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Review Article

Existing Insomnia Therapeutics, their Key Limitations and the Potential of Emergent Therapies

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Abstract

Introduction: Sleep disorders are complex to understand and hence forth is their treatment. Currently multiple treatment options are available for insomnia management. Better understanding of pathophysiology, newer diagnostic techniques have led to multiple opportunities in the diagnosis and management of the Sleep disorders. However, success rate in the management of Insomnia still remains a challenge.

In the current review, we focus on the efficacy and key limitations of already existing treatment options of Insomnia. Along with this, we critically evaluated the emergent therapies for insomnia. Current review provides an opportunity to get aquatinted with some of the novel Insomnia management strategies and treatment options.

Methods and Results: In the current paper we reviewed original and other related literature to evaluate and establish limitations in the existing therapies for Insomnia management. We critically analysed cognitive behavioural therapy, cognitive therap. behavioural therapy, pharmacotherapy including use of hypnotics. All these therapies though had effect on the insomnia management however need of novel therapies in the insomnia management still prevail.

Conclusion: Insomnia management is quite complex which creates scope for novel emergent insomnia therapeutics as the current treatment options might be having significant limitations.

Keywords: *Insomnia; Sleep Disorders; Insomnia Treatment; CBT; Exercise*

Abbreviations

BT: Behavioural Therapy; CBT: Cognitive Behavioural Therapy; CT: Cognitive Therapy; DSM IV: Diagnostic and Statistical Manual of Mental Disorders (IV); GCBT: Group Delivered Cognitive Behavioural Therapy; ISI: Insomnia Severity Index; ICBT: Internet Guided Cognitive Behavioural Therapy; PSG: Polysomnography; RCT: Randomized Control Clinical Trial; SOL: Sleep Onset Latency; TST: Total sleep time; WASO: Wake After Sleep Onset

Introduction

Sleep disorders are complex to understand and hence is their treatment. "DSM IV criteria of Insomnia is being defined as difficulty in initiating, maintaining and non-restorative sleep related symptoms for at least 1 month along with day time symptoms. Clinically significant distress or impairment in social, occupational, or other important areas of functioning". Figure 1 illustrates sleep British association of psychopharmacology proposed algorithm for insomnia [1].

Increased understanding with respect to pathophysiology of insomnia has led to critical evaluation of current existing treatments for insomnia which have been associated with multiple limitations. These limitations provide an opportunity to look into novel therapeutic approaches in management of insomnia

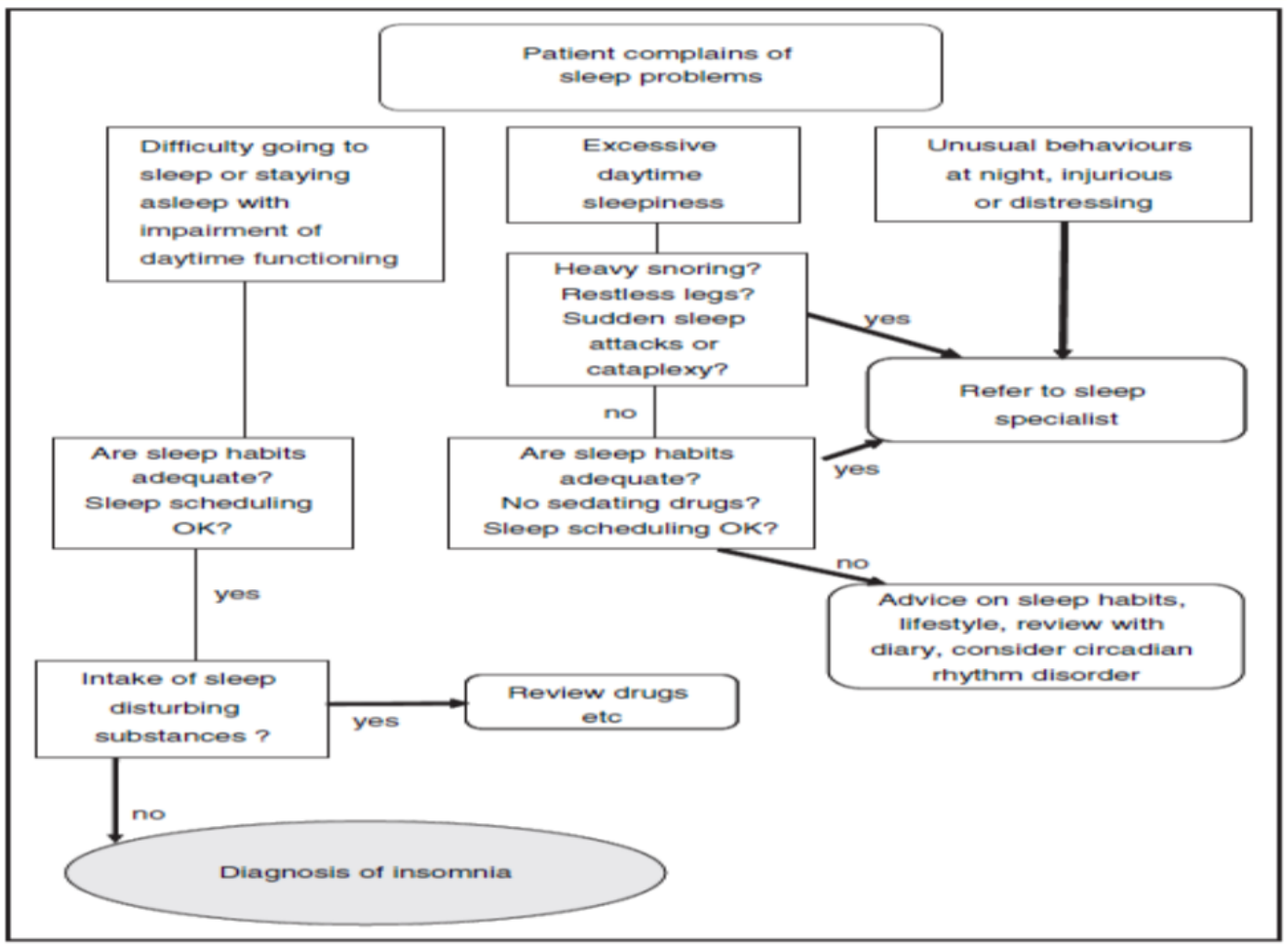

Figure 1: *Algorithm for insomnia diagnosis [1].*

In current write up, focus is laid on illustrating limitations of existing insomnia therapies and highlighting efficacy of novel/emergent therapies for treatment of insomnia.

To start, cognitive behavioural therapy and its limitations in treatment of insomnia will be discussed. CBT seems a promising therapeutic tool however there are important limitations of therapy which will be addressed in this write up. Multiple clinical trials have been conducted in this area and evidence with respect to benefits and pitfalls in cognitive behavioural therapy for insomnia management has been evaluated. Limitations of different modes of CBT administration like telephonic, internet based and face to face will be discussed [2-6].

Focus will be on current pharmacotherapies available for management of insomnia. Limitations of hypnotics, antidepressants and antihistamines with respect to efficacy, adverse effects, misuse, abuse, mortality and cancer causing agents will be reviewed in details [1,7-14].

In second section, multiple novel therapies will be evaluated for their potential for insomnia treatment. Firstly, role of broadband sound in management of insomnia will be discussed [15], followed by role of thermal treatment based forehead device in management of insomnia (Roth., et al. 2017), novel drug delivery systems for existing approved drugs for insomnia management (Brodner., *et al.* 2017) slow oscillating current in management of insomnia [16] and finally role of exercise and physical activity in treatment of insomnia [17].

Methods

In the current paper, we reviewed original and other related literature to evaluate and establish limitations in the existing therapies for insomnia management. We critically analysed studies comprising of cognitive behavioural therapy, cognitive therap. behavioural therapy, pharmacotherapy including use of hypnotics. Also, interventional studies comprising of the novel treatment options for insomnia management were considered.

