Finding Sleep in Multimorbidity: A Systematic Review of Evidence on Effective Treatment Modalities for Insomnia in People Living with Multimorbidity.

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Abstract

Background: Comorbid insomnia is a common presenting condition in medical clinics and primary care practice. This is often managed with pharmacotherapy with little success and higher healthcare costs. Despite the high prevalence of insomnia in people living with multimorbidity, its management remains challenging for primary care physicians as many of these patients have multiple symptoms, multiple comorbid conditions and are taking multiple medications. This study set out to systematically review the evidence on effective treatment modalities for comorbid insomnia with a view to determine what interventions ultimately translate to better therapeutic outcomes.

Methods: Published RCT studies were identified via medical and allied health online databases EMBASE, OVID, MEDLINE, CINAHL, Cochrane database and PubMed. Study selection and extraction was obtained from 32 randomised control trials were systematically extracted, collated and analysed. Those included were studies that examined the effects of interventions for comorbid insomnia in adults while studies without clear outcomes were excluded. The interventions included pharmacological and non- pharmacological methods while the outcome variables were subjective and objective sleep parameters.

Results: A total of 4,578 participants were reviewed (from 32 RCTs) with a mean age of 48.72 years. There was paucity of data from low-income regions, especially Africa. In developed countries, pharmacotherapy, cognitive behavioural therapy (CBT-I) and herbal therapy were effective in treating comorbid insomnia with moderate to large effect sizes.

Conclusion: While pharmacotherapy and CBT-I have both been found to be efficacious in managing comorbid insomnia, we advocate for more research in low- and middle- income countries.

Keywords: Insomnia, sleep, multimorbidity, comorbid insomnia, systematic review.

Introduction

Managing insomnia (also known as insomnia disorder) is a major challenge for patients, primary care physicians, health care providers, care givers and policy makers in medical practice.[1] It is said that about 1/3rd of patients in primary care present with sleep problems as part of their complaints and only a few of these will have satisfactory treatment or amelioration of symptoms. [1,2]About 25% of the adult population will present with sleep problems in their lifetime and 10-15% of these people will have symptoms of insomnia.[1] However, the prevalence of insomnia varies due to varying definitions.[1,2] According to a population based survey by Chung et al[3] in China, they defined the prevalence of insomnia based on the International Classification of Sleep Disorders (ICSD-2) as 15.1%, International Classification of Diseases (ICD-10, ICD-11, World Health Organization) as 4.7% and the prevalence based on the Diagnostic and Statistical Manual (DSM 1V and V) as 22.1%.Whereas, according to the American Insomnia Survey,[4,5] the prevalence of insomnia in the general population was estimated to be between 22.1% (DSM-IV TR) and 3.9% (ICD-10). Managing insomnia is costly; in the United States of America (U.S.A), the annual average cost of managing insomnia was estimated to be 1254 US Dollars per patient.[6] The indirect cost due to loss of work productivity was 1554 USD. [6]

Sleep problems are common in primary care but are often overlooked. The majority of sleep complaints occur within the context of medical and mental health multimorbidity.[2] According to Chung *et al.,*[3] a total of 46%- 80% of patients who complain of insomnia have co-morbid medical or psychiatric disorders. Also, multimorbidity is a risk factor for insomnia, with a 7- fold increase in the odds.[4]Insomnia is an heterogeneous complaint that may involve difficulties falling asleep (initial or sleep onset insomnia), trouble staying asleep with prolonged nocturnal awakenings (middle or maintenance insomnia) or early morning awakening with inability to resume sleep, causing dissatisfaction with daytime function.[5]The hallmark of the DSM-5 and ICSD-3 criteria for diagnosis is the emphasis on daytime functioning, and the persistence of symptoms for at least one month.[5] The DSM-5 also defines persistent insomnia (chronic insomnia in ICSD-3) as when symptoms persists for more than three months, and suggests CBT-I as a treatment modality. Insomnia is still under- diagnosed in primary care settings and often remains untreated even when the medical conditions have been effectively managed.[6]

The goal of the study was to determine the effective interventions for the management of insomnia in adult

patients living with multimorbidity, in order to develop management protocols for insomnia co- existing with other chronic medical conditions.

Research Methods

A systematic review was carried out to answer the research question using the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines.[7] The review included all randomized controlled trials with population of adult patients (> 18 years) who were living with multimorbidity and insomnia. The diagnosis of insomnia was based on either DSM V or ICSD criteria,[8-10] the use of sleep diaries and/or actigraphy, whereas multimorbidity was defined as the presence of 2 or more long-term health conditions.

