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Frederico Miguel Cruz Martins  
Non-Pharmacological Treatments  
Targeting Circadian Rhythms In  
Bipolar Disorder

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Non-Pharmacological Treatments Targeting Circadian Rhythms in Bipolar Disorder

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## RESUMO

A perturbação afetiva bipolar é uma das doenças mais debilitantes do espectro psiquiátrico e continua a ser uma das mais difíceis de tratar.

Pensa-se agora que os ritmos circadianos têm um importante papel na patofisiologia da perturbação afetiva bipolar e foi demonstrado que estes se encontram alterados não só nas fases depressivas e maníacas da doença mas também quando os pacientes estão numa fase dita eutímica.

O objetivo desta revisão é proporcionar uma visão geral dos atuais tratamentos não farmacológicos da doença afetiva bipolar direcionados aos ritmos circadianos. Estes são divididos em dois grupos: o primeiro grupo são cronoterapias, que são tratamentos que se baseiam em exposições controladas a estímulos ambientais que têm a capacidade de alterar os ritmos circadianos. Estas incluem: privação do sono, fototerapia, antecipação do início do sono e terapia do escuro. O segundo grupo é uma psicoterapia que tem como objetivo a regulação de ritmos sociais chamada de Terapia dos Ritmos Interpessoais e Sociais.

Os tratamentos aqui descritos têm como objetivo restaurar o balanço dos ritmos circadianos e revestem-se de importância pois aparentam atuar mais rápido e com menos efeitos laterais do que os tratamentos farmacológicos disponíveis atualmente, podendo assim ser a chave para tratar sintomas depressivos e maníacos rapidamente após a sua manifestação.

Palavras-Chave: Perturbação Afetiva Bipolar, Privação do Sono, Fototerapia, Antecipação do Início do Sono, Terapia do Escuro, Terapia dos Ritmos Interpessoais e Sociais

## **ABSTRACT**

Bipolar disorder is one of the most debilitating illnesses within the psychiatric spectrum and remains one of the most difficult to treat.

Circadian rhythms are now thought to play an important role in the pathophysiology of bipolar disorder and it has been shown that they are altered not only during major depressive and manic phases of the disorder but also when patients are said to be euthymic.

The aim of this review is to give an overview of the current non-pharmacological treatments of bipolar disorder which target circadian rhythms. These are divided into two groups: the first group is chronotherapeutics which are controlled exposures to environmental stimuli which alter circadian rhythms. These include: sleep deprivation, bright light therapy, sleep phase advance and dark therapy. The second group, Interpersonal and Social Rhythm Therapy, is a psychotherapy aimed at regulating social rhythms.

The treatments described herein aim to restore balance to circadian rhythms and, importantly, they seem to act faster, and with fewer side-effects, than current pharmacological treatments and could be the key to treat depressive and manic symptoms as soon as they appear.

**Keywords:** Bipolar Disorder; Sleep Deprivation; Bright Light Therapy; Sleep Phase Advance; Dark Therapy; IPSRT.

## INTRODUCTION

### *Bipolar Disorder*

Bipolar disorder is one of the most debilitating illnesses of the psychiatric spectrum and, according to a World Health Organization report, it is the sixth leading cause of disability among all diseases [1].

Bipolar disorder can be divided in two main subtypes: bipolar disorder type 1 in which patients have major depressive and manic episodes (or a mixed episode) and bipolar disorder type 2 in which patients have major depressive episodes and hypomanic episodes. Patients can also experience a subtype called rapid-cycling in which they have at least four acute mood episodes within a year. Finally, when patients have subsyndromal manic or depressive episodes but do not meet the criteria for a major episode, they are diagnosed with cyclothymic disorder [2].

When all subtypes are taken into account the prevalence of the disorder is 4.4% in the world population. However, this data is underestimated since misdiagnosis is common (ranging from 30% to 69% in Europe and USA) [3].

Unlike the name suggests, most patients do not swing between a full blown manic episode to a major depressive episode with periods of euthymia in between. Rather, patients are now thought to have a more subtle chronic course with impairments in emotions, sleep pattern, circadian rhythms and cognition even during euthymic phases as well as a high risk for medical comorbidities [3].

Importantly, a lot of times, between episodes, patients are not euthymic but rather have subsyndromal symptoms which are risk factors for relapse to a major episode [3]. Strikingly, a study with 146 bipolar type 1 patients, spanning 3 years, concluded that patients are symptomatic 47.3% of the time thus highlighting the need for attention not only during major acute mood episodes but also in the periods between them [4].

Recently, bipolar disorder has been characterized not only as a mental disorder but also as a multisystemic illness. Despite up to 75% of the patients having at least one other psychiatric illness, most premature deaths are due to cardiovascular and cerebrovascular events which occur, in bipolar patients, twice as much as in the general

population [3]. This is thought to be due to an increase in risk factors with high prevalence among bipolar patients such as smoking (up to 70% of patients), alcoholism, poor diet and a sedentary lifestyle. However, other factors intrinsic to the disease itself, such as disruption in neuronal and hormonal systems and an increase in the expression of pro-inflammatory cytokines, may also contribute to an increase in cardiovascular risk [3].

### *Circadian Rhythms*

A zeitgeber is a cue that entrains (synchronizes) the biological rhythms to the 24 hour light/dark cycle and the yearly 12 month cycle. The social zeitgeber theory says that stressful life events lead to disruptions in the sleep patterns which then lead to alterations in circadian rhythms. These changes, in susceptible individuals, can lead to profound changes in mood which, in bipolar disorder, ultimately lead to acute depressive and manic episodes. Moreover, television, computers, traveling and some work patterns all have the power to disrupt circadian rhythms and thus be deleterious to susceptible individuals [5].

Sleep disturbances are a hallmark of bipolar disorder and an important bridge between bipolar disorder and circadian rhythms is the sleep pattern. Measurements made using polysomnography and actigraphy showed that bipolar patients have abnormal qualitative and quantitative sleep not only during acute mood episodes but also when they are euthymic. Sleep patterns in bipolar patients show reduced Rapid Eye Movement (REM) latency, increased REM density, prolonged slow wave latency and poor sleep continuity. It has also been shown that bipolar patients are of the “evening type” (preference for waking up late and sleeping late) [6] and that “evening type” people are more likely to develop depression than “morning type” people [7]. Sleep is controlled by two processes, Process S and Process C. Process S is sleep pressure which builds throughout the day, as one gets tired, and dissipates after a night's sleep. Process C is controlled by the circadian clock which is controlled by zeitgebers, with being light the most important [8].