Inclusion criteria for selection of the articles

- Original research article published in a peer-reviewed journal.
- Primary aim/focus was to find interventional studies on cognitive behavioural therapy, cognitive therap. behavioural therapy, pharmacotherapy including use of hypnotics.
- Secondary focus was incorporating the interventional studies comprising of the novel treatment options for insomnia management.
- Published in english.

Exclusion criteria for elimination of the articles

- Study was not published in a peer-reviewed publication, such as a dissertation.
- Non-english journal.

Article search

A total of 567 articles were searched for and out of which those meeting the inclusion criteria were taken into consideration. This list of articles were screened for relevant titles, and abstracts of all marginally relevant titles were examined. The large majority of the articles were excluded because they did not meet inclusion criteria we only focused on the original articles covering the following: cognitive behavioural therapy, cognitive therap. behavioural therapy, pharmacotherapy including use of hypnotics. Focus was also laid on the interventional studies comprising of the Novel treatment options for Insomnia management. Of these studies, 23 were finalized taken into consideration that met inclusion criteria.

Cognitive behavioural therapy and its limitations in treatment of insomnia

Cognitive behavioural therapy has emerged as one of the important non-pharmacological therapeutic tool in treatment of insomnia. Although CBT as therapy has gained significant popularity, there are multiple drawbacks/questions which need to be addressed [2-6].

Telephonic CBT delivery and its limitations

Arnedt and his group evaluated telephonically delivered CBT I (n = 15) versus Information pamphlet control (IPC) group (n = 15) in a randomized control trial in chronic insomnia patients. Sleep and day time performance were recorded at baseline, after treatment (4 - 8 weeks treatment of 15 - 60 minutes duration) and follow up (12 weeks). Tools used were: "Sleep diary, insomnia severity index, pittsburgh sleep quality index, 16-item dysfunctional beliefs and attitudes about sleep, and symptoms like fatigue, depression, anxiety and quality of life recordings during the day" [3].

One of the major drawback of the study is use of IPC in control arm and not a standard CBT I face to face treatment by therapist. Screening and enrolment of patients was done based on telephonic interviews which seems to be an ethical issue. Table 1 demonstrates that in CBT1 group, parameters like day time symptoms were improved, however similar results were also observed in control group. IPC used in study was different from American academy of Sleep Medicine which raises validity issues. Only a single phone follow up was done in this study. Out of 30 subjects, 27 patients were women making results difficult to be translated in general population. Results are prone to information bias of patients as all activities were virtual. Further, there was no utilization of PSG or actigraphy in current study.

CBT I and its limitations in treatment of insomnia in post trauma stress patients

Tablot investigated efficacy of CBT I in management of Insomnia in patients with post trauma stress conditioning a randomized control clinical trial [4].

Variable	CBTI-Phone		IPC		Time effect P value[b]	Group by time interaction P value[b]
	Mean (SD)	Effect size (Cohen d)[a]	Mean (SD)	Effect size (Cohen d)[a]		
Sleep/Wake Diary						
Sleep efficiency (%)					< 0.001	0.04
Pretreatment	72.4 (12.5)		69.2 (10.4)			
Posttreatment	91.2 (6.0)	1.9	83.6 (7.5)	1.6		
12-wk (follow-up)	87.9 (7.6)	1.5	85.6 (7.3)	1.8		
Total sleep time (min)					< 0.001	0.31
Pretreatment	368.5 (63.2)		338.0 (65.7)			
Posttreatment	406.8 (67.0)	0.6	391.7 (57.6)	0.9		
12-wk (follow-up)	416.5 (64.2)	0.8	405.8 (50.1)	1.1		
Sleep latency (min)					< 0.001	0.09
Pretreatment	51.9 (28.2)		55.9 (29.2)			
Posttreatment	16.1 (9.8)	1.7	23.9 (12.4)	1.4		
12-wk (follow-up)	18.3 (9.8)	1.6	20.2 (10.5)	1.6		
Frequency of awakenings (No/night)					< 0.001	0.86
Pretreatment	2.2 (0.9)		2.0 (0.6)			
Posttreatment	1.3 (0.9)	1.0	1.2 (0.7)	1.2		
12-wk (follow-up)	1.4 (0.9)	0.9	1.2 (1.0)	1.1		
Wake after sleep onset (min)					<0.001	0.06
Pretreatment	87.9 (51.9)		95.6 (46.5)			
Posttreatment	20.0 (13.5)	1.8	52.9 (37.3)	1.0		
12-wk (follow-up)	35.9 (31.0)	1.2	47.0 (31.3)	1.2		
Sleep quality (1-5)[c]					< 0.001	0.85
Pretreatment	2.8 (0.5)		2.8 (0.4)			
Posttreatment	3.7 (0.5)	1.7	3.6 (0.5)	1.8		
12-wk (follow-up)	3.5 (0.9)	1.0	3.6 (0.6)	1.5		
Sleep Questionnaires						
Insomnia Severity Index					< 0.001	0.23
Pretreatment	16.5 (4.6)		16.8 (2.4)			
Posttreatment	5.2 (3.7)	2.7	7.8 (4.9)	2.4		
12-wk (follow-up)	5.8 (4.4)	2.4	8.9 (5.6)	2.0		
Pittsburgh Sleep Warily Index					< 0.001	0.48
Pretreatment	11.3 (2.6)		12.6 (1.9)			
Posttreatment	4.6 (2.9)	2.4	5.9 (3.7)	2.3		
12-wk (follow-up)	4.0 (2.8)	2.7	6.8 (4.1)	1.8		
Dysfunctional Beliefs and Attitudes about Sleep Scale					< 0.001	< 0.001
Pretreatment	6.2 (1.3)		5.5 (1.4)			
Posttreatment	3.2 (1.0)	2.6	4.0 (2.0)	0.9		
12-wk (follow-up)	2.9 (1.1)	2.6	4.3 (2.1)	0.7		

Table 1: *Illustrates results pertaining to Sleep Diary and questionnaires at different stages of study. (baseline, treatment end and 12 week follow up) [3].*