The interventions were pharmacological and non-pharmacological therapies for insomnia. The comparator groups had treatment as usual (TAU) or were put on a waiting list for the treatment. The primary outcome variables were changes in sleep parameters as measured by the Insomnia Severity Index or the Pittsburgh Sleep Quality Index while secondary outcomes were depression and anxiety scores, pain scores and other symptom scores associated with the comorbid condition.

Selection Criteria:

The review included all randomized controlled trials from 1996 to 2021. The studies were those involving treatment of insomnia in the context of multimorbidity (insomnia plus one or more chronic medical condition) in adults 18 years and above. The authors excluded studies on primary insomnia, those with very small sample size, and grey literature.

Search Strategy:

Published studies were identified via medical and allied health online databases, EMBASE, OVID, MEDLINE, CINAHL, Cochrane database and PubMed. Hand searching was also done from identified references using google scholar.

The required data were systematically extracted and recorded in a data collection form and meticulously reviewed by the authors. The studies included in the review were described, the information collated, narrated and organized into themes. The findings from the studies were critically appraised and analyzed. The search terms used were multimorbidity/ comorbidity, comorbid insomnia/ secondary insomnia, treatment/ management. The search was from 1996 till 2021, and only English articles were considered.

Results:

The formal search strategy identified a total of 102 articles for review. After removal of duplicates, the number of articles reduced to 81. Out of the 81 identified articles, 12 did not have their full texts available. A total of 69 full texted articles were screened for eligibility and only 32 met the inclusion criteria; (See Figure 1). A total of 37 studies were excluded. The main reason for exclusion was they had an inappropriate study design (not randomized control trials or clinical trials). Also, three studies were excluded due to their very small sample size of less than ten participants as this would have reduced the power of the said studies and this was an exclusion criterion.

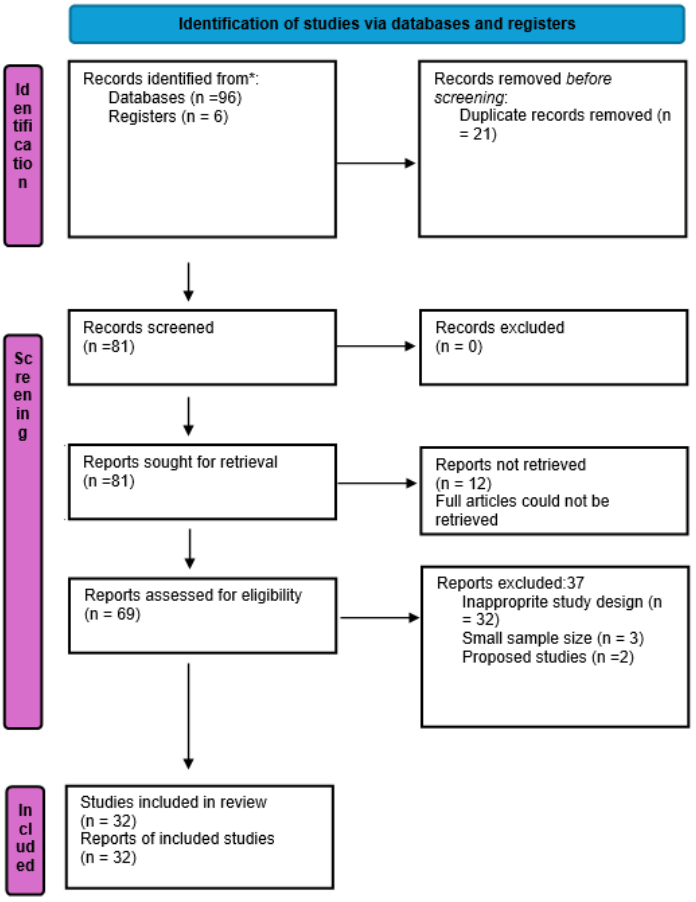

Figure 1: PRISMA Flow Chart of Study

Study Characteristics

Table I shows the descriptive data of the 32 studies included in the systematic review. The total sample size was 4578(range of 10- 1385 patients). Majority of the patients were middle-aged with an average age of 48.72 years from the 27 studies that reported a mean age. The participants were predominantly females (70%) and most of the studies in the review were carried out in economically affluent countries. There was a dearth of studies from low- and middle- income countries as there was no study from Africa, just three studies from Asia, and one study from the Middle East. Only 10 studies reported the socio- economic status of participants, where an average of 49.5% participants were employed.