The suprachiasmatic nucleus (SCN) is the main circadian regulator and receives input from three main sources: the retinohypothalamic tract (RHT), the geniculohypothalamic (GHT) tract and the dorsal and median raphe nuclei.

The retina contains non image forming photosensitive retinal ganglion cells which express melanopsin which highly sensitive to blue wavelength light [8, 9]. These cells send information to the SCN via the RHT. The molecules involved in this pathway include Glutamate and Pituitary Adenylate Cyclase Activating Protein (PACAP). This signaling leads to the expression of clock genes. Another input signal is influx of  $Ca^{2+}$  which is modulated by activity in the inositol triphosphate receptor and in the ryanidine receptor. The RHT also projects to the intergeniculate leaflets (IGL). The IGL projects to the SCN via the GHT tract thus also, indirectly, relaying photic information. The neurotransmitters involved in this process are neuropeptide Y (NPY) and gamma aminobutyric acid (GABA). The IGL also receives non photic input from the dorsal raphe nucleus in a process involving the neurotransmitter serotonin (5HT). Finally, both dorsal and median raphe nucleus send non-photoc information, via 5HT, to the SCN. Importantly, through the autonomic nervous system, SCN controls pineal and adrenal cortex function and thus the release of hormones [10].

Circadian clocks of peripheral tissues can work independently from the SCN, as evidenced in mice with lesions at the levels of the SCN that maintain rhythmicity in the peripheral tissues. However, the SCN is key in synchronizing the peripheral clocks thus acting as a type of zeitgeber (peripheral clocks work without the SCN but do not synchronize properly without it) [10].

The primary zeitgeber to SCN is light whereas the zeitgebers sent by SCN include body temperature and feeding cycles (and the hormones released during them). The SCN also sends direct humoral and sympathetic signals to the peripheral organs [10]. Moreover, resistance to temperature entrainment has been shown to be a property of the SCN. This way, the SCN is able to regulate circadian rhythms in body temperature which then act as cue for the entrainment of the peripheral clocks [11].

The main molecular mechanism controlling the circadian clock is a negative feedback loop: transcription factors lead to the upregulation of clock genes which, in turn, inhibit the transcription factors. Brain and Muscle Arnt-like Protein (BMAL1/2) dimerizes with Circadian Locomotor Output Cycles Kaput (CLOCK) or Neuronal PAS Domain Containing Protein 2 (NPAS2) which leads to the transcription of Period (Per1-3) and Cryptochrome (Cry 1/2). Per and Cry form complexes in the cytoplasm. When the complex migrates to the nucleus it inhibits transcription of CLOCK and BMAL. The

complex is then degraded, in the proteasome, by casein kinase I $\epsilon$  (CKI $\epsilon$ ) [12]. There are many other points of control although, this is beyond the scope of this review.

### *Chronotherapeutics and Interpersonal and Social Rhythm Therapy*

In attempting to control depressive symptoms, the usage of antidepressants has tripled in the last 15 years. However, pharmacotherapy alone is clearly not enough as only about one third of the patients achieve remission [5]. Moreover, the response to pharmacological treatments is still not fast enough and a fast onset of action, which is provided by chronotherapeutics, is crucial during mood episodes, especially in individuals with suicide ideation [8].

Chronotherapeutics are controlled exposures to environmental stimuli which influence circadian rhythms and are now thought to be a worthy tool in the treatment of bipolar disorder. It is especially useful in enhancing treatment protocols that include pharmacotherapy. The response to chronotherapeutics in acute episodes ranges from 2/3 to 3/4 of patients which is a rate similar to those reported for pharmacological treatments. Moreover they have been proven useful in the treatment of patients who are resistant to pharmacological treatment. Importantly, the rate of switch to mania is less common with chronotherapeutics than it is with drugs [13] and side-effects are usually minimal.

One of the most commonly used chronotherapeutic protocols is a combination of three techniques: sleep deprivation, bright light therapy and sleep phase advance – triple chronotherapy (there are many variations to this protocol and thus these are described in more detailed in the results section). These are used in the treatment of acute depressive episodes. The treatment of manic phases using chronotherapeutics is not as widely studied as treatment of depressive episodes, however, dark therapy is a promising technique with great results in some patients.

Finally, Interpersonal and Social Rhythm Therapy (IPSRT), which was developed by a group led by Ellen Frank [14], is a type of psychotherapy which is specifically aimed at regulating social rhythms which in turn, according to the social zeitgeber theory, will lead to a regulation of circadian rhythms and thus an amelioration in the control of bipolar disorder.

The basic protocol of IPSRT starts by having patients using a charting instrument called the Social Rhythm Metric (SRM) where they record the time at which they get out of bed, make the first contact with another person, start work, have dinner and go to bed. Then, patients and clinicians work out the factors that might disrupt the daily routines. Afterwards, they both decide which area, of the four main interpersonal problem areas described by Klerman et al in 1984, namely unresolved grief, role transitions, role disputes and interpersonal deficits, the work should be focused in [14]. The basic protocol of IPSRT has four phases [14]. The first phase (3 to 5 sessions) consists of: collecting a detailed history of the patient in order to try to establish links between mood swings, social rhythms and interpersonal issues; educating the patient and his family about bipolar disorder and about triggers that might affect the mood; studying the nature of the patient's relationships, a process referred to as "Interpersonal Inventory"; evaluating social routines by studying the patient's SRM; and establishing which of the four interpersonal problem areas is most important to the patient. The second phase (typically 10-12 weekly sessions) aims to help the patient to establish regular social routines and to resolve the interpersonal problem chosen in the first phase. The third phase (starting with weekly then biweekly and then monthly sessions for an undetermined amount of time) has the objective to build up the patient's confidence to deal with events that might disrupt the social rhythms established in phase two. This is done using several techniques which include communication analysis, decision analysis and role-play. The final phase (usually 3 to 5 monthly sessions) aims to prepare the patient for the termination of the therapy. In some cases it might be better not to completely terminate the treatment but rather to decrease the frequency to occasional sessions when needed by the patient.