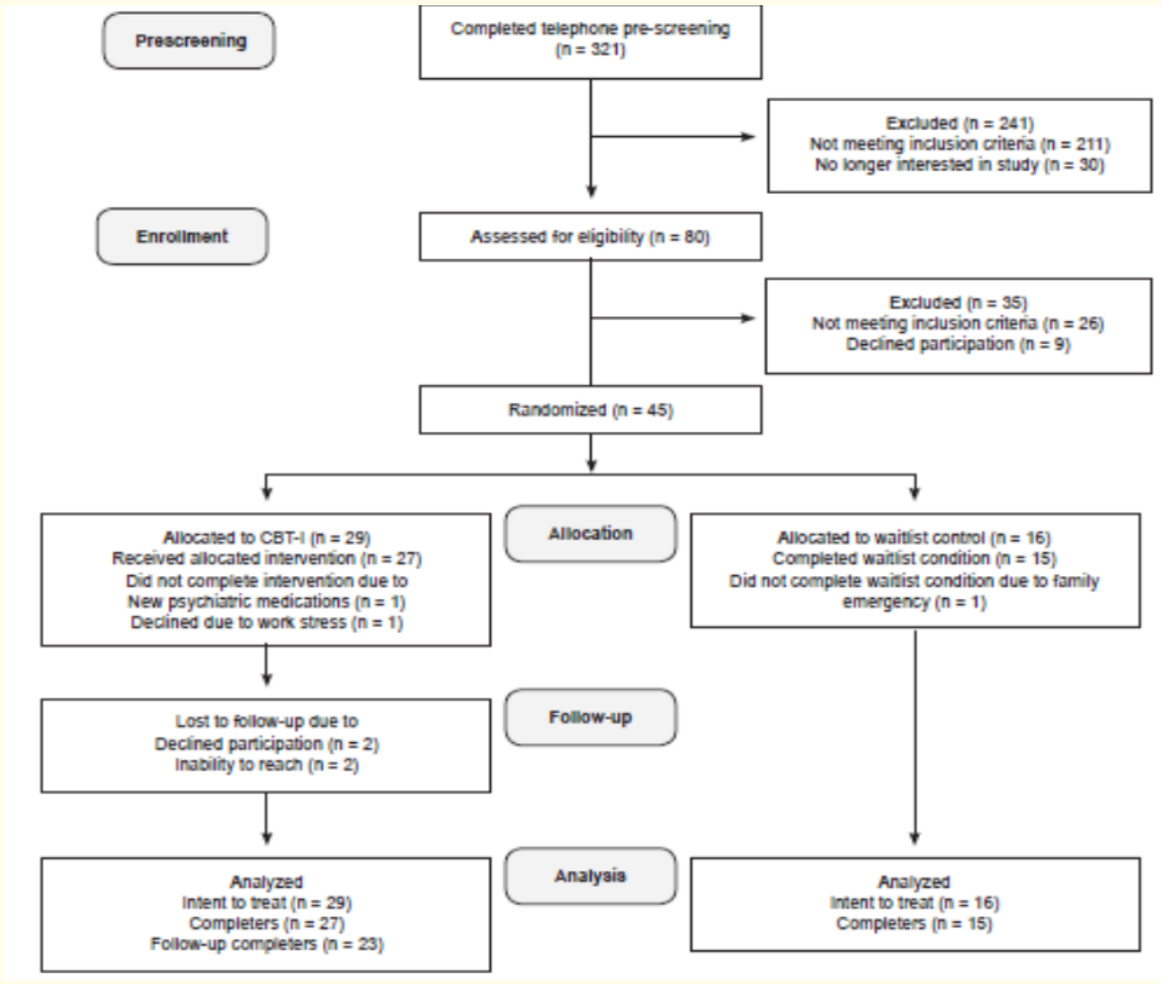

Figure 2: *Flowchart describing randomization, follow up and final analysis in both arms [4].*

CBT I arm patients (sleep diary group) did show good results in TST (total sleep time) improvement initially, however once alpha was made more strict in control arm significance in TST was lost. Similarly, there was no significant difference as compared to control arm in recordings WASO in treatment arm as measured by PSG. TST recording after 8 week of CBT treatment has been done based on single PSG reading. In actigraphy group, there were no differences seen in Sleep improvement [4]. Sample size (n = 45) was not enough to draw solid conclusions regarding robustness of results. Studies should be conducted in larger population including multiple evaluations using gold standard of sleep measurement like PSG to provide efficacy evidence of CBT.

CBT, BT and CT therapies efficacy comparison and their limitations

In a RCT conducted by Harvey and his group CBT, BT and CT were compared in terms of efficacy in patients with chronic insomnia [5]. Total randomized patients were (n = 188) out of which BT arm constituted n = 63, CT arm n = 65 and CBT arm comprised of n = 60 patients (Refer figure 3).

CBT/BT/CT treatment was given for total of 8 weeks all 3 arms and outcomes were measured at baseline, 8 weeks and 6 months (follow up). Efficacy was measured based on Insomnia Severity Index (ISI), Sleep diary and PSG. Multiple questionnaires were also used to evaluate efficacy with respect to day time complaints in Chronic Insomnia e.g. day time fatigue [5].

Overall results were beneficial in CBT arm (ISI responder rate 67%) when compared with BT (ISI responder rate 67%) and CT (ISI responder rate 42%) arm individually. Similarly, insomnia remission rate was highest in CBT (57%) as compared to BT (39%) and CT (31%) alone.

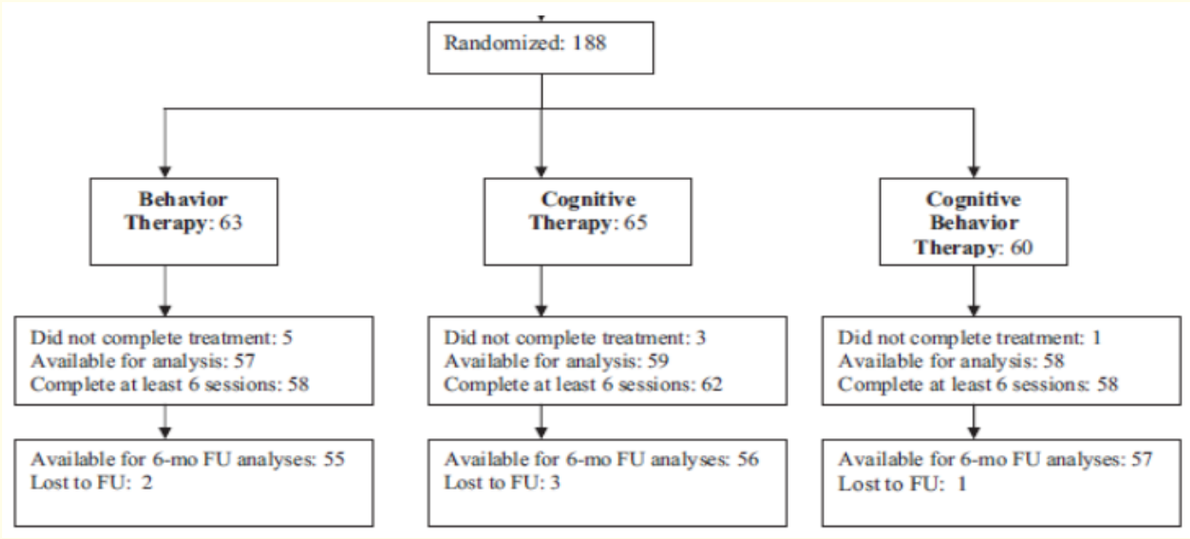

Figure 3: *Flowchart illustrating randomization pattern in 3 arms: CBT, BT and CT [5].*

BT was linked with much quicker improvements however results were not sustainable. In contrast CT arm, the initial response was comparatively poor however at 6 months follow up response increased from 44% to 62%. The variation in ISI results is practically very challenging with respect to drawing conclusion pertaining to treatment strategy making it key drawback of individual BT and CT therapy when compared with CBT.

In BT arm, though there was change in responders after 8 week of treatment (reduction was observed at time of 6 months follow up, there was no reduction found in remission cases signifying possibility of this group of patients to develop more complicated insomnia.

In terms of PSG measures, BT was found superior than CT alone in terms of Sleep efficacy and even CBT results were found similar to BT. These results are confusing enough with respect to selection of therapy for insomnia management. Further, all 3 therapies provided good responses in management of day time symptoms of insomnia, making it difficult to choose amongst 3 therapies. Another aspect to be focussed is difference in duration of therapies. While CBT was given for 75 minutes/per session, CT and BT sessions were given 45 - 60 minutes each. Difference in duration of therapies can potentially lead to significant bias in results of trial. Also number of sessions given in this trial (8 sessions) were not aligned to earlier studies in which upto 50 sessions had been given to insomnia patients based on chronicity and etiology of disease [5].

Another challenge was therapies were delivered majorly by students (approximately 79%) based on a very short duration of training. This raises questions with respect to validity of study results as CBT/CT/BT requires significant training and experience to deliver on appropriate basis.

Internet based CBT delivery and its limitations

Blom and his colleagues investigated efficacy of CBT delivery methods i.e. internet based CBT versus group delivered CBT in patients with chronic insomnia. Total of 48 patients were randomized (n = 24 per arm) (Refer figure 4). Study primary end points were recorded based on ISI (Insomnia severity index) while for secondary measures, sleep diary, symptoms pertaining to depression and response/remission rates were observed [6].

Results pertaining to primary and secondary end points were found significantly efficacious. Following graph indicates both arms were comparable with respect to ISI post treatment till 6 months follow up (Refer figure 5).