No.	Study	Country	Mean/ median age in yrs. (SD)	Gender (% females)	Socio-economic status
1.	Contreneo et al, 2002 [11]	Italy	78.9	70%	Not reported
2.	Mc Curry et al 2021[12]	USA	70.2 (6.8)	74.6%	Not reported
3.	Cheng et al, 2019[13]	USA	44.5 (15.8)	79%	30% employed
4.	Von Koff et al, 2012[14]	USA	Not reported	Not reported	Not reported
5.	Smitherman et al 2016[15]	USA	30.8	90.3%	Not reported
6.	Jasson- Frojmark et al 2012[16]	Sweden	57.8(6.6)	58.9%	96.7% employed or student
7.	Pollack et al[17]	USA	40	66%	Not reported

8.	Casault et al, 2015[18]	Canada	Not reported	95%	66% at least college or university degree
9.	Manber et al, 2008[19]	Stanford	35(18)	61%	Not reported
10.	Alessi et al 2021[20]	Italy	Not reported	Not reported	Not reported
11.	Tanaka et al, 2015[21]	Japan	69.7(8.1)	78%	73% had good economic situation
12.	Baron et al, 2011[22]	USA	48.6 (9.6)	78%	27% employed
13.	Sweetman et al, 2019[23]	Australia	58.2(9.9)	45%	Not reported
14.	Tang et al, 2021[24]	USA	66.7(5.2)	87%	Not reported
15.	Roth et al, 2018[25]	USA	52.1 (9.5)	86.9%	Not reported
16.	Ranjbar et al, 2018[26]	Iran	38.6(12.5)	Not reported	Not reported
17.	Javaheri et al, 2019[27]	USA	71.6 (9.5)	25%	79.9% had at least college education
18.	Mc Crae et al, 2019[28]	USA	54.1(11.0)	97%	37.1% employed
19.	Sadler et al, 2018[29]	Australia	74.7(7.1)	55.6%	79.1% on pension
20.	Norrel Clarke et al, 2015[30]	Sweden	49.3 (12.5)	Not reported	68% employed or student
21.	Hsu et al, 2015[31]	Taiwan	52.4	60.6%	39.4% employed
22.	Ashworth et al, 2015[32]	USA	Not reported	61%	Not reported
23.	Garland et al, 2016[33]	Canada	58.9(11.08)	72%	48% employed
24.	Wagley et al, 2013[34]	USA	43.6	70%	Not reported
25.	Vitiello et al 2009[35]	USA	Not reported	Not reported	Not reported
26.	Jasson- Frojmark et al, 2021[36]	Sweden	57.8	62.7%	96.7% employed or student
27.	Latif et al, 2018[37]	Norway	36.4(8.8)	76.3%	Not reported
28.	Redeker et al, 2013[38]	USA	59.2(14.8)	52.1%	Not reported
29.	Taylor et al, 2015[39]	USA	50.1(13.1)	91%	56.5% had at least high school education
30.	Okajima et al, 2013[40]	Japan	45.5(15.5)	66.7%	Not reported
31.	Epsie et al, 2008[41]	UK	61(10.5)	68.7%	38% employed
32.	Savard et al, 2005[42]	Canada	58.8(7.8)	Not reported	44% employed

Pattern of Multimorbidity

Multimorbidity was reported as a combination of two conditions in 26 studies, a combination of three conditions in two studies and a combination of four conditions in a study. (Table II).

Table II: Pattern of multimorbidity in the systematic

Insomnia + Psychiatric conditions	Insomnia + Chronic medical conditions	Insomnia + physical Disability	Insomnia + Cancer	Insomnia + Mixed disorders
Insomnia+depression [6,13,29,30-32,34,40]	Insomnia+ osteoarthritis [12,14,24,35]	Insomnia+ hearing impairment[16]	Insomnia+ breast cancer [42]	Insomnia+ depression+ multiple sclerosis [22]
Insomnia+ generalized anxiety disorder [21,36]	Insomnia+ chronic headache [15]		Insomnia+ mixed cancers [18,41]	
Insomnia+ anxiety+ depression [26]	Insomnia+ coronary artery disease [27]			
Insomnia+mixed psychiatric disorders [39]	Insomnia+ fibromyalgia [28]			
Insomnia+ opioid dependence+ anxiety+ depression [39]	Insomnia+ heart failure [38]			
	Insomnia+ hypertension+ diabetes [11]			
	Insomnia+ rheumatoid arthritis[25]			
	Insomnia+ obstructive sleep apnoea [20,23]			

