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Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: An open label pilot study

Gregory L. Sahlem [a, *], Benjamin Kalivas [a, b], James B. Fox [a], Kayla Lamb [a], Amanda Roper [a], Emily N. Williams [a], Nolan R. Williams [a, c], Jeffrey E. Korte [d], Zachary D. Zuschlag [a], Salim El Sabbagh [a], Constance Guille [a], Kelly S. Barth [a, b], Thomas W. Uhde [a], Mark S. George [a, c], E. Baron Short [a, b]

[a] Departments of Psychiatry, Medical University of South Carolina, 67 President Street, Charleston, SC, USA
[b] Departments of Medicine, Medical University of South Carolina, 67 President Street, Charleston, SC, USA
[c] Departments of Neurology, Medical University of South Carolina, 67 President Street, Charleston, SC, USA
[d] Departments of Public Health Sciences, Medical University of South Carolina, 67 President Street, Charleston, SC, USA

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ABSTRACT

Previous studies have demonstrated that combined total sleep deprivation (Wake therapy), sleep phase advance, and bright light therapy (Triple Chronotherapy) produce a rapid and sustained antidepressant effect in acutely depressed individuals. To date no studies have explored the impact of the intervention on unipolar depressed individuals with acute concurrent suicidality. Participants were suicidal inpatients ($N = 10$, Mean age $= 44 \pm 16.4$ SD, 6F) with unipolar depression. In addition to standard of care, they received open label Triple Chronotherapy. Participants underwent one night of total sleep deprivation (33–36 h), followed by a three-night sleep phase advance along with four 30-min sessions of bright light therapy (10,000 lux) each morning. Primary outcome measures included the 17 item Hamilton depression scale (HAM17), and the Columbia Suicide Severity Rating Scale (CSSRS), which were recorded at baseline prior to total sleep deprivation, and at protocol completion on day five. Both HAM17, and CSSRS scores were greatly reduced at the conclusion of the protocol. HAM17 scores dropped from a mean of 24.7 ± 4.2 SD at baseline to a mean of 9.4 ± 7.3 SD on day five ($p = .002$) with six of the ten individuals meeting criteria for remission. CSSRS scores dropped from a mean of 19.5 ± 8.5 SD at baseline to a mean of 7.2 ± 5.5 SD on day five ($p = .01$). The results of this small pilot trial demonstrate that adjunctive Triple Chronotherapy is feasible and tolerable in acutely suicidal and depressed inpatients. Limitations include a small number of participants, an open label design, and the lack of a comparison group. Randomized controlled studies are needed.

1. Introduction

Major depressive disorder is a neuropsychiatric condition that consists of core symptoms including a persistently depressed mood, anhedonia, sleep disruption, anergia, poor concentration, guilt, hopelessness, appetite changes, and suicidal ideation. Currently there are no commonly used rapid treatments for depression. Suicide is the 10th leading cause of death in the United States, and is even higher among younger individuals between the ages of 10–24, where it is the second leading cause (Heron, 2013). Untreated depression is known to be associated with suicide risk with estimates that 60% of all suicides are associated with inadequately treated depression (Mann et al., 2005). There is an apparent stratified risk of suicide in those who have been admitted to the inpatient unit for depression, with those who have suicidal thoughts, or suicide attempts, posing the highest lifetime risk of committing suicide (Bostwick and Pankratz, 2000). Depression is a major medical issue both domestically and abroad. Depression is

* Corresponding author. 67 President Street, Charleston, SC, 29425, USA. Tel.: +1 843 792 2123; fax: +1 843 792 5702.
E-mail address: Sahlem@musc.edu (G.L. Sahlem).

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the 4th leading cause of disability in the world and has an approximate lifetime prevalence of 16.5% in the United States (Kessler et al., 2003; Murray and Lopez, 1996). Pharmacotherapy, and psychotherapy are the most commonly used treatments but only approximately 67% of non treatment resistant depressed individuals achieve remission with medications or psychotherapy, taking an average of 5–7 weeks to achieve remission in those who find an effective regimen (Rush et al., 2006). Even electroconvulsive therapy (ECT), which is our most dependable, and effective treatment, still takes 2–3 weeks for therapeutic benefit, and has limited availability and cognitive side effects (Sackeim et al., 2007). Although there are promising newer treatments such as repetitive transcranial magnetic stimulation (rTMS) (George et al., 2014) and ketamine (Caddy et al., 2014), there are at this time no commonly used treatments that rapidly treat depression.