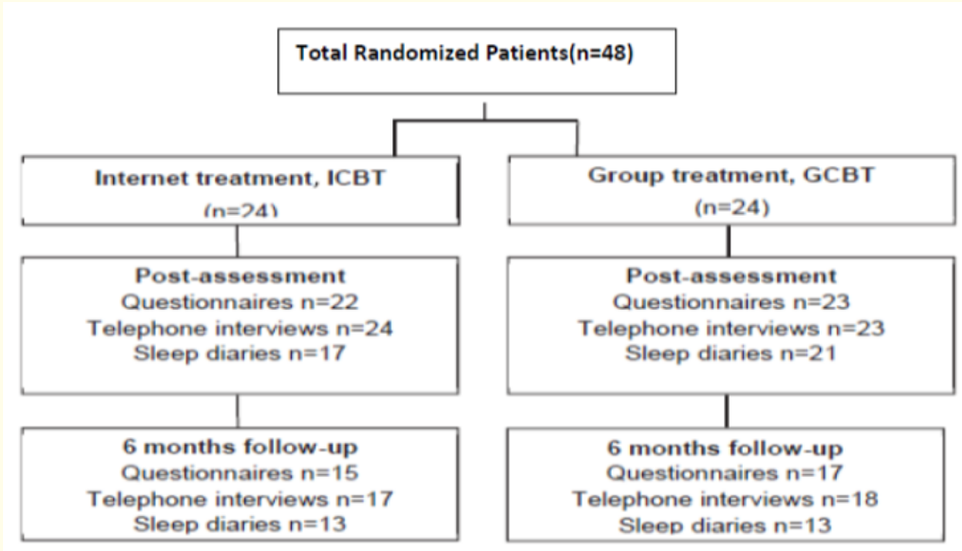

Figure 4: *Randomization schedule in both arms [6].*

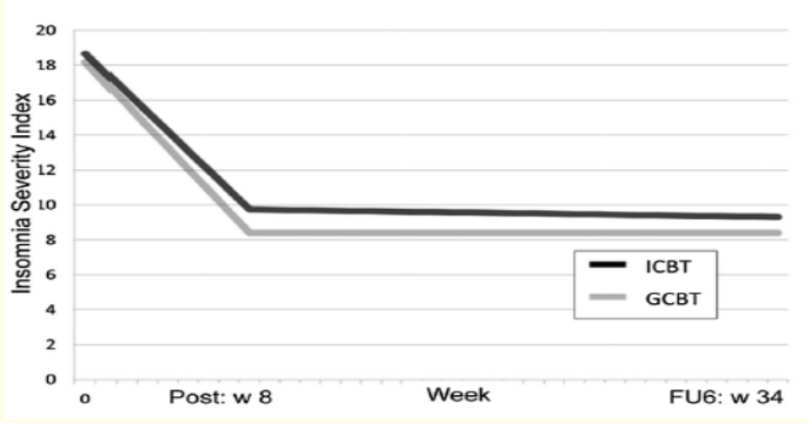

Figure 5: *Comparison between ICBT and GCBT with respect to ISI (Insomnia Severity Index) [6].*

The current study alohas significant limitations. Firstly, sample size was too low to actually compare two arms in an effective manner. Secondly, overall 19% of adverse events were reported. One minor accident in morning time has also been reported which raises safety concern. Lastly, results of study cannot be generalised to population based on differences in subjects observed in study.

Limitations of pharmacological treatment of insomnia

Hypnotics, tricyclic antidepressants, certain selective serotonin reuptake inhibitors are being used for treatment of insomnia depending upon etiology of disease. Antihistamines have been used as no prescription sleeping drugs since long. Here focus will be laid on individual drug categories.

Hypnotics have been main stay in treatment of Insomnia. There are multiple attributes requried for an ideal hypnotic [1] tabulates key parameters for ideal hypnotic (Refer figure 6) like quick absorption, long action, fast induction of sleep, no hangover, no walking problem.

Hypnotics used for insomnia treatment associated withdrug abuse

Z drugs (zopiclone, zolpidem and zaleplon) have similar mode of action like benzodiapines and thus have tendency to be misused [8].

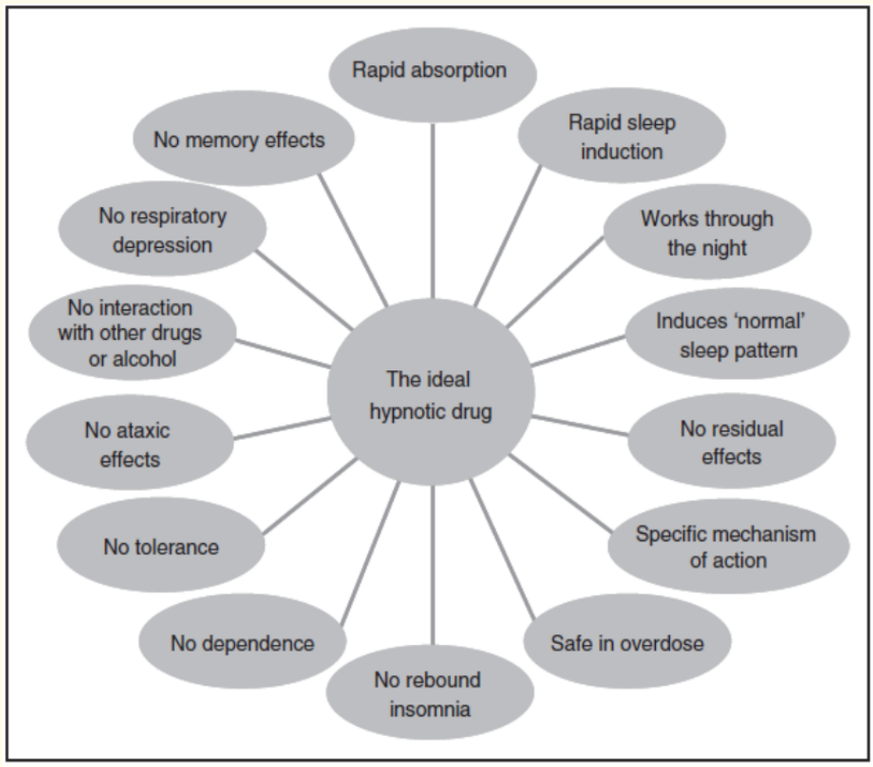

Figure 6: *An Ideal Hypnotic desirable key elements [1].*

Extensive and increased dosage (10 mg to 300 mg in 3 months) of Zolpidem in insomnia can lead to psychosis like symptoms [13].

Hypnotics associated with increased next day accidents

Staner., *et al.* [18] investigated next day impact on driving post (9 - 11 hours) usage of hypnotics. This was a crossover design enrolling 23 subjects (DSM IV primary insomnia). Dosage shchedule was: baseline zolpidem, zopiclone, lormetazepam (10 mg, 7.5 mg and 1 mg) respectively. Control arm comprised of placebo. Parameters used for assessment were EEG, driving EEG, collisions and driving speed assessments. Zopiclone arm had increased number of accidents while lormetazepam group had challenges pertaining to vehical speed. Similar responses have also been found in other studies [14].

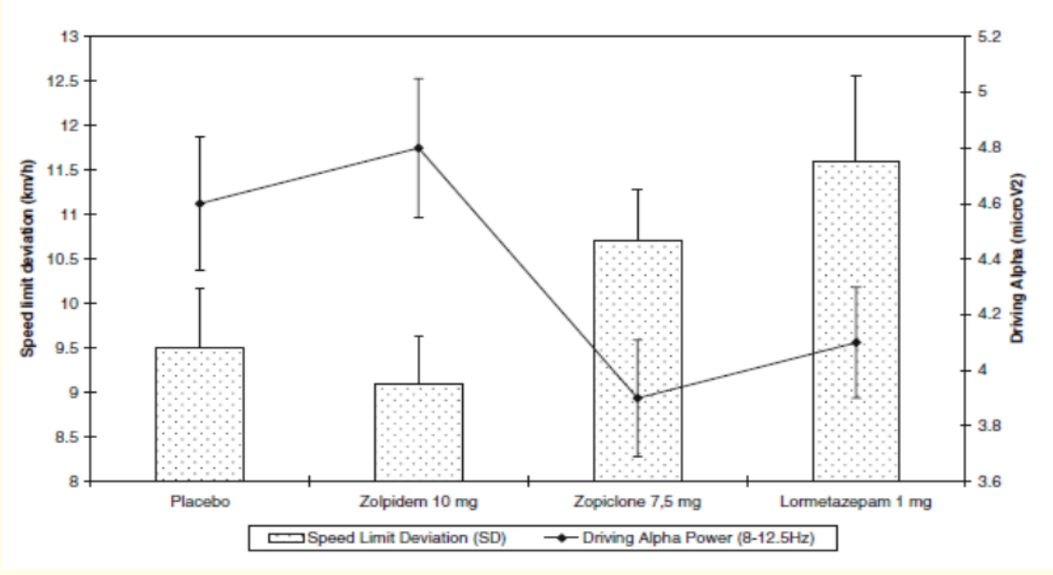

Figure 7: *Speed deviation in all arms post 9 - 11 hours drugs/placebo administration [18].*

In a randomized 5 way (1 mg, 2 mg, 3 mg of eszopliclone, placebo and zolpidem 10 mg) cross over clinical trial, eszopliclone was evaluated for its efficacy and safety in primary insomina patients (n = 72) [11].