Pharmacological Treatment of Comorbid Insomnia

A total of five randomized control trials[11,17,25,26,31] (table III) examined the effectiveness of pharmacological agents in treatment of comorbid insomnia: Zolpidem, escitalopram with add-on ezopiclone, 3mg eszopiclone nocte, extended-release naltrexone and the herb, Melissa officialis with Nepta menthoides.[11,17,25,26,37] There was an increase in the sleep hours and quality of sleep as compared to 'treatment- as- usual' when 10mg zolpidem was used in the management of insomnia/hypertension/diabetes multimorbidity. The effect size and level of statistical significance was however not stated.[11]The use of 10mg Escitalopram oxalate with 3mg eszopiclone for insomnia/ generalized anxiety disorder multimorbidity showed a significant improvement in sleep latency when compared with the control (d= -25minutes versus -11minutes), p< 0.001.[17] There was also a significant increase in total sleep time (d= 61 minutes versus 35minutes, p< 0.001) and a reduction in the anxiety component of the Hamilton Depression Scale (d= -11.96 versus -10.80, p= 0.007).

Table III: Effectiveness of Pharmacological Treatment of Comorbid Insomnia.

Study	Setting	Multimorbidity	Intervention	Control	Primary outcome measure/ outcome	Secondary outcome measure/ outcome
1. Contreneo et al[11]	hospital	Insomnia + Hypertension + Diabetes	10mg Zolpidem nocte	Treatment as usual	Sleep diary: increase in sleep hours and quality	Not reported
2. Pollack et al[17]	hospital	Insomnia + GAD	10mg Escitalopram + 3mg eszopiclone x 8 weeks	10mg Escitalopram+ placebo	Sleep Latency: Reduced SL (-25 vs -11 minutes) p< 0.001	TST increased (61 mins. Vs 35 mins.) P< 0.001 HAM-A Score reduced (-11.96 vs-10.8) P=0.007
3. Roth et al[25]	hospital	Insomnia + Rheumatoid arthritis	3mg eszopiclone nocte x 4 weeks	placebo	ISI: significant reduction in ISI score (d= 1.30 vs 0.43) P< 0.0001 WASO: Reduced WASO (20 mins. Vs 40 mins.) P< 0.0001 SL: Reduced SL (27.0 VS 43.8min.) P= 0.003 TST: Increase in TST (402 VS 364.7 mins.) P< 0.0001 Improved sleep quality (7.5vs 5.9) P< 0.0001	ASES: Improved ASES scores (0.61vs 0.17) P= 0.05 SF-36 Improvement in role physical and bodily pain P<0.05
4. Ranjbar et al[26]	hospital	Insomnia + Anxiety + depression	Melissa officialis 1000mg+ Nepeta menthoides 400mg	placebo	ISI: d= -5.39 P= 0.08	BDI: d= -9.03 P= 0.05 BAI: d= -6.35 p<0.001
5. Latif et al[37]	hospital	Insomnia + Opioid dependence + Depression + anxiety	Extended- release Naltrexone hydrochloride 380mg IM every 4 weeks.	4- 24mg (target dose 16mg) daily dose of oral combined Buprenorphine-Naloxone	ISI: Effect size= -0.32 P=0.008	Depression: Effect size= -0.12 Anxiety Effect size= -0.14 p> 0.05

ISI- Insomnia Severity Index; SL-Sleep Latency; TST- Total Sleep Time; WASO- Wake up After Sleep Onset; HAM- Hamilton Anxiety Scale; ASES- Arthritis Self Efficacy Scale; SF-36- Short-Form 36 of Health- related Quality of life Questionnaire; BDI- Beck's Depression Inventory; BAI- Beck's Anxiety Inventory; p- p value; d- within group difference.

Non- pharmacological Management of Co-morbid Insomnia

Audio-visual stimulation

Tang et al [24]reported that the use of audio- visual stimulation in the management of insomnia/ osteoarthritis co- morbidity showed no statistically significant difference in sleep parameters, pain and depression when compared to a placebo (table IV). There was however some improvement from baseline to follow up in both groups.

Table IV: Effect of Audiovisual Stimulation in the Management of Co- morbid Insomnia

Study/ multimorbidity	setting	intervention	control	Primary outcome measure/ result		Secondary outcome measure/ result	
Tang et al[24]	Hospital	30- minute delta wave- audio-visual stimulation	placebo		Cohen d	p	Cohen d	p
				ISI	0.41	0.659	BPI	0.41
				PSQI	0.60	0.314	0.597	
				SOL	1.35	0.131	PHQ	0.60
				WASO	0.69	0.192	0.701	
				TST	-0.15	0.066		
				SE	-1.39	0.145		

ISI- Insomnia Severity Index; PSQI-Pittsburgh Sleep Quality Index, SOL-Sleep Onset Latency; TST- Total Sleep Time; WASO- Wake up After Sleep Onset, SE- Sleep Efficiency- Brief Pain inventory, PHQ- Patient Health Questionnaire, p- p value; d- within group difference.

