

A Systematic Review of Efficacy and Safety of Pharmacological Treatments for Insomnia in Patients with Substance Use Disorder



Sarah HJ Lee, B.Sc.(Pharm).; Jane Dumontet, B.Sc.(Pharm), ACPR, Pharm.D.; Renee Bjarnson, B.Sc.(Pharm), ACPR.; Jacky Siu, B.Sc.(Pharm), ACPR, Pharm.D.

Background

- Substance use disorder (SUD) affects 22% of Canadians.¹ Alcohol, cannabis, heroin and cocaine are the most commonly abused substances.¹⁻²
- Reported prevalence of insomnia is up to 96% in the SUD population.³ Insomnia is associated with worsening psychiatric conditions and relapse of substance use.⁴⁻⁶
- There is a limited guidance in treating insomnia in SUD patients because of 1) concern for prescription drug abuse and 2) exclusion of SUD patients in studies.⁷⁻¹⁰

Objective

- To conduct a systematic review evaluating the efficacy and safety of pharmacological treatments for insomnia in SUD patients.

Methods

Design: Narrative systematic review

Types of studies: Controlled studies

Types of patients:

Inclusion	Exclusion
<ul style="list-style-type: none"> >18 years of age SUD (alcohol, cannabis, opioids and/or stimulant) Insomnia 	<ul style="list-style-type: none"> Acute substance withdrawal No insomnia prior to study Insomnia due to medical or situational cause(s)

Types of intervention:

- Benzodiazepines
- Antipsychotics
- Melatonin analogues
- Z-drugs
- Antidepressants
- Valerian root
- Antihistamines
- Anticonvulsants
- Tryptophan

Types of outcomes:

- Primary efficacy outcome:** insomnia improvement
- Secondary efficacy outcome:** substance abstinence
- Safety outcome:** serious adverse events (SAE), number of patients experiencing adverse events (ADE), drop outs due to ADE

Databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsychInfo (January 1946 to October 2015)