### Objective

The aim of this review is to give an overview of the current non-pharmacological treatments of bipolar disorder which target circadian rhythms. These are divided into two groups: the first is chronotherapeutics which include sleep deprivation, bright light therapy, sleep phase advance and dark therapy, the second group is a psychotherapy that aims to regulate social rhythms called IPSRT.

## METHODS

The following query was used in NCBI PubMed database: “(Bipolar Disorder) AND (Bright Light OR Dark Therapy OR Extended Bed Rest OR IPSRT OR Sleep Deprivation OR Sleep Phase Advance OR Chronotherapy OR Chronotherapeutics)”, with restrictions to the last 10 years, full text available in English and research using Humans.

The query yielded 97 results. From these 56 were excluded upon reading the title and abstract.

From the 41 articles remaining 19 reviews were excluded upon reading the full text.

The 22 articles used included 4 reviews and 18 original articles.

Upon reading these 22 articles and based on their references 9 other original articles were included.

Also included are 1 textbook and 10 reviews, found in subsequent searches on PubMed, using the following keywords “*bipolar disorder*”, “*circadian rhythm*”, “*twenty-four hour rhythm*”, “*circadian clock*”, “*bright light*”, “*dark therapy*”, “*extended bed rest*”, “*sleep deprivation*”, “*sleep phase advance*”, “*IPSRT*”, “*Interpersonal and Social Rhythm Therapy*”; “*chronotherapeutics*” and “*chronotherapy*”, which were important in understanding the topic.

## RESULTS

### *A) Chronotherapy*

#### *A1) Sleep Deprivation, Bright Light Therapy and Sleep Phase Advance*

Various protocols have been tested using chronotherapy in bipolar disorder.

Benedetti et al. treated 60 inpatients with a major depressive episode in the course of bipolar disorder type 1 (Hamilton Rating Scale for Depression (HRS-D) score of at least 18) with the following chronotherapy protocol [15]:

They divided the patients in three groups: in group 1 (n=33) patients had no history of drug resistance, in group 2 (n=10) patients had stage I resistance (“failure of at least one trial of one major class of antidepressant”) and group 3 (n=17) had stage II or II+ resistance (“stage I resistance plus failure of an adequate trial of at least one antidepressant in a distinctly different class from that used in stage I”).

The treatment protocol was as follows. On days 1, 3 and 5 patients were sleep deprived from 7am until 7pm on the following day; on days 2, 4 and 6 they were allowed to sleep. Patients were also administered 30 minutes of 400 lux green light every morning. Two measures of mood were used: HRS-D and the self-reported Visual Analog Scale (VAS). The response was defined as a 50% reduction in HRS-D scores between day 1 and 7. For patients who responded the follow up was 9 months (weekly during the first month and monthly from months 2 to 9).

In the first group 70% achieved a response and 39% maintained it during the 9 months of follow-up, whereas in the second and third group only 44% achieved a response and only 7% maintained it during the 9 months of follow up. Patients who achieved a response also showed an increase in the VAS scores.

The same research team treated 19 inpatients with a major depressive episode in the course of bipolar disorder type 1 (HRS-D score of at least 18) [16], using the same protocol as above [15]. The scales used were HRS-D and VAS. Once again this treatment lead to significant decreases in the HRS-D scale and significant increases in the VAS

scale thus pointing once more towards the antidepressant efficacy of the protocol. Moreover, using single proton magnetic resonance spectroscopy (1H-MRS) they were able to demonstrate that the brain “glutamine plus glutamine with GABA contamination” (Glx)/creatine ratio followed a trend towards decrease and that this decrease significantly correlated with improvement in both HRS-D and VAS scales

The same protocol [15] was used to treat 39 bipolar disorder type 1 patients, 13 of which had a history of drug resistance, currently in a depressive episode [17]. The scores used were HRS-D and VAS. Response criteria was a 50% reduction in HRS-D on day 7. Two thirds of the patients responded. This response was marginally higher in patients with no history of drug resistance. Interestingly, at day 7, patients who responded to the treatment had higher activity levels, especially in the morning. The treatment also induced changes in sleep patterns with responders sleeping less during the recovery nights and at the end of the treatment.

Finally, Benedetti’s team has also studied the effects of chronotherapy on suicidality [18]. In this study 143 bipolar patients currently in a major depressive episode (HRS-D score of at least 18) were treated with a chronotherapy protocol similar to the studies described above [15] except bright light therapy (BLT) was switched to 1000 lux of white light. The scales used were the HRS-D and the Beck Depression Inventory (BDI), for self-perceived depression. The criterion for suicidality was having at least one documented suicide attempt and current suicidality was rated according to the corresponding item in HRS-D. Response was defined as a 50% reduction in the HRS-D score.

Of the 143 patients, 141 completed the treatment. From these, 99 patients responded to the treatment with HRS-D scores decreasing significantly. Interestingly, the response was not influenced by a positive history of suicide attempts. Importantly, a subgroup of 16 patients who reported current suicidal thinking or planning also showed a significant decrease in HRS-D, although, scores on the suicide item did not decrease for any of them. BDI scores correlated with HRS-D scores. Patients with ongoing lithium treatment had better improvements after the first night of sleep deprivation however, final scores were similar to those of patients with newly started lithium treatment. Responders to the treatment were continued on lithium treatment for another month. Out of the 99 responders 21 showed signs of relapse and were administered antidepressant treatment

while the other 78 continued in remission with lithium monotherapy. Considering the results of the research 55.3% of the patients responded positively to the combination of chronotherapy and lithium.

A team led by Wu developed a slightly different protocol for triple chronotherapy and designed a randomized trial to test it [19]. In this study 49 bipolar disorder patients currently in a depressive episode (HRS-D of at least 18) were randomly assigned to either a medication only group (n=17) or a triple chronotherapy plus medication group (n=32). The triple chronotherapy procedure was as follows: 1 night of sleep deprivation in which patients were kept awake from 9am to 6pm on the following day followed by 3 days of BLT with 5000 lux for 2 hours in the 3 consecutive mornings following the night of sleep deprivation and 3 nights of sleep phase advance in the first evening following sleep deprivation. In the first night patients would sleep from 6pm to 1am, on the second from 8pm to 3am and on the third from 10pm to 5am. The follow up period was 7 weeks with assessments every day on the first week following sleep deprivation and weekly assessments from weeks 2 to 7.