Cognitive Behavioural Therapy

A total of N=26 studies reported the effectiveness of Cognitive Behavioural Therapy for insomnia (CBT-i). These were administered as physical or face-to-face CBT-I (individually or in groups), Remote CBT-I (via telephone or internet- based) or a combination of several modalities of administering CBT-i. These interventions produced low to moderate effect sizes in sleep parameters. (See tables V- VII)

Table Va: Effect of Face- Face CBT-I on Comorbid Insomnia

Study	Setting	Intervention	Control	Primary outcome	Secondary outcome
Von Korff et al[14]	population	6 sessions of CBT-PI and CBT-P alone	Education only	D P ISI 1.3 <0.001	D P AIMS 0.7 <0.001
Smitherman et al[15]	hospital	30 minute bi- weekly CBT-I sessions	Lifestyle modification	D P HIT 1.06 0.883	D P PSQI 13.7 0.009 SE 3.7 0.001
Jasson Froimark et al[16]	hospital	10- weekly individual face-face therapy	TAU	D P ISI 2.7 <0.001	D. P GAD7 1.0<0.001 PHQ 0.84 BBQ 0.45 TST. 0.87 SOL. 1.30
Alessi et al[20]	hospital	5 sessions of 5- weekly CBT-I+ PAP adherence	5 sessions of 5- weekly sleep education	D P PSQI. -0.82<0.001 SOL -0.50 0.013 WASO 0.64 0.39 SE 0.64. 0.001 CPAP 0.42 0.021	D P ISI -0.81 <0.001 ESS -0.81 0.001 FOSQ 0.49 0.002
Sweetman et al[23]	hospital	4- weekly, 45 -minute individual or small group sessions of CBT-I	TAU	D P ISI 0.6 0.497 CPAP 0.38 0.023	D P TST 0.6 <0.001 SOL 0.72 <0.001 WASO 0.74 <0.001 SE% 1.30 <0.001
Mc Crae et al[28]	hospital	8 sessions of individual CBT-I and CBT-P	Wait list	D P WASO 0.86. 0.26 SOL. 1.09. 0.50 SE. 1.55. 0.06 TST. 0.38 0.19	D P PDI 0.39. 0.059 BDI 0.51 0.007
Sadler et al[29]	hospital	Group or individual CBT-I or CBT-I plus mood strategies	psychoeducation	D. P ISI. 2.57. 0.023 GDS. 2.64. 1.39	D P SOL 1.65. 0.05 WASO 1.07. TST. 2.21 SE 2.73 SQ 2.48

ISI- Insomnia Severity Index; PSQI- Pittsburgh Sleep Quality Index; AIMS- Arthritis Impact Measurement Scale; HIT 6- Headache Impact Test; PHQ- Patient's Health Questionnaire; GAD- Generalized Anxiety Disorder; SE- Sleep Efficiency; SOL- Sleep Onset Latency; TST- Total Sleep Time; WASO- Wake After Sleep Onset; EMW- Early Morning Wakening; DBAS- Dysfunctional Beliefs About Sleep; TIB- Time in Bed; PDI- Pain Disability Index; BDI- Beck's Depression Inventory; GDS- Geriatric Depression Scale; MBSR- Mind Based Stress Reduction program; SLAT- Sleep Latency; MPQ- Mc Gill Pain Questionnaire; SF- Pain- Pain component of Short Form- 36 Questionnaire; EMA- Early Morning Awakening; WSAS- Work and Social Adjustment Scale; PSWQ- Penn State Worry Questionnaire; BBQ- Brunnsvoken Brief Quality of Life; HADS-Hospital Anxiety and depression scale (anxiety component); HADS-D - Hospital Anxiety and Depression Scale Depression component; CBT-i- cognitive behavioural therapy for insomnia; ESS- Epworth Sleepiness Scale; FOSQ- Functional Outcomes of Sleep Questionnaire; AIS-Athens Insomnia Scale; SDS-Self-rating Depression Scale.

Table Vb: Effect of Face- Face CBT-I on Comorbid Insomnia Contd.

