-hour schedule later in the day. Their schedule would then look like a DSPS person's.

H. The Myth of the Good Night's Sleep [Myth slide]

I want to touch on another misconception. When you read in the journals about Circadian Rhythm Sleep Disorders, you often read that if permitted to sleep during our bodies' preferred times, our sleep would be fine, and we would awaken alert and refreshed. But for many of us this is not the case. Even when we sleep on our bodies' preferred schedule, we may not sleep well, we may awaken often during the night, and we may feel tired and even dysfunctional in the morning.

I hear this also from friends with narcolepsy and sleep apnea: the treatments help, but they still struggle, they still feel tired, they still need naps.

It seems to be a common theme with many of these sleep disorders, that even with treatment, we're still tired, we still struggle. Clearly, there is a lot we still don't understand.

1. Circadian rhythm amplitude [slide – CBT 3 line]

One thought occurs to me: in this talk we have focused on the phase of the circadian rhythm, that is, its timing. But like all such cyclical rhythms, it has amplitude as well as phase – amplitude referring to how strong the cycle is. I've shown this CBT slide earlier, with two lines. The green is a normal temperature rhythm, while the red has its phase (its timing) shifted six hours later. Here I've added an aqua line, which has the timing of a normal rhythm but with smaller amplitude. That means less variation in core body temperature between day and night.

It's not hard to imagine that someone with such a reduced amplitude circadian rhythm might not sleep as soundly at night, nor be as alert and energetic during the day. I've not had a chance to look into this further.

V. Research issues [slide]

I want to quickly mention several areas where more research is urgently needed.

A. Tailoring treatment to cause

Earlier we mentioned several possible causes for these disorders. The studies of treatments done to date do not distinguish between these various causes.

I would conjecture, for example, that for people who are not sensitive enough to light, very bright light in the morning is what works. For those overly sensitive to light, light restriction in the evening is key.

Without distinguishing the underlying cause, the success rate of a given treatment is bound to be low, because it is successful only on some of the causes.

We need research into the specific underlying causes of circadian rhythm disorders, and into tailoring the various treatments to the underlying causes.

B. Therapy parameters

We need more specific guidance on therapy parameters – what time should light be used? What time should dark therapy commence? How bright (and what color) should the lights be? And so forth.

We need these parameters to be determined by studying patients with these disorders, not just normal sleepers.

We need data on how often treatment succeeds in practice, including the combination of light and dark therapy, which may be more promising than either alone. Success to us is not only laboratory measurements (e.g. shifts in melatonin timing), but subjective improvement. These don't always correlate.

Can light therapy harm eyesight? In particular, there is controversy over whether bright light containing blue may contribute to macular degeneration later in life.

C. Better tests for easier diagnosis

We need simpler and cheaper tests to measure the biological markers.

We need insurance coverage for these tests.

We'd all really love an objective measure of tiredness - a simple test that objectively measures impairment due to poor sleep.

D. Incidence

Our estimates of how often these disorders occur are based on very limited research. Some researchers believe we greatly underestimate the prevalence. We need better surveys, which must involve careful diagnosis.

E. Comorbidities

People who suffer from Circadian Rhythm Sleep Disorders often seem to have other conditions as well, such as fibromyalgia, chronic fatigue syndrome, depression, ADHD, etc. It has been suggested that years of sleep deprivation, from trying to live on a normal schedule with a broken clock, may lead to these conditions. More work needs to be done to investigate possible connections.

VI. Circadian Sleep Disorders Network

A. Need [mission slide]

Most people have not heard of DSPS or Non-24. Our friends and families did not believe these were real disorders. Even sleep specialists often did not recognize the disorders, or believed that they were easily treatable. Patients could not get accommodations at work or school.

We needed an organization to raise awareness. Three years ago we formed Circadian Sleep Disorders Network. This is our mission statement.

B. Web site and brochure

We have a web site with extensive information and links at csd-hyphen-n.org. ***And don't forget the hyphen***, or you'll get the Chinese Software Development Network!

We have several brochures, both printed and on our web site. Some are on display here at the conference, you can pick up a copy, or see me in person.

C. Closing thought

I'd like to close with this analogy: You wouldn't say to a blind person "My eyes can see, therefore yours must be able to see also." Similarly, you can't say, "My eyes can entrain my sleep, therefore yours must be able to entrain also."

D. Thank you [slide]

Thank you.

Please visit our web site at csd-hyphen-n.org