The criteria for response was a decrease of 50% in the HRS-D score compared to baseline and the remission criteria included the response criteria plus an HRS-D score of less than 7 at the end of the seventh week. Patients in the triple chronotherapy group showed a significant decrease in HRS-D scores at all time points (except at day 7). Importantly, at week 7, 12 of the 19 responders in the triple chronotherapy group achieved criteria for remission. Side-effects of triple chronotherapy were rare with only a brief hypomanic switch in 2 of the patients (which resolved within 24 hours without additional measures).

A study of triple chronotherapy in drug-resistant patients was also conducted [20]. In this study 13 patients in a major depressive episode with a score on HRS-D of at least 15 (10 with major depressive disorder and 3 with bipolar disorder) were treated with the following protocol of triple chronotherapy: 1 night of sleep deprivation (6am to 5pm) followed by 3 consecutive nights of sleep phase advance and 5 mornings of BLT (5000 lux for 2h upon waking). The follow up then lasted 20 days. The measures used were HRS-D, VAS and Zung Self Rating Depression Scale (ZSRDS). The therapy resulted in

a decrease in HRS-D score. Concerning the subjective mood ratings the ZSRDS score decreased significantly and the VAS scores increased significantly.

The effects of chronotherapy in cognition have also been studied [21]. One study included 100 healthy controls and 100 bipolar disorder type 1 patients in a depressive episode. To a subset of 42 of these 100 patients the following protocol was applied: 3 cycles of total sleep deprivation, in alternating days, with each cycle lasting 36h. They were also treated with exposure to 10000 lux bright white light for 30 minutes at 3am during the sleep deprivation night and 30 minutes after awakening from the nights of recovery sleep. The scales used were the HRS-D and the Brief Assessment of Cognition in Schizophrenia (BACS). Concerning depression, the remission criteria was a score of less than 8 in the HRS-D at day 7. The treatment resulted in a significant decrease in HRS-D scores and, importantly, 31 of the 42 patients had criteria for full remission. Concerning cognitive function 6 domains of BACS were studied: verbal memory, working memory, psychomotor memory, psychomotor coordination, verbal fluency, selective attention and executive functions. Bipolar patients showed deficits in all 6 domains when compared to healthy controls. Despite the antidepressant effects of the treatment, in regards to cognitive function only for the domain of selective attention (symbol coding) were there significant differences between pre and post treatment assessments.

Bright light therapy has also been studied separated from sleep deprivation. One trial treated bipolar disorder patients with either BLT, low-density (LDNI), or high-density (HDNI) negative air ionization [22]. In this trial 44 patients were studied all of which met DSM-IV criteria for Bipolar Disorder type 1 or 2 and were currently in a depressive episode for at least 1 month with a score of at least 20 in the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS). Response was defined as a decrease in the SIGH-ADS score of 50% or more from baseline and remission was defined as a score of 8 or less on SIGH-ADS at end point (follow up of 16 weeks). Patients were randomly assigned: 18 to BLT, 20 to LDNI and 6 to HDNI. This last group was used to evaluate possible benefits of high density negative air ionization.

The protocol consisted of 3 phases: the first was screening and stabilization (0-31 days), the second was treatment (8 weeks) and the third was follow up (8 weeks). Treatment started with 7.5 minutes upon waking each morning, and after 3 days, if it was safe it would be increased to 15 minutes. Each week the duration could be increased 15 minutes (in 7.5 minutes increments) to a maximum of 45 minutes. If any signs of hypomania were detected the treatment was reverted to 7.5 minutes/day for the rest of the week or withdrawn until symptoms were resolved and then reinstated.

23 subjects completed the study (10 in the BLT, 11 in the LDNI and 2 in the HDNI). At end point there were no statistically significant differences when comparing the response to bright light treatment and to low density negative air ions. There were also no statistically significant differences in regards to side effects measured by the Systematic Assessment for Treatment Emergent Effects (SAFTEE) score. Assessments regarding the high density negative air ionization were not possible to be made due to the fact that there were only 2 completers.

The use of chronotherapeutics has also been described in case reports:

A case report study on the efficacy of bright light therapy included 9 women with bipolar disorder type 1 or type 2 in the depressive phase [23]. Patients had a SIGH-ADS score of 20 or more and Mania Rating Scale (MRS) score of less than 12. The study lasted for 8 weeks and was divided into 4 time periods (lasting 2 weeks each). The follow up phase lasted 12 weeks.

In the first 2 weeks patients were administered a placebo of 70 lux morning dim red light for 30 minutes daily. During the placebo period women showed mild improvements in the SIGH-ADS score. In the second to fourth 2 week time periods active light dose (7000 lux) was administered (starting with 15 minutes daily with 15 minutes increments every time period, until a maximum of 45 minutes). Treatment response was defined as an improvement in the SIGH-ADS scores of at least 50% compared to baseline.

Two slightly different protocols were applied: the first 4 women received morning light therapy. One of them responded with 30 min of daily exposure whereas the other 3 developed mixed states with 2 requiring immediate cessation and the other eventually withdrawing. The second group of 5 women was started with midday light exposure. In

this group 2 women experienced a full response, 1 responded partially but then achieved full response by being switched to morning exposure and the other 2 showed “unsustained” responses. At the end of the study 4 patients were full responders and 2 patients were partial responders.

Another case study used a triple chronotherapy approach with good results in a 20 year old female bipolar disorder outpatient [24]. The protocol for the chronotherapy was similar to the one described by Wu and colleagues [19]. The SIGH-ADS scale was used to assess results. The patient score before the treatment was 29 and the post-treatment score was 2. To stabilize her circadian rhythms the patient was then kept on 30 minutes of bright light each morning and 0,2mg melatonin each evening. With this treatment full remission of depressive symptoms lasted for 6 months until the patient decided to stop bright light therapy against medical advice.

Understandably, staying awake for an entire night is not easy for some people. One case report has been written on how modafinil, a wakefulness promoting agent, might be associated with sleep deprivation treatment in order to make it more bearable [25]. In this case report, a 70 year old, male, bipolar inpatient in a severe depressive phase was treated with 4 partial sleep deprivation (PSD) (awakening at 2am) nights over 2 weeks (twice each week). Measurements were made using the HRS-D and the VAS. PSD had already been tried in this patient with good results but, despite the patient considering it the best treatment for him, he was unable to carry it out due to exhaustion. At admission the HRS-D score was 27 and after the last PSD night it was 3. Moreover, VAS score also improved after PSD. The effects were long lasting as the patient remained euthymic after 12 weeks of follow-up.