Study	Setting	Intervention	Control	Primary Outcome	Secondary Outcome
Norell- Clarke et al[30]	hospital	4 bi-weekly sessions of group CBT-I	Group relaxation training	D P ISI 0.79 <0.01 BDI 0.31 0.014	D P SOL 0.42. 0.78 WAS0 1.06 0.002 EMW 0.08 0.850 TST 0.8 0.190 SQ 0.53 0.008
Hsu et al[31]	hospital	Weekly 90- minute group CBT-I for 6 weeks	Health education	D P PSQI -3 0.58	D P DBAS. -27 0.307
Ashworth et al[32]	hospital	4 sessions of individual CBT-I	Self- help CBT-I	D P ISI 3.65 0.35 PSQI 2.53 0.001	Not reported
Garland et al[33]	hospital	Weekly 90- minute group CBT-I	90- minute group MBSR counselling	D P ISI 3.65 0.35 PSQI2.53 0.001	D P SOL 1.30 0.001 WASO 1.41 0.073
Okajima et al[40]	hospital	6 bi- weekly individual CBT-I + behavioural analysis	TAU	D P PSQI 1.25 <0.01 SQ 0.75 <0.01	D P AIDS 0.92 <0.01 SDS. 0.70 <0.01
Epsie et al[41]	hospital	5- weekly, 50- minute group CBT-I	TAU	D P HADS- A -0.57 0.01 HADS-D -0.54 0.004	D P SOL -0.86 <0.01 TST 0.27 0.001 WASO -0.97<0.001 SE. 1.09 0.001
Savard et al[42]	hospital	8- weekly group CBT-i	Waiting list	D P ISI 3.55 <0.05 TST 2.75 <0.05	D P Anxiety11.10 <0.05 QOL 15.63

Table VI: Effect of Remote CBT-I on Co- morbid insomnia

Study	setting	Intervention	Control	Primary outcome measure/ outcome	Secondary outcome measure/ outcome
Mc Curry et al[12]	population	Six sessions of telephone-delivered CBT-I over eight weeks	Telephone-delivered 'education only on attention control'	d p ISI 0.30 0.05	d BPI 0.31. PHQ8 0.30 Fatigue 0.31
Baron et al[22]	hospital	Weekly-administered CBT-I for 16 weeks	Telephone supportive emotion-focused therapy	d p ISI -0.23 NS	Depression D P 0.05 <0.01
Cheng et al[13]	hospital	Weekly sessions of digital CBT-I (Sleepio[R] program via internet) over 6 weeks	Online sleep education via emails.	d p ISI -4.4 <0.01	D P QIDS 0.64 <0.001
Javaheri et al[27]	hospital	Web- based CBT-I + general sleep education	General sleep education	D p ISI 0.56 0.1 PHQ8 0.39 0.2 ESS 0.30 0.7	D p SBP 0.22 0.5 DBP 0.25 0.4 PGH 0.22 0.5 PPH 0.67 0.07

QIDS- Quick Inventory of Depression Symptomatology; CHD-Coronary Artery Disease; SBP- Systolic Blood pressure; DBP- Diastolic Blood Pressure; PGH- Perceived General Health; PPH- Perceived Personal Health; ISI- Insomnia Severity Index; BPI- Brief Pain Inventory; PHQ-8- Patient's Health Questionnaire 8; ESS- Epworth Sleepiness Scale; d= within group difference; D= between group

difference , p= p value.

Table VII: Effect of Mixed Methods CBT-I on Comorbid Insomnia

Study	setting	intervention	control	Primary outcome measure/ outcome	Secondary outcome measure/ outcome
Casault et al[18]	hospital	Minimal self- help CBT-I offered in bibliography format + three brief phone consultations.	Treatment as usual	D p ISI -1.2 <0.001 SOL -0.46 <0.01 WASO -0.46 < 0.05 TST 0.77 <0.01 SE. 1.25 <0.001	D p HADS-A 0.60 <0.001 HADS-D- 0.7 <0.001 MFI 0.56 <0.05
Tanaka et al[21]	community	One 60- minute group session, one 45- minute individual session + two follow up telephone sessions of CBT-i.	Wait list	D p PSQI 1.71 0.16	D P GDS SF 1.83 <0.01
Wagley et al[34]	hospital	Two CBT-I sessions consisting of one 60- minute in-person session and a follow up telephone session.	Wait list	D p PSQI. 1.62 0.216 PHQ9 3.58 0.01	No secondary outcome
Redeker et al[38]	hospital	Bi- weekly group CBT-I + telephone calls	Attention control	D P ISI 0.65 0.03 SL. 0.33 0.35 GSQ. 0.46 0.14 Sleep duration 0.15 0.61 Time in bed 0.30 0.31 Sleep efficiency 0.38 0.21	D p Fatigue 0.64 0.04 Sleepiness 0.06 0.82 Depression 0.06 0.83 Anxiety 0.12 0.68 Physical function 0.25 0.39
Taylor et al[39]	hospital	Five sessions of individual CBT-I + follow up phone call	Treatment as usual	D p ISI 1.05 >0.05 SOL 0.80 >0.05 TST 0.89 >0.05 WASO 0.09 >0.05 SE 1.37	D P PHQ9 0 > 0.05 GAD7 -1 >0.05 SF-36. 1 >0.05