Following table 2 shows list of adverse events. Dysgeusia and somnolence were observed in all 5 arms while dizziness was found in 3 mg Eszopidone and 10 mg Zolpidem group.

Adverse event, n (%)	Placebo (n = 71)	Eszopidone			Zolpidem
		1 mg	2 mg	3 mg	10 mg
		(n = 70)	(n = 69)	(n = 68)	(n = 70)
Any adverse event	12 (169)	16 (22.9)	16 (23.2)	18 (26.5)	13 (18.6)
Dysgeusia	1 (1.4)	4(5.7)	6 (8.7)	11 (16.2)	1 (1.4)
Somnolence	2 (28)	1 (1.4)	3 (4.3)	4 (5.9)	3 (4.3)
Dizziness	0 (0)	0(0)	0 (0)	2 (2.9)	3 (4.3)
Dermatitis contact	2 (28)	2 (2.9)	1 (1.4)	0 (0)	1 (1.4)
Feeling abnormal	0 (0)	3 (4.3)	0 (0)	0 (0)	0 (0)

Table 2: *Adverse events reported by ≥ 2% of patients in any treatment group (safety analysis set) [11].*

Hypnotics associated with mortality and cancer

Kripke, Langer and Kline [10] conducted a longitudinal cohort study evaluating hypnotics use and its relation with mortality or cancer. A total of n = 10529 in hypnotic group and n = 23676 in control group (without treatment) were followed up for 18 months. Table 3 illustrates patients on hypnotics like zolpidem and temazepam had greater mortality rate (4 times) when compared to non-hypnotic control group. The dosage duration was found to be linked with higher mortalities. There was increased risk of cancer by 35% in patients exposed to higher dosage of hypnotics as compared to controls.

Hypnotic	Deaths		Cancers	
	p Value	HR (95% CI)	p Value	HR (95% CI)
Any hypnotic: doses/year	< 0.001		< 0.001	
No hypnotics, N = 23 676	Reference		Reference	
0.4 - 18 pills/year, mean 8, N = 3491	< 0.001	3.60 (2.92 to 4.44)	0.086	0.86 (0.72 to 1.02)
18 - 132 pills/year, mean 57, N = 3548	< 0.001	4.43 (3.67 to 5.36)	0.022	1.20 (1.03 to 1.40)
> 132 pills/year, mean 469, N = 3490	< 0.001	5.32 (4.50 to 6.30)	< 0.001	1.35 (1.18 to 1.55)
Zolpidem only: mg/year	< 0.001		0.035	
No zolpidem or other hypnotics, N = 23 671	Reference		Reference	
Zolpidem 5 - 130 mg/year, mean 60, N = 1453	< 0.001	3.93 (2.98 to 5.17)	0.095	0.79 (0.60 to 1.04)
Zolpidem 130 - 800 mg/year, mean 360, N = 1456	< 0.001	4.54 (3.46 to 5.95)	0.585	1.07 (0.83 to 1.39)
Zolpidem > 800 mg/year, mean 3600, N = 1427	< 0.001	5.69 (4.58 to 7.07)	0.023	1.28 (1.03 to 1.59)
Temazepam only: mg/year	< 0.001		< 0.001	
NO temazepam or other hypnotics, N = 23 674	Reference		Reference	
Temazepam 1 - 240 mg/year, mean 98, N = 798	< 0.001	3.71 (2.55 to 5.38)	0.003	0.48 (0.30 to 0.77)
Temazepam 240 - 1640 mg/year, mean 683, N = 613	< 0.001	4.15 (2.88 to 5.99)	0.024	1.44 (1.05 to 1.98)
Temazepam > 1640 mg/year, mean 7777, N = 665	< 0.001	6.56 (5.03 to 8.55)	< 0.001	1.99 (1.57 to 2.52)

Table 3: *Hypnotic usage and corresponding associations with hazard rations of deaths or cancers [10].*

Antidepressants and their limitations in management of insomnia

In a study conducted by Bertschy., *et al.* [19] role of trazodone (an antidepressant) in insomnia management was investigated in patients (n = 42) on already 300 mg/day venlafaxine (SRI and nor epinephrine reuptake inhibitor). This was a 4 weeks study and introduction of trazodone was planned on 14th day of treatment. Trazodone was not found to be associated with improvements in daytime insomnia symptoms. It was not a placebo controlled clinical trial and number of subjects were too low to predict actual benefits of drug. Study

results were based on MADRS scale and there was no use of tools like PSG (gold standard for sleep measurement). Certain challenges in statistical analysis were also reported.

In a double blind placebo controlled study conducted in 20 subjects (men = women) with olanzapine (5 mg) single morning dose it was observed that concentrations of drug were more in women group than men group indicating drug concentration may be liked to sex of patients.

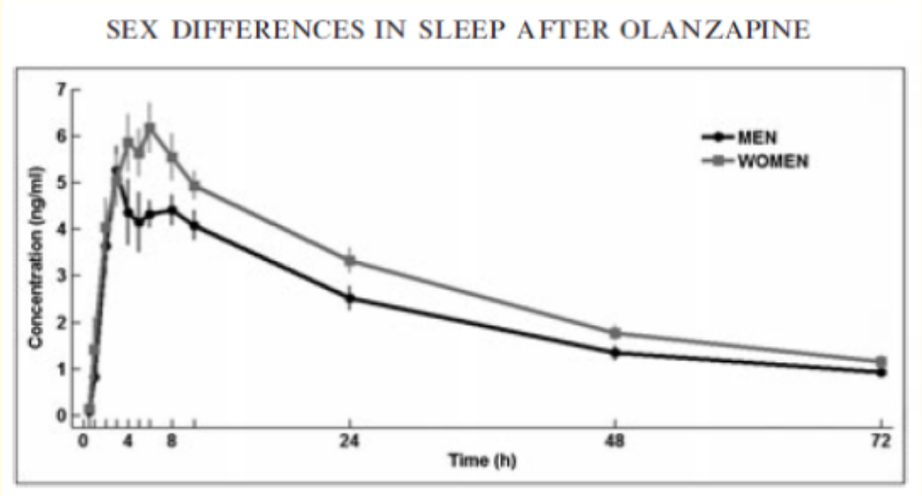

Figure 8: *Single morning dose Olanzapine concentrations differences in men and women (n = 20) (Gimenez., et al. 2011).*

Further, olanzapine 20 mg/day has been associated to restless leg syndrome. Later is one of factor leading to insomnia. Reduction in dosage to 10 mg/day reduced symptoms related to RLS [9].

Limitations of antihistamine use in insomnia

In a 3 arm placebo controlled study [7] arm 1 comprised of standardized extract combination of valerian -hops "(187-mg native extracts; 5-8:1, methanol 45% m/m) and hops (41.9-mg native extracts; 7-10:1, methanol 45% m/m)", 25 mg x2 diphenhydramine tablets followed by placebo in arm 2 and only placebo arm 3. Arm 1 (n = 59) treatment given for 28 days, arm 2 (n = 60) 14 days active drug followed by placebo for another 14 days, arm 3 (n = 65) 28 days (Refer figure 9 for details).