#### *A2) Dark Therapy*

Two case studies of dark therapy [26, 27] in rapid cycling bipolar patients triggered the hypothesis that the therapy might be useful in treating bipolar disorder. In the first study [26] the patient was asked to remain in bed rest for 14 hours each night (later reduced 10 hours) with the effects on mood being self-recorded twice a day and studied by an observer once a week. The study spanned several years in which the patient's mood and sleep patterns stabilized when he adhered to the regimen. In the second [27] a patient with a refractory rapid cycling bipolar disorder was treated with a 10 hour

dark period along with daytime light therapy with the rapid cycling stopping almost immediately following the initiation of the therapy and mood gradually improving.

In the first clinical trial of dark therapy [28], 32 patients in a manic episode were divided into 2 groups: one of the groups was treated with pharmacotherapy alone and the other group was treated with pharmacotherapy and dark therapy which consisted on a 14 hour period of enforced darkness during 3 consecutive days. The severity of mania was assessed using the Young Mania Rating Scale (YMRS). Patients in a manic episode for more than 2 weeks showed little benefits but patients in a manic episode for less than 2 weeks showed a 50% reduction in YMRS. Moreover these patients were discharged on average 8.9 days earlier than patients receiving pharmacological treatment alone.

Ensuring complete darkness is a difficult task. A group of researchers hypothesized that the use of amber tinted safety glasses that block blue wavelength light (the wavelength to which retinal ganglions, responsible for regulating circadian rhythm, respond to) would create a “virtual darkness” and thus could be used in a protocol for dark therapy [29]. In this case series, 19 bipolar disorder outpatients with evidence of circadian rhythm disruption, such as fragmented sleep and insomnia, were given amber tinted glasses to use after 8pm. 9 of them said their insomnia was “very much improved”, 1 said it “much improved” and 1 said it “slightly improved”, whereas 8 did not respond.

#### *B) Interpersonal and Social Rhythm Therapy (IPSRT)*

The team that developed the procedure conducted a trial comparing intensive clinical management (ICM, a therapy focusing on understanding bipolar disorder and medication side effects) with IPSRT [30]. In this trial 175 patients, recruited during either during a manic episode (score of 15 or more in the Bech-Rafaelsen Mania Scale (BRMS)) or a depressive episode (score of 15 or more in the HRS-D), were randomly assigned to one of four treatment strategies: acute and maintenance IPSRT, acute and maintenance ICM, acute IPSRT and maintenance ICM, and acute ICM and maintenance IPSRT. The two major outcomes studied were time to stabilization in the acute phase and time to recurrence in the maintenance phase. The two-year outcomes were reported.

There was no difference in time to stabilization between IPSRT and ICM and there were also no differences in the percentage achieving stabilization (70% with IPSRT vs

72% with ICM). The maintenance treatment assigned had no impact on the time to recurrence. However, patients assigned to acute IPSRT survived longer without a recurrence during the maintenance phase, independently from the maintenance treatment assigned. This was true even after controlling for parameters that had positive effects (which lead to longer time to recurrence) such as marital status and lack of medical and psychiatric comorbidities. Moreover, a higher SRM score at remission was predictive of lower probability of recurrence during the maintenance phase. Importantly, IPSRT was not beneficial to all patients and to some, mainly those affected with higher levels of medical burden and anxiety disorders, ICM was more beneficial.

Using the protocol and the patients of the study above [30], the same team studied the influence of IPSRT on improving occupational functioning [31]. Occupational functioning was assessed at baseline, at the end of acute treatment and at the end of 1 and 2 years of maintenance treatment using the UCLA Social Attainment Scale (SAS). There were no significant differences at baseline between the four treatment groups described above. Patients assigned to acute IPSRT showed a faster improvement in occupational function when compared to patients assigned to ICM. The response was maintained regardless of the treatment assigned in the maintenance phase. Patients assigned to acute ICM showed slower recovery of occupational function, however, at the end of 2 years there were no significant differences when compared to those assigned to IPSRT in the acute phase. Women showed a faster and more marked improvement when compared to men. The authors also analyzed whether the improved occupational functioning mediated time to recurrence and the results suggest that they are independent positive effects of IPSRT.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a National Institute of Mental Health (NIMH) sponsored outpatient study which aims to study novel treatments in bipolar disorder. It is a large study with over 4300 participants across 21 sites [32]. From this main study several other small studies have spawned that furthered our understanding on how IPSRT might be used in treating bipolar disorder.

A 1 year randomized trial with 293 bipolar disorder patients, during a depressive episode, compared 3 types of intensive psychotherapy with a brief collaborative care

intervention [33]. The features of the treatments, which are also used in the following two studies ([34, 35]) are summarized in Table 1.

Table 1: Description of the procedures used in the studies based on STEP-BD [33-35]

Treatment	Features
Collaborative Care (CC)	Three 50 minute individual sessions in which patients received a videotape and a workbook with information regarding various aspects of the disease such as diagnosis, management, treatment, scheduling and communication skills and the development of a treatment contract
Cognitive Behavioral Therapy (CBT)	Thirty 50 minute sessions across 9 months focusing on psychoeducation regarding the disease but also regarding stress management, scheduling life events so they don't cause inactivity or overactivity, problem solving, cognitive restructuring and developing strategies for early detection of mood swings
Family-Focused Therapy (FFT)	Consists on trying to give patients a better understanding of their disease but also focuses on a shared understanding of the disease between the patients and their family as well as on the development of a plan when relapsing occurs
IPSRT	Based on the protocol described in the main text [14]

Patients were randomly assigned to the different treatments: 130 were assigned to collaborative care (CC) and 163 to intensive psychotherapy. Of the 163 assigned to intensive psychotherapy 26 were put on the family focus therapy (FFT) group, 62 on the IPSRT group and 75 on the cognitive behavioral therapy (CBT) group. The primary outcomes were time to recovery and proportion of patients classified as “well” during the 12 months of the study.

From the 293 patients, 195 completed 1 year of follow up and no differences in the likelihood of finishing CC versus intensive psychotherapy were found. Out of the 293 patients, 172 recovered from the depressive episode while 60 did not recover and 61 terminated before determination of recovery was possible. The average time to recovery in the intensive psychotherapy group was 113 days whereas in the CC group it was 146

days. Importantly, no differences were found in the time to recovery when the 3 different intensive psychotherapies groups were analyzed separately. Patients in the intensive psychotherapy groups had an odds of being classified as “well” 1.58 greater than patients in the CC group.