HADS-A – Anxiety aspect of Hospital Anxiety and Depression Scale; HADS- D- Depression aspect of Hospital Anxiety and Depression Scale; GSQ- Global Sleep Quality; ISI- Insomnia Severity Index; PSQI- Pittsburgh Sleep Quality Index; SOL- Sleep Onset Latency; WASO- Wake up After Sleep Onset; TST- Total Sleep Time; SE- Sleep Efficiency; GDS- Geriatric Depression Scale Short Form; PHQ-9- patient Health Questionnaire 9; MFI- Multidimensional Fatigue Inventory; SF-36- Short form 36 of Health Related Quality of L

Risk of Bias Assessment

This systematic review considered whether the conclusions made by the included studies were reliable and valid based on the methodological quality of the summarised research. Therefore, all included studies were appraised by using the Cochrane Collaboration's tool for assessing risk of bias. This involves appraising bias in selection, performance, detection, attrition and reporting domains. In each domain, studies were given a rating of low, high or unclear risk.

A total of 15 studies [12-21,26,28,29,31,33] included in the review were judged to have a low risk of bias, while 14 studies,[16, 22-25, 30,32,34,35,37-39,41,42] had a medium risk. For these studies who were found to have a medium risk of bias, the factors which increased their bias risk were: no allocation concealment, the participants were not blinded and carers and the people delivering the interventions were aware of which group received what treatment. Only three studies[11,27,40] had an adjudged high risk of bias. The study by Controneo et al [11] was a clinical trial with no randomization, blinding or allocation concealment. In addition, missing data were not accounted for and information was not provided regarding the process of data analysis. While in the study by Javaheri et al,[27] no information was provided regarding randomization, allocation concealment, blinding and the process of analysis. Also, in the study by Okajima et al,[40] there was no randomization, allocation concealment or blinding.

Discussion

It was observed from this review that majority of the studies were hospital- based studies from high- income countries. There was a paucity of studies from low- and middle- income studies and most especially, there was no study from Africa. This emphasizes the need for research in these resource poor regions where the burden of disease, and multimorbidity is high and resources for healthcare is abysmally scarce.

For the studies that provided data on the mean age of participants, a pooled average age 48.76 years was obtained. This agrees with the study by Linnet et al[43] where it was found that the prevalence of multimorbidity begins to peak at the age bracket (40-49) years and steadily increases with age. It was also observed that the studies that reported older mean ages were associated with medical conditions such as osteoarthritis,[12,24] coronary heart disease[27] and depression.[21,29] Although Contreneo et al also reported a mean age of 78.9 years for insomnia/ hypertension/diabetes comorbidity, the study included only participants greater than 75 years.[11] It was observed that in more than half of the study participants (2,528) had insomnia comorbid with a psychiatric condition. This fits the epidemiology of comorbid insomnia as it is commonly associated with psychiatric conditions.[44]

In this study, the primary outcome variables were the subjective sleep parameters using the self- reporting insomnia severity index and Pittsburgh sleep quality index. Objective sleep parameters such as SOL, TST, WASO, SE% and DBAS recorded by actigraphy and polysomnography were also included. The secondary outcomes varied widely due to the heterogenous combinations of diseases in the review. The outcome measures were tools for depression and anxiety (PHQ-9, HADS, HAM, BDI, GDS, QIDS, SDS), pain (BPI, MPQ), loss of function (MFI, ASES, FOSQ) and quality of life (SF-36, PGH,

PPH, MBSR, WSAS, BBQ).