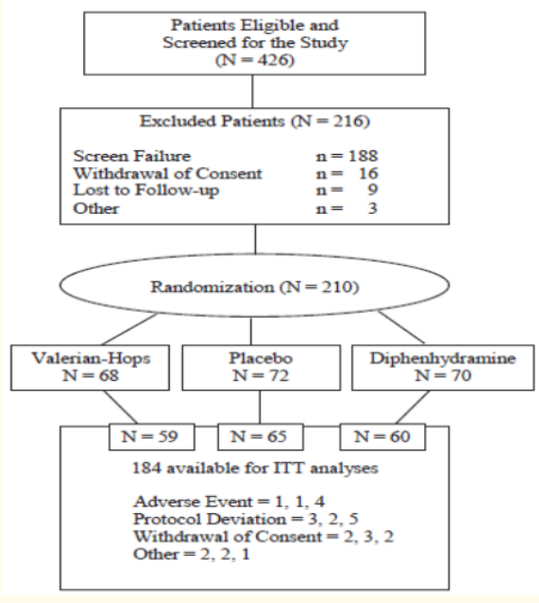

Figure 9: *Study flowchart [7].*

In this study against 210 randomized patients there were 216 corresponding adverse events (arm 1 = 63, arm 2 = 77 and arm 3 = 76). The adverse events occurring in arm 1 and 2 were significantly comparative ($p < 0.08$). Though there no serious adverse events, number of adverse events associated with active drug arms raises concern about safety of these compounds.

In a cross sectional study conducted by Roussin., *et al.* [12] dependence and misuse of H1 antihistamines was studied. In this 3 arm study, group 1 comprised codeine plus paracetamol (n = 142), H1 antihistamines sedatives (n = 110) and control group with paracetamol (n = 131). Evaluation of drug dependence, misuse and abuse was based on multiple questionnaires earlier used in different studies (Refer table 4).

	Codeine	H1 antihistamines	Paracetamol (control)
	(N = 118)	(N = 70)	(N = 107)
Misuse	8 (6.8%)***	26 (37.1%)***	0 (0%)
Abuse	1 (0.85%)**	0 (0%)	0 (0%)
Dependence	21 (17.8%)**	1 (1.3%)	4 (3.7%)

Table 4: *Illustrates misuse (non-prescription use) in H1 antihistamine group was 37.1% and reported dependence (questionnaire based)only 1% [12].*

***p<0.01;*

****p<0.001 (comparison to the control group).*

Innovative emergent therapies in treatment of insomnia

Role of broadband sound in management of insomnia

Messineo., *et al*. [15] conducted a randomized single blinded control clinical trial in heathy subjects (n = 18) in a transient insomnia model (participants were advised to bed 1 hour 30 minutes earlier than normal bed time with "lights out"). Group 1 received normal noise (40.1 [1.3] dB) of environment (n = 10) and group 2 was administered equally distributed broadband sound by speakers (46.0 [0.9] dB) in a room (n = 8) (Refer figure 10). The measurement parameters electroencephalography, electrooculography, chest and abdomen movements and oxygen saturation in blood were analysed during night. Two sleep studies were conducted in 1 week difference with a focus on SOL, architecture of sleep and sleep quality.

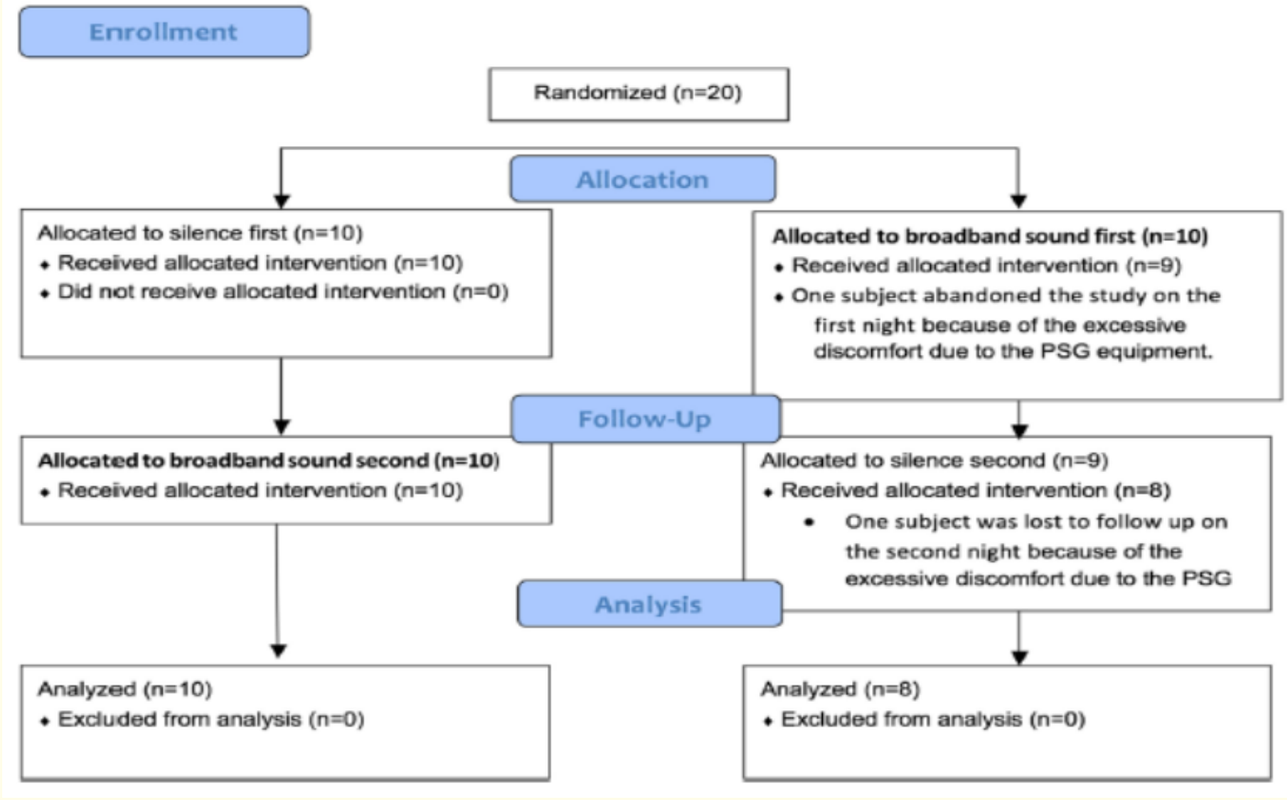

Figure 10: *Study randomization and patient flow (n = 20) [15].*

It was observed that SOL to stage N_2 was reduced by 38% which was statistically significant (p = 0.011) in broadband sound administration group as compared to controls (Refer figure 11).