Another study [34], examined the impact of the protocol described above on comorbid anxiety disorders. Out of the 293 patients on the study above [33], 269 had information regarding the presence or absence of anxiety disorders. Of these, 177 had a past or current anxiety disorder and 92 did not.

For patients with an anxiety disorder 5.88 patients need to be treated with psychotherapy compared with CC to have one additional patient recover from the depressive episode (Number Needed to Treat (NNT) = 5.88). Concerning specific anxiety disorders, the NNT patients with a generalized anxiety disorder is 3.03 favoring psychotherapy and the NNT patients with PTSD is 5.56 also favoring psychotherapy. In other types of anxiety disorders there were only small non-significant differences. The authors also studied the hypothesis that a current anxiety disorder could have an effect on psychotherapy. They found that the NNT a patient with a current generalized anxiety disorder was 2.44, a current PTSD was 4.17, a current panic disorder 10, a current social phobia 8.33 and a current OCD 6.25, all favoring psychotherapy over CC. The influence of the number of anxiety disorder diagnosis on psychotherapy was also studied. Regarding patients with only one lifetime anxiety disorder diagnosis 3.22 patients needed to be treated with psychotherapy compared with CC to have 1 additional patient recover from the depressed episode, whereas for patients with more than one anxiety disorder diagnosis the NNT was 12.5.

The impact of intensive psychotherapy on work functioning in bipolar disorder was also studied [35]. In this trial 152 patients with bipolar disorder type 1 or 2, currently in the depressive phase and receiving pharmacotherapy were randomly assigned to either intensive psychotherapy (n=84) or CC (n=68) (protocol similar to [33]). The Longitudinal Interval Follow Up Evaluation – Range of Impaired Functioning Tool (LIFE-RIFT) was used as a measurement with evaluations every 3 months during a 9 month period. LIFE-RIFT scores, ranging from 1 (no impairment) to 5 (severe impairment), are given in 4 areas: relationships, satisfaction, work/role performance and recreational activities/hobbies. Patients in the intensive psychotherapy groups had better LIFE-RIFT

scores during the study when compared to patients in CC. Relationship functioning and satisfaction areas were also better over the 9 months in the intensive psychotherapy groups. There were no differences between CC and intensive psychotherapy in work/role performance or in recreational activities/hobbies areas.

IPSRT might also be useful as monotherapy in the treatment of bipolar depression type 2 [36]. In one study 17 unmedicated patients received IPSRT for 12 weeks as an acute treatment of depression, followed by an additional 8 weeks of follow up treatment in which lamotrigine was given to the non-responders. Out of the 17 patients, 10 completed the treatment. The use of low dose benzodiazepine for the management of insomnia was permitted and indeed 5 subjects were prescribed low dose lorazepam or clonazepam. There were significant improvements in both manic and depressive symptoms as measured by YMRS and HRS-D, respectively. Of the 10 patients completing the 12 week acute treatment program, 7 had responded to IPSRT monotherapy and on week 20, 9 had achieved a response and 5 had achieved full remission.

In regards to comparing IPSRT to pharmacotherapy, to our knowledge only one study has been conducted [37]. In this study, 25 unmedicated bipolar disorder type 2 patients, currently in a depressive episode, were assigned to either weekly IPSRT sessions (n=14) or to 25-300mg doses of quetiapine, with weekly meeting for dose management (n=11). The follow-up was 12 weeks. At baseline there were no significant differences between the 2 groups. 6 patients dropped out, 4 patients responded to IPSRT monotherapy and 3 patients responded to quetiapine (defined by a decrease in HRS-D of at least 50% and an YMRS of less than 10 at end-point). There were, however, no significant differences in response rates between the 2 treatment groups. Satisfaction with both treatments was high.

Two other protocols based on IPSRT have been developed: IPSRT group program (IPSRT-G) [38] and an adolescent specific IPSRT (IPSRT-A) [39, 40].

Nine bipolar disorder patients currently in a depressive episode participated in a proof of concept study of IPSRT-G [38]. The protocol included 2 individual therapy

sessions followed by 6 group sessions over the course of 2 weeks. 7 participants completed all sessions and baseline depression decreased significantly at 2 weeks and at 12 months of follow-up. Notably, 6 of them showed a preference for group sessions rather than individual sessions while the other showed no preference.

An open trial applied IPSRT-A in 12 patients with bipolar disorder who were either in a depressive, manic, hypomanic or mixed episode [39]. IPSRT-A is a protocol similar to IPSRT but with changes to make it more appropriate for the use in adolescents [40]. The outcomes were measured by the Brief Psychiatric Rating Scale for Children (BPRS-C), the Children's Global Assessment Scale (C-GAS), the MRS and the BDI. The Treatment Satisfaction Scale (TxSat) was also used as a measure. Out of the 12 patients, 11 completed the study and session attendance was 97%. At the end of the study all outcome measures showed an improvement when compared to baseline. Importantly, patients were satisfied with the treatment (as measured by TxSat). Notably, 9 of the subjects showed a 50% or greater decrease in their BPRS-C score and 3 showed more than 50% improvement in C-GAS score.

A case study of a 15 year old female adolescent treated with IPSRT has also been described [41]. The study reported an improvement in mood swings and the development of an improved sense of self identity, following 30 sessions of IPSRT during a period of 18 months. By the end of the study the patient was euthymic and felt an increased ability to cope with changes in social rhythms and interpersonal relationships. The patient also felt that IPSRT helped her in managing her mood and in developing a better sense of self.

Finally, one study used IPSRT as an approach to adolescents not with bipolar disorder but rather adolescents at high risk of developing it (with first degree family member affected) [42]. 13 adolescents were selected (12 had a parent affected and 1 had a sibling). The protocol was based on the IPSRT-A but with some modifications, perhaps the most importantly being a bigger focus on the feeling of the adolescent towards having a family member affected by the disorder. Both adolescents and parents reported high levels of satisfaction with IPSRT. Concerning the sleep patterns there were significant changes in school night bed times (became later), weekend wake times (became earlier) and weekend night total sleep time (became less), however school night total sleep time, school night wake time and weekend night bed time did not vary significantly. There were no changes in mood symptoms, however, these were minimal at baseline.