Also, in this review, we found that pharmacological management of comorbid insomnia significantly increased sleep hours and quality in the various combinations of comorbid insomnia reviewed.[11,17,25,26,37] Hypnotics still remain one of the most commonly used drugs for insomnia, although their safety and side effects are questionable.[43] The antidepressants have the dual advantage of being sedating, and acting as antidepressants or anxiolytics.[44] In this study, CBT-I, delivered face-to- face or remotely, was found to be an effective treatment modality for comorbid insomnia with clinically meaningful effect sizes. A combination of both face-to-face and remote methods however produced mixed results with no added advantage. This is in keeping with more homogenous studies that have shown CBT-I to be effective in the management of comorbid insomnia and enhancement of one method with another may not produce a significant difference.[44-46] However, Lancee and colleagues found that motivational support via e mails improved the effectiveness of internet- delivered self- help treatment for insomnia. [47]

According to the American Academy of Sleep Medicine and the European Sleep Research Society, CBT-I is recommended as first line management of insomnia.[48] Although pharmacologic treatments such as benzodiazepine receptor agonists and low dose antidepressants are commonly used in primary care, randomized control trials comparing medications for insomnia and CBT-I indicate that CBT-I yields more durable sleep improvement over the course of time with fewer side effects. [48,49] A study by Natsky et al also found that in addition to the proven efficacy of CBT-I, it was also more cost effective when compared to pharmacotherapy or no treatment at all.[50] According to them however, this was a conservative submission due to the limited studies included in their review.[50]

Despite the proven benefits of CBT-I, access to psychotherapy is still very poor worldwide. Barriers include the initial cost of treatment, the time commitment involved, the stigma of psychotherapy, lack of public awareness and grossly inadequate behavioural sleep therapists.[51] A review by Thomas et al found that the population of clinicians trained in either behavioural sleep medicine or CBT-I is grossly inadequate worldwide with low- and middle- income countries being most affected.[51] In their study, they noted that apart from USA and Canada, no other country had more than seven board certified behavioural medicine specialists. [51] As a way to reduce this deficit, the task force of the European Sleep Research Society and European Insomnia Network in 2018 proposed a simpler approach to the 'stepped care' proposed by Epsie et al.[52] In addition to Epsie and colleagues' model of leveraging on remote CBT-I to provide stepped care, the European task force proposed the establishment of a CBT-I academy to train healthcare professionals and standardize CBT-I treatment. As family physicians are likely to see majority of patients with comorbid insomnia, they proposed that family physicians have the basic CBT-I training and they be in a position to prescribe CBT-I treatment for their patients.[52] Where face-to- face CBT-I may not be feasible, remote CBT-I has been found to be equally efficacious.[46,53,54] It has the advantage of reaching the approximately 3 billion internet users that would probably not have the luxury of meeting with a sleep therapist.[46] In addition, with the healthcare challenges currently being faced as an aftermath of COVID-19 pandemic, remote CBT-I is a perfect option for people with comorbid insomnia as it reduces hospital visits. Perhaps, remote CBT-I will be the solution to address the deficit in low- and middle- income countries. However, Ali et al posited that although remote CBT-I is promising in low- and middle- income countries, most of the internet- designed modules were developed in the Western world, they suggested that more culturally- suited modules be developed for low- and middle- income countries.[55] This should be the policy direction for these deprived regions of the world.

In conclusion, this systematic review found that there is paucity of information regarding effective treatment options for comorbid insomnia in low- and middle- income countries, especially in Africa. In the high- income countries, hypnotics (zolpidem and eszopiclone), herbal therapy of Melissa officialis with Nepeta menthoides were found to be effective treatment options for comorbid insomnia. The authors also found face-to-face and remote cognitive behavioural therapy to be highly effective with moderate to large effect sizes.

Strengths and Limitations of the Study

The strength of this study is that it sought to provide a simple and effective treatment modality for comorbid insomnia as an entity. The risk of bias in this review is low, as all but three of the included RCTs had low to medium risk of bias.

The study might be prone to publication bias, as only published articles were reviewed. The authors were unable to carry out a meta- analysis due to the heterogeneity of the combinations of morbidities and interventions reviewed. Also, due to the heterogeneous nature of the review, the author did not consider the time effect of the individual studies.

Implications for Practice

There is an urgent need for more studies on comorbid insomnia in Low- and middle- income countries to further understand and meet the needs of the regions.

This study highlights treatment options for comorbid insomnia and has provided information interventions that offer additional benefits tailored to the needs and circumstances of practice.

Family physicians in resource- poor settings may require basic CBT-I training to offer such services to their patients.

Implications for Policy

There should be policy drive towards developing and providing culturally acceptable CBT-I modules to be accessed online.

The authors also advocate for more training of psychotherapists to offer services, especially at primary care level.

Finally, supportive services such as internet network will enhance stepped care, skill mix and collaboration with more advanced countries in the management of comorbid insomnia.

Conflict of Interest

We declare that we have no financial or personal

relationship(s) which may have inappropriately influenced us in writing this paper.

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