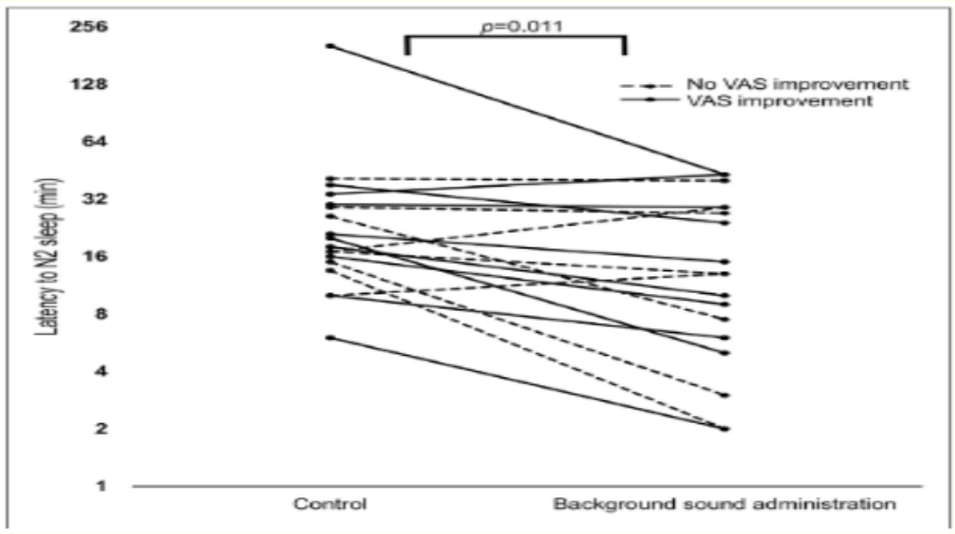

Figure 11: *SOL to stable stage N2 comparison between therapy and control arm [15].*

With respect to sleep quality, arousal index was strongly correlated with therapy administration (r = 0.51 at p = 0.03). Major limitations of study were small sample size, young healthy adults participants as Insomnia prevalence increases with age. Further instruments like nasal cannula, electrodes could have interfered with sleep onset. This was a single blinded study and hence not gold standard randomized placebo control double blind study. In spite of few limitations, current study provides an evidence that with a broadband sound therapy of measured frequency, sleep onset latency to stable sleep stage N_2 can be reduced by 38% at a statistically significant levels. Future studies investigating this concept in insomnia patients will be really helpful.

Role of thermal treatment based forehead device in management of insomnia

Roth investigated role of forehead placed temperature regulating device (maintaining frontal cerebral region temperature 14 - 16 degree centigrade) in a randomized parallel arm clinical trial in patients (n = 106) with primary insomnia (DSM IV classified). Active arm received therapy for 2 nights and control arm was put on sham vestibular stimulation. Significant results based on PSG evaluation were achieved with this device with respect to improvement in sleep latency to statistically significant levels {N1 (p = 0.006), N2 (p = 0.002) and N3 (p = 0.055)}. Safety of thermal device was found similar to control (Roth., *et al*. 2017).

Current study provides novel and efficacious approach with respect to improvement in sleep latency in insomnia patients. Future studies in larger population are required to establish thermal therapy for insomnia management.

Novel drug delivery systems for existing approved drugs for insomnia management (Brodner., *et al*. 2017)

In a PK (Pharmacokinetic) study IPR protected "IPP-melatonin delivery device" which tends to increase plateau phase to 7 hours, to maintain Melatonin concentration was evaluated in 10 healthy participants. Dosage regime was 5 mg melatonin administered through IPP device and PK parameters like Cmax, Tmax and plateau phase duration was recorded. The plateau phase was increased to 6.7 hours thanerst while reported 4.4 hours. Increase in duration of plateau phase can be associated with maintenance of sleep and its duration in patients with insomnia.

Slow oscillating current in management of insomnia

In a study conducted by Saebipour., *et al.* [16], slow oscillating direct current of frequency (0.75 Hz) was administered in transcranial region along with control (sham) in 6 patients with insomnia (non-restorative type) for 2 nights (Refer figure 12 for the study process).

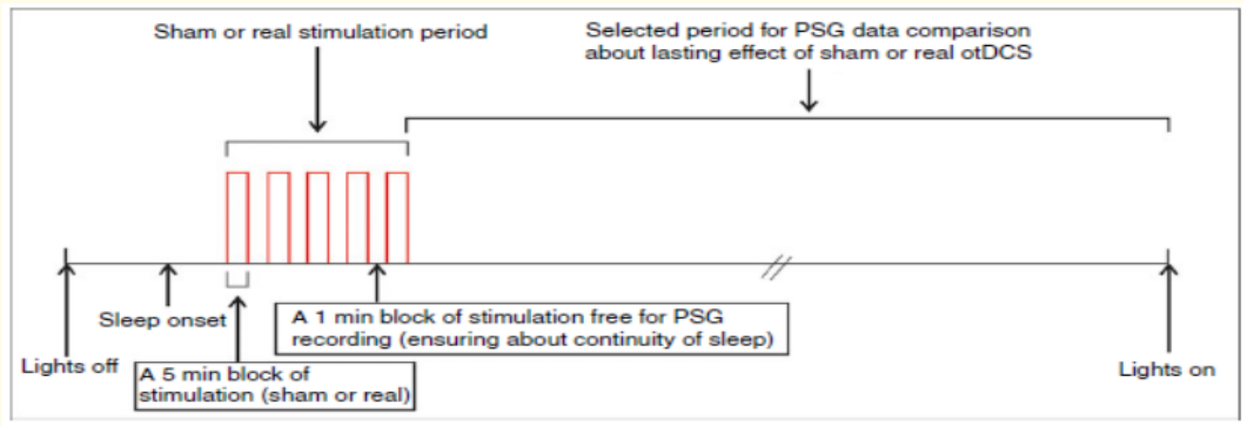

Figure 12: *Illustration of whole study process [16].*

In current study, significant difference in duration of sleep stages N3 (increased duration 33+ - 26 minutes), N1 (decreased by 22+-17.7 minutes) and N1 (55.4+ - 51 minutes) plus wake was found as compared to control group while N2, REM there was no significant difference (Refer figure 13 for details).

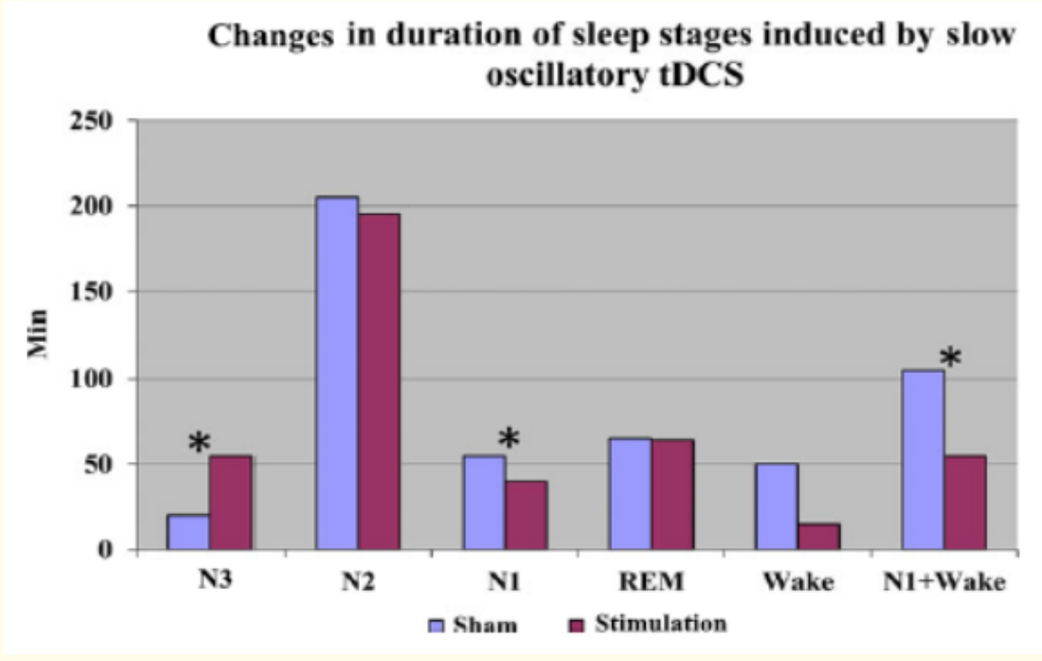

Figure 13: *Impact of slow oscillatory current therapy comparison between two arms on various sleep stages in trial subjects (*p value <= 0.05) [16].*

Figure 14 illuatrates statistically significant decreased probality (**p <= 0.01) of sleep stage conversion from N2 to wake. Further,there was increased conversion from stage N2 to N3 (*p value <= 0.05) when compared with control group.

This study provides novel therapy for management of insomnia and results are in alignment with other researchers [20,21]. Study was sham control trial and hence quality results are expected, though number of subjects was less. In this study first night was given for adaptation and 1 night for baseline PSG before actual treatment gave an adapting atmosphere to patients.