## DISCUSSION

Despite the need for further research, from the evidenced gathered, it appears that chronotherapeutics and IPSRT are new treatment options for managing bipolar disorder.

The various studies described are consistent with the hypothesis that chronotherapy, with sleep deprivation, bright light and sleep phase advance, is useful in treating bipolar disorder patients during a depressive episode, as evidenced by the reduction in the HRS-D and SIGH-ADS and also by subjective, patient self-rated scales, such as VAS and BDI.

The mechanism of action of these therapies is not yet totally understood but there are certain aspects that link the treatment to some features of bipolar disorder.

Firstly, it has been shown that bipolar patients have disruptions in sleep pattern which is controlled by Process S and Process C. Bipolar patients have disturbances in both these processes which can be, at least partly, corrected by chronotherapeutics. Sleep deprivation acts on Process S because it increases sleep pressure whereas sleep phase advance and bright light therapy act mainly on Process C as it aims to re-synchronize the circadian rhythms [8].

Secondly, sleep deprivation is able to increase levels of 5HT, norepinephrine and dopamine which are the neurotransmitters also targeted by antidepressant drugs. Serotonergic activity seems to be the most relevant. An increase in 5HT neuronal activity, in extracellular 5HT and in 5HT turnover as well as an increase in the response to 5HT precursors have been shown in depressed patients treated with sleep deprivation. Moreover, a depletion in tryptophan, an essential co-factor for the synthesis of 5HT, reversed the effects of bright light therapy and a polymorphism in the promotor gene for 5HT transporter linked polymorphic region (5HTTLPR), which leads to a decrease in expression of 5HT transporter, results in a reduced response to both 5HT uptake inhibitors and sleep deprivation (with and without BLT) [13]. Sleep deprivation also decreases the ratio Glx/creatine. Glx appears to be elevated in the brain of bipolar disorder patients in all phases of the disease (mania, depression, euthymia). Moreover, lithium, the mainstay treatment for bipolar disorder, has also been shown to decrease Glx in bipolar and antidepressant medications reduce the Glx synaptic outflow. Thus, a decrease in Glx

might be one of the pathways through which sleep deprivation exerts its antidepressant effects [16].

The main criticism to chronotherapeutics was that patients quickly relapsed after treatments were discontinued. Recently researchers have been able to improve this limitation through the use of chronotherapy protocols combining different types of treatments (such as in triple chronotherapy protocols) or by combining chronotherapy with pharmacological treatments. This way, the remission of symptoms is now able to be maintained for longer periods of time.

Importantly, although it seems to be influenced by previous drug resistance, chronotherapy has been useful in treating drug-resistant patients [15]. Chronotherapy has also been useful in the treatment of bipolar patients in a depressive episode with suicide risk as evidenced by the fact that after chronotherapy HRS-D scores decrease significantly regardless of the history of suicide attempts. It was also useful even in patients reporting suicidal thinking at the time of the treatment [18]. Perhaps the most useful aspect of chronotherapy is that it induces responses faster than any other treatment in the market and, even if it does not eliminate the need for pharmacological treatment, in most patients it could provide an important bridge between the beginning of the symptoms and the time antidepressant drugs start to have an effect and, this way, minimize the suicide risk present during this phase.

The role in improving cognition however is not yet clear as there was only one study concerning the topic and the authors only observed improvements in the domain of symbol coding. However, unlike healthy subjects, bipolar patients did not show a worsening of performance after sleep deprivation, when compared to baseline [21].

Only one of the analyzed studies did not describe a positive effect of chronotherapy as patients showed no significant differences after being treated with BLT when compared to controls (negative air ionization). This could be because a single type of chronotherapy is not as effective as a combination of various treatments. There is also the possibility, as the authors note, the placebo effect might be the cause of the lack of differences between BLT and negative air ionization [22]. The problem with placebo effect is a common one in psychiatry as evidenced by the average response in clinical trials being 64% to active drugs and 29% to placebo, in depressed patients [22]. Since the

placebo effect has been clearly characterized in drug trials, it is unlikely that it does not happen in chronotherapy trials as well.

One of the main criticisms to the studies done so far is the lack of controls that could evidence a possible placebo effect. However, for some therapies it is not possible to provide controls, for example, how can one control for sleep deprivation? This is problematic as some of the most promising studies are the ones combining the three chronotherapies, a protocol for which it is not possible to provide placebo controls. Without a feasible control it is also not possible to do blind the studies which is another hallmark of a well-designed and conducted clinical trial. Another criticism is that, in most of the studies, the clinicians doing the research are the ones rating the changes in the patients. This is however a solvable problem that can be overcome by having clinicians outside the study independently rating the subjects. Finally, obtaining funds for research on chronotherapy is a difficult task as, nowadays, most trials are done through pharmaceutical industry-based funding which, understandably, are not interested in investing in something that is not patentable.

Clearly there is still room for improvements in the protocols and there is still a lack of uniformity between the protocols and scales used by the different research teams making the comparison between them a difficult task. Questions also remain regarding the dosage of the treatments, for example, partial versus total sleep deprivation, or different light intensities in bright light therapy. After there is a consensus regarding the best treatment protocol it is also important to individualize the treatment. The importance of individualization was highlighted in one case study which described one patient who found sleep deprivation treatment impossible to endure despite being the treatment that he felt most improved his mood. For this patient, the use of modafinil, as a wakefulness promoting agent, helped him overcome the “intolerance” to sleep deprivation [25].

Regarding dark therapy, in manic episodes of bipolar disease, there is still very little evidence. However, the two case reports and the small trial highlighted here [26-28] are good indications that this is an area with great potential but for which there is a great need for further research. Just like sleep deprivation is a fast acting treatment for depression, dark therapy could play the same role in mania and induce regression of

symptoms faster than any other available therapy. There is, however, still a long way to go before dark therapy can be recommended to all patients in a manic episode. The use of amber tinted glasses looks promising as it would be much simpler than enforcing darkness for large periods of time although only a case series [29] has been reported and more studies are needed to confirm the efficacy of this protocol.

Regarding IPSRT, most studies have compared it to other psychotherapies. When compared to patients treated with ICM in the acute phase of a mood episode it was shown that patients treated with IPSRT survived longer without recurrence during the maintenance phase. This was true regardless of the treatment used during the maintenance phase (IPSRT or ICM). This result hints that IPSRT is most useful at the beginning of a new acute episode. The effect of IPSRT, at least partially, has to do with the regularity of social routines as evidenced by the fact that a higher SRM score at remission (following treatment of an acute episode with IPSRT), was predictive of a lower probability of recurrence during maintenance phase. Importantly, IPSRT might not be beneficial to all patients as some, mainly those affected by higher levels of medical burden and anxiety disorders, responded better to ICM, which might be due to the fact that ICM is more somatically focused [14].