Studies have consistently reported a rapid antidepressant response to total sleep deprivation in both unipolar and bipolar depression, first studied by Pflug and Tolle (1971), and reviewed extensively by (Wu and Bunney (1990); Wirz-Justice et al. (2005); Benedetti et al. (2007). The clinical utility of this technique is limited however, because responders typically relapse rapidly following recovery sleep. The addition of pharmacotherapy (Benedetti et al., 2001; Colombo et al., 2000; Smeraldi et al., 1999; Martiny et al., 2012; Shelton and Loosen, 1993; Szuba et al., 1994; Wu et al., 2009), sleep phase advance (Riemann et al., 1999; Echizenya et al., 2013), and bright light therapy (Echizenya et al., 2013; Martiny et al., 2012, 2013; Neumeister et al., 1996; Wu et al., 2009) to sleep deprivation have each demonstrated efficacy in preventing some individuals from relapsing into depression. Some early studies have reported that combined total sleep deprivation, sleep phase advance, and bright light therapy, dubbed Triple Chronotherapy, along with concomitant pharmacotherapy, produces a rapid improvement in depressive symptoms which endures for as long as 9 weeks (Echizenya et al., 2013; Martiny et al., 2012; Wu et al., 2009). If the early, encouraging results of Triple Chronotherapy hold up to further study, the technique represents a near ideal inpatient treatment, as it is inexpensive, relatively easy to carry out, and has minimal side effects.

Despite encouraging early results, only one published report has attempted to use Triple Chronotherapy in suicidal patients, and in that trial only bipolar depressed patients were included. That study used a slightly different variation of chronotherapy that included three nights of sleep deprivation every other night with three light therapy sessions, combined with lithium (Benedetti et al., 2014). The lack of data utilizing Triple Chronotherapy in acutely suicidal patients significantly limits its utility in the United States, where few non-suicidal patients are admitted to the inpatient unit. Furthermore, published trials to this point have excluded those with comorbid illness, which also limits the clinical usefulness of this intervention to a minority of patients. We subsequently sought to determine if adjunctive Triple Chronotherapy was safe and feasible in acutely depressed and suicidal inpatients.

2. Materials and methods

2.1. Participants

We included participants with non-psychotic unipolar, or bipolar depression (who were on a therapeutic dose of a mood stabilizer), age 18–75. We excluded patients who were in a mixed state, had active psychosis, had active panic disorder, were actively withdrawing from a substance of abuse, had a history of seizures, or had active unstable medical or neurologic illness.

We recruited participants from inpatient units at the Medical University of South Carolina (MUSC) Institute of Psychiatry (IOP) during the months of October 2013–March 2014 after referral from the treating inpatient team. Inpatient teams first briefly explained the chronotherapy intervention to patients who were admitted. Study team members then met with interested patients to obtain informed consent. All interested patients who met inclusion criteria, and did not meet exclusion criteria were included in the study. A total of 21 potential participants were referred, with three not being interested in the study, and four meeting exclusion criteria. Of the remaining referrals, 14 signed written informed consent, one of which later failed initial screening. The remaining sample of 13 enrolled in the below described protocol which was approved by the MUSC intuitional review board (IRB). Of the included participants one participant withdrew from the study prior to the first sleep deprivation and stated they were no longer wanting to participate, and two others were excluded from data analysis due to protocol deviations related to the investigative team, leaving a final sample of 10. Of the two that were withdrawn, our team missed awakening the first following the first recovery sleep night, and our team placed the second in an excessively noisy room during the first recovery night of sleep, and they were unable to sleep (They have a diagnoses of bipolar type I, and following two sleepless nights we thought the risk of manic switch outweighed any possible therapeutic benefit of continuing the protocol) (Fig. 1). The mean age of participants was 44 ± 16.4, six of whom were women, and none of whom had bipolar depression (Table 1). All but one participant carried comorbid Axis I, or Axis II diagnosis, which consisted of the following: Five participants met criteria for generalized anxiety disorder, four participants met criteria for dysthymia, three participants met criteria for borderline personality disorder, three participants met criteria for post traumatic stress disorder, three met criteria for alcohol dependence in early remission, two met criteria for social anxiety disorder, and one met criteria for opiate dependence in early remission. We initially recruited two participants with a diagnosis of bipolar disorder, however both of those participants were excluded from analysis due to protocol deviations as described above. Only three participants were initially admitted for a suicide attempt, while all patients were admitted for suicidal ideation.

This was an adjunctive procedure, and with the exception of holding hypnotics on the night of sleep deprivation, all standard of care pharmacotherapy was allowed. In addition to pharmacotherapy, all patients on the unit received milieu therapy, group therapy, and social work interventions. The group was heterogeneous as far as treatment resistance. The group had an average of 5.5 ± 5.7 medications that were either failed or were not tolerated. One participant previously failed ECT. The medications that were either started or continued by the treating team were as follows: All participants were on antidepressants during the study; five were on serotonin selective reuptake inhibitors (SSRI)'s, two were on serotonin non-selective reuptake inhibitors (SNRI)'s, four were on trazodone, three were on mirtazapine, one was on vilazodone, one was on phenelzine, two were on cytomel, three were on benzodiazepines, one was on quetiapine, one was on gabapentin, one was on belladonna, and one was on melatonin. Prior to, or during the weeklong protocol, the following medications were started, or titrated: One had an SNRI titrated, one had phenelzine started, three had mirtazapine started or titrated, two had titrations of an SSRI, one had cytomel started, one had quetiapine started, one had prazosin started, one had a benzodiazepine started, and one had gabapentin started.

2.2. Triple Chronotherapy procedure

The Triple Chronotherapy procedure we used closely resembled the one described in the manual written by Wirz-Justice at al (Wirz-Justice et al., 2013). Recruited participants filled out the