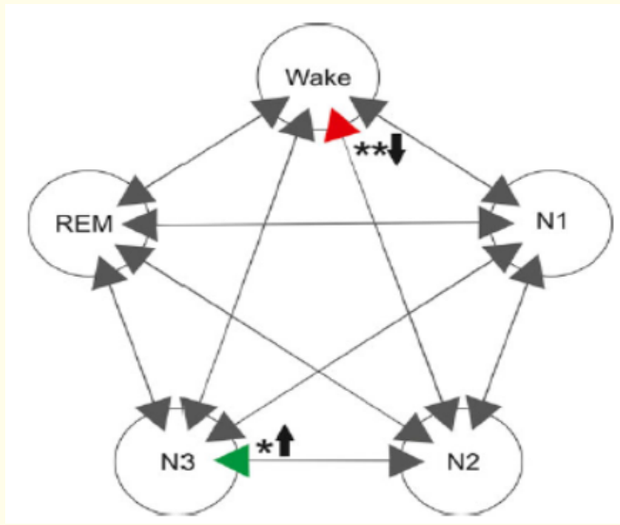

Figure 14: *Diagram illuatrates different Sleep stages convesrion in treatement versus control arm [16].*

Use of transcranial direct current has been earlier evaluated for safety parameters in different indications [22] reviewed safety of 567 transcranial direct current sessions in approximately 100 patients.

Data suggests that (refer table 5) during therapy patients complained about tingling, itching, burning sensation, pain and fatigue. These complaints were found during active therapy, tingling sensation being commonest. Other complaints like headache may be associated with diseases like migraine. Overall, transcranial direct current therapy seems promising in management of insomnia, however multi centric clinical trials involving significant number of patients should validate the therapy.

		During tDCS vs. after tDCS	**Motor vs. visual cortex stimulation**	**Motor vs. temporal cortex stimulation**	**Visual vs. temporal cortex stimulation**
Tingling	Incidence	$p < 0.005$*	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Itching sensation	Incidence	$p < 0.05$*	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Burning sensation	Incidence	$p < 0.005$*	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Pain	Incidence	$p < 0.005$*	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Headache	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Fatigue	Incidence	*$p < 0.05$**	$p < 0.05$*	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difficulties in concentrating	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Nervousness	Incidence	$p < 0.05$*	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difference between stimulations	Incidence	—	$p < 0.05$*	n.s.	n.s.
Visual sensation, associated with the start/end of the stimulation	Incidence	—	n.s.	n.s.	n.s.

Table 5: *Complaints pertaining to the transcranial Direct current stimulation [22].*

The columns 2-4 contain the results of t-test compared the side effects depending on the tDCS electrodes.

**: Significantly higher during stimulation.*

***: Significantly higher in case of motor cortex stimulation but only during tDCS sessions.*

Role of exercise and physical activity in treatment of insomnia

In a randomized control trial [17] investigated role of weekly 150 minutes moderate physical activity for 6 months in insomnia patients: active group (n = 17) with control group without intervention (n = 18). Outcome measures observed: ISI (Insomnia severity index) at baseline versus at end of 6 months intervention (Primary outcome). Other secondary efficacy measures included: day time symptoms, fatigue and mood of patients. Results were promising in active group showing significant reduction in severity of insomnia symptoms (p = 0.03). Refer figure 15 for ISI scoring in active versus control group at baseline and post 6 month therapy. There was significant reduction in anxiety (p = 0.02) and depression (p = 0.05) levels as well.

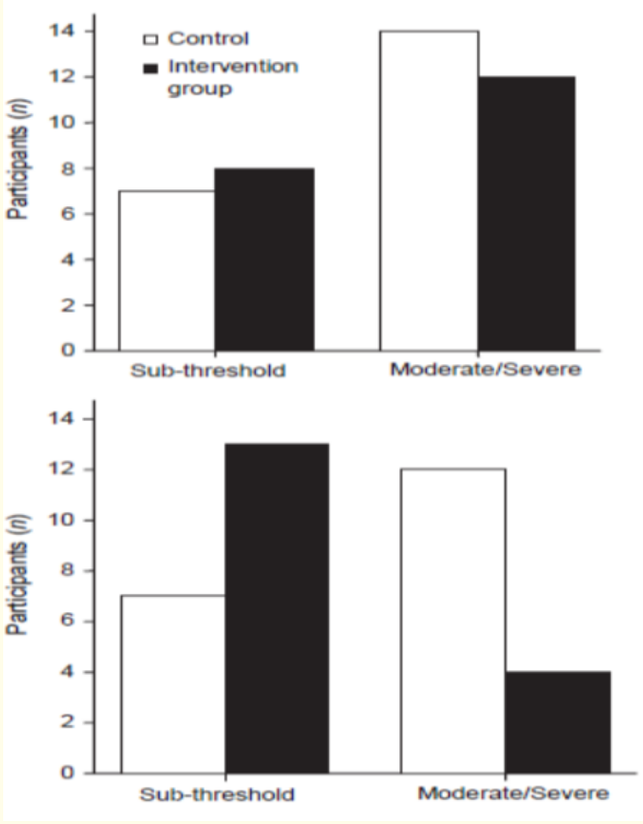

Figure 15: *ISI scoring in active versus control group [17].*

The concept of 150 hours/week moderate activity is in alignment with WHO prescribed standards 2010 was adopted in this study. There was 4 points reduction in ISI making study results favourable. Significant results were observed in active arm with respect to anxiety and depression symptoms. With respect to limitations, results in reduction in fatigue during day time did not show significant results in active group (p = 0.18). Also, number of subjects was limiting factor of study. Future studies are required in a large population for concept validation [23].

Limitations of the Study

Major limitation of the study was limited number of Interventional studies available for review. Further, the sample size used in these interventional studies was not significant to provide a direction or solid conclusion. This challenge was found in studies pertaining to the current available treatment options for insomnia and the novel emergent therapies of the same. Further, duration of the studies was not significant enough to evaluate the long term efficacious and/or adverse impacts on the newer technologies. Thus, it is critical that studies be conducted in much bigger sample size and for longer duration.

Limitations pertaining to cognitive behavioural therapy, pharmacotherapies (hypnotic, antidepressants antihistamine drugs) or insomnia treatment were critically reviewed.

In telephonic CBT, patients enrolled via telephonic interviews seems to be an ethical issue results are prone to information bias as all activities were telephonic [3].

In internet based CBT study, 19% of adverse events along with 1 minor accident in morning time was reported which raises safety concern with respect to CBT treatment. In case of individual BT and CT therapies, BT was found to be superior than CT alone in terms of Sleep efficacy and even CBT results were found to be similar to that of BT. These results are confusing enough with respect to selection of therapy for Insomnia management [5]. Sample size used in most of studies was very small and study results were difficult to be translated in general population.

With respect to pharmacotherapies, hypnotics were linked to mortality, cancer and day time accidents due to hangover [10,11]. Antihistamine use was found to be associated with misuse and drug dependence [12]. In a study conducted by Morin., *et al.* [7] 77 adverse events were reported in antidepressant drug arm.

Conclusion and Way Forward

The limitations of existing therapies provide an opportunity to look forward and explore novel potential treatments for insomnia.

Broadband sound in management of insomnia was found to significantly reduce sleep onset latency by 38% [15]. Similarly, thermal treatment based forehead device was efficacious with respect to improvement in sleep latency to stage N1 ($p = 0.006$), N2 ($p = 0.002$) and N3 ($p = 0.055$) (Roth., *et al*. 2017).

Novel drug delivery systems for melatonin could increase plateau phase duration of melatonin concentration from 4.4 to 6.7 hours in a PK study (Brodner., *et al*. 2017).

Slow oscillating current was also found safe and efficacious in insomnia treatment [16] and finally exercise and physical activity was found to be linked with treatment of insomnia in a positive manner [17].

Overall, all of these novel emerging technologies/treatments seem to have great potential in insomnia treatment. Future studies in a much larger population covering multiple demographics needs to be conducted to further evaluate their efficacy.

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