IPSRT may also improve occupational function and help with the deterioration of work ability and employment which affects bipolar patients. When compared to ICM, patients treated with IPSRT showed a faster improvement in occupational function. Interestingly, this effect was more pronounced in women which might be due to a number of factors, including a higher rate of legal problems, more behavioral problems during the manic phases of the disease, more antisocial behavior in early life and more alcohol abuse in men. However, authors note that this could also be an artifact of the protocol due to the fact that more women were enrolled in the study [31]. It would be interesting to develop a protocol which could compare the effects of IPSRT in men and women.

Intensive psychotherapy seems to be more useful than CC when treating an acute mood episode of bipolar disorder. However, a most challenging issue with IPSRT is understanding if it is better than other intensive psychotherapies available. Three large

studies within the STEP-BD used IPSRT as one of the 3 intensive psychotherapy modalities with the others being FFT, CBT [33-35].

The problem with these 3 studies is that none found significant differences between the 3 psychotherapies. All 3 protocols address some similar items and the small sample sizes in these studies did not have enough power to distinguish between the areas where the 3 therapies differ. Another common problem of the 3 studies is that medication was not similar between patients. Evidence points towards bipolar disorder patients being better treated with intensive psychotherapy rather than with CC. However, more studies are needed, employing larger and more homogeneous populations, to compare the different modalities of intensive psychotherapy and thus shed light on which of them should be applied to a particular patient.

The use of IPSRT as monotherapy, rather than adjunctive to pharmacotherapy, is a topic that has been explored in bipolar disorder type 2. One study has shown that some patients responded to IPSRT in monotherapy which was true for patients both in depressive and in manic episodes [36]. Another study found similar mood improvements and response rates when comparing patients treated with IPSRT in monotherapy and patients treated with quetiapine while also highlighting the fact that both treatment modalities seem to be equally accepted [37]. The obvious limitation of these two studies is that sample sizes were very small. However, the fact that both treatments seem to be equally accepted and, importantly, the fact that, unlike pharmacotherapy, IPSRT does not have side-effects raises the question of whether it could be applied as monotherapy to certain subgroups within bipolar disorder.

The notion of a group based IPSRT is an interesting one, not only because it would decrease costs when compared to individual therapy sessions but also because it might be more helpful in certain patients. This is mostly due to the fact that the work in interpersonal relationship areas could perhaps be better implemented in a group setting. It has also been described that most patients prefer group therapy as they felt it was useful to “bounce ideas from others with the same problems” [38]. Despite describing a promising protocol this study has the limitation of having a small number of participants and also because the tools used for evaluation lacked testing for validity or reliability.

A protocol of IPSRT adapted to adolescents, IPSRT-A, has been developed and it could be an interesting possibility for helping younger patients. A small open trial with 12 patients showed an improvement in all outcome measures when compared to baseline [39]. Moreover satisfaction was high and session attendance was 97%. However, sample size was small and there was no control group. Moreover, the clinicians involved in the study were the ones rating the patients and thus results could be biased [39]. One case report of a 15 year old adolescent also showed marked improvements in social rhythms, interpersonal relationships, mood management and sense of self [41]. Clearly more research is needed with larger samples and a control group before IPSRT can be recommended to adolescents with bipolar disorder. However, these are certainly interesting results which warrant those studies.

One group also proposed that a shorter version of IPSRT-A could be applied to adolescents not with bipolar disorder but rather at risk of developing it [42]. The hypothesis here is that IPSRT-A could help stabilize social routines and sleep patterns which would prevent their disruption as a trigger for developing mood episodes and eventually bipolar disorder. There were no significant changes in mood at the end of the study when compared to baseline which was expected because mood symptoms were minimal at the beginning of the study. There were however, some changes in sleep patterns perhaps the most notable being a decrease in oversleeping during weekends. The main problem researchers came across was that most subjects declined participating in the program as they felt there was nothing wrong with them. This is likely to happen in future studies. However, the possibility of helping adolescents at risk is certainly enough to warrant further research.

## CONCLUSION

It seems clear that there still a lot of research to be done before chronotherapeutics and IPSRT are applied to all patients with bipolar disorder. Dysregulation of circadian rhythms play an important role in bipolar disorder and the treatments described here are a way to bring much needed balance to them. Importantly they seem to act faster, and with fewer side-effects, than current pharmacological treatments and could be the key to treat depressive and manic symptoms as soon as they appear.

Concerning chronotherapy for patients in a depressive episode, studies with larger populations are needed in order to answer the following questions: what is the best sequential treatment? Is there a dose-response curve? What is the efficacy in populations with other comorbid psychiatric conditions? And finally, are there any side-effects that are yet to be described?

Dark therapy for mania is still in an early stage of research. It is however an interesting concept and, as sleep deprivation and bright light therapy in depressive episodes, it could become an important and rapid acting treatment in manic episodes.

IPSRT could be the type of psychotherapy that many bipolar patients need as it helps in regulating social rhythms (and thus circadian rhythms) and in improving interpersonal relationships. There are trials evidencing its efficacy but more studies still need to be done with larger populations to distinguish the effects of IPSRT from other available intensive psychotherapies. This studies would help clinicians understand which therapy should be applied to a certain patient in a more effective way.

Concerning psychiatric illnesses, bipolar disorder is one of the most complex ailment to treat. There is still a long way to go but it is certainly interesting to envision a future where the combination of chronotherapy, pharmacotherapy and IPSRT (among other types of psychotherapy) can help a bipolar disorder patient remain euthymic for longer periods by providing a rapid relief and preventing recurrences.

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## ANEXOS

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### Instructions for Authors

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- Chapters in Edited Book

0. Beckenbough RD, Linscheid RL. Arthroplasty in the hand and wrist. In: Green DP, ed. *Operative Hand Surgery*, 2nd ed. New York: Churchill Livingstone; 1988: 167-214.
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[http://www.who.int/csr/sars/country/table2003\\_09\\_23/en/](http://www.who.int/csr/sars/country/table2003_09_23/en/)
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