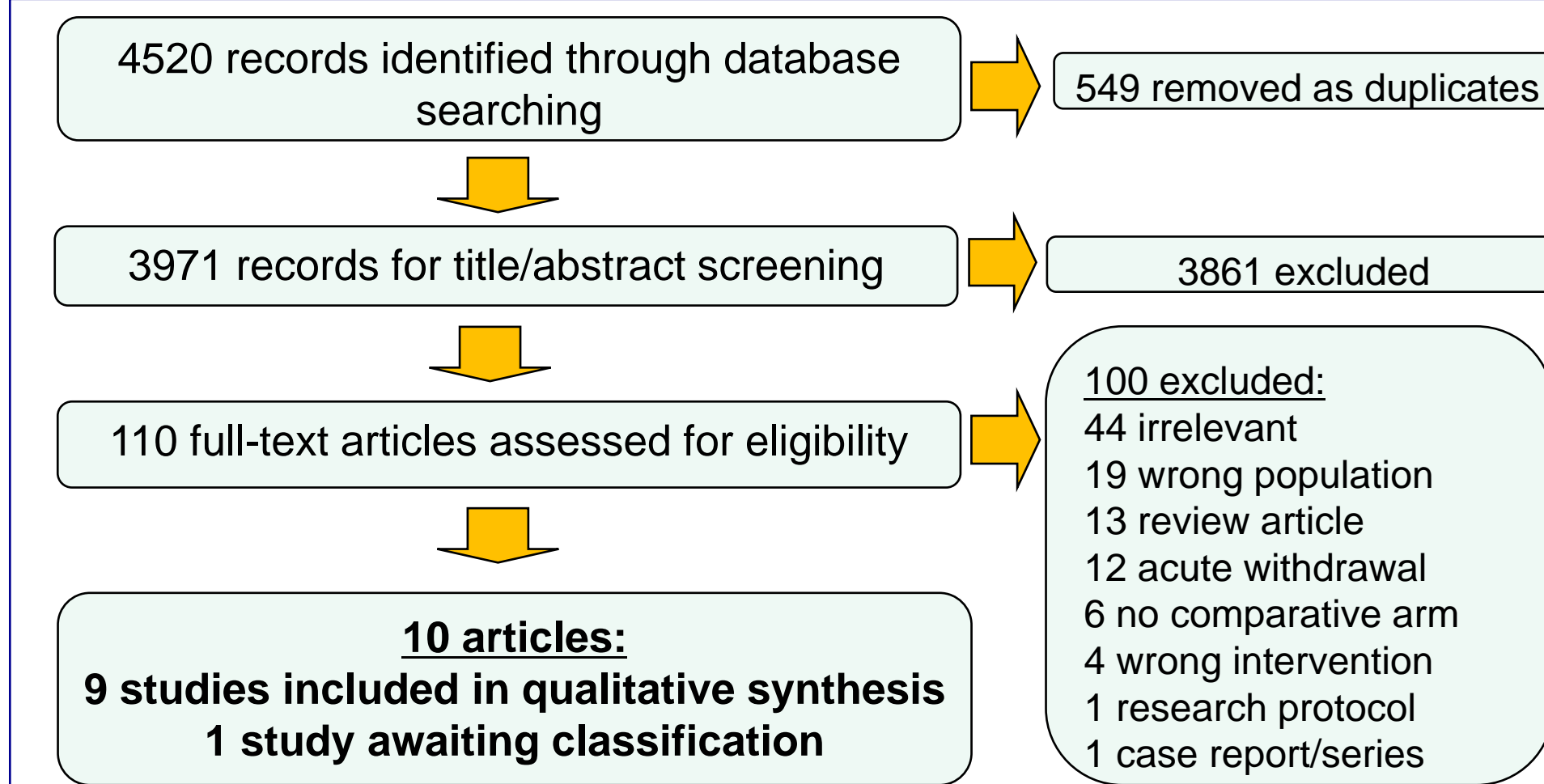


Figure 1: Trial Flow Diagram

Study design	Number of studies (N=10)
Placebo-controlled RCTs	5
Non-placebo-controlled RCTs	2
Non-randomized trials	2
Substance use	Number of studies (N=10)
Alcohol	7
Opioids	3
Cannabis	0
Stimulant	0
Pharmacological agents	Number of studies (N=10)
Trazodone	4
Gabapentin	2
Amitriptyline	1
Lormetazepam	1
Melatonin	1
Mirtazapine	1
Nitrazepam	1
Quetiapine	1
Zolpidem	1

Table 1. Results

	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome	Selective reporting
Ansoms	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	High risk of bias
Brower	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Chakravorty	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Friedmann	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Karam-hage	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Le Bon	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Ramdrug	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Stein	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Stoychev	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table 2. Risk of Bias

References

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Author	Design	Intervention	Control	n	Duration	Sleep Outcomes	ADE	Abstinence
Methadone Use								
Stein 2012	PC, DB, RCT	Trazodone 50-150mg PO HS as needed	Placebo	137	6 months	PSG PSQI Survey Sleep diary	NSS NSS NSS NSS	NSS Not reported
Stoychev 2009	OL, RCT	Melatonin 5mg PO in the evening	Zolpidem 10mg PO daily	21	4 weeks	Leeds Sleep Evaluation Questionnaire	NSS	Not reported Not reported
Alcohol Use								
Brower 2008	PC, DB, RCT	Gabapentin 1500mg PO HS	Placebo	21	12 weeks (Treatment 6 weeks)	PSG SPQ Sleep diary:	NSS NSS NSS	No SAE NSS NSS
Chakravorty 2014	PC, DB, RCT	Quetiapine XR 400mg PO HS	Placebo	22	8 weeks	PSG PSQI ISI	NSS except WASO NSS NSS	NSS NSS
Friedmann 2008	PC, RCT	Trazodone 150mg PO HS	Placebo	143	6 months (Treatment 3 months)	PSQI	Improved sleep quality No absolute differences given	NSS NSS
Le Bon 2003	PC, DB, RCT	Trazodone 50-200mg PO HS	Placebo	23	4 weeks	PSG	NSS except: -SEI2% ↑9% (p=0.015) -WASO ↓9% (p=0.015)	NSS Not reported
Karam-Hage 2003	OL	Gabapentin 300-1800mg PO HS	Trazodone 25-300mg PO HS	55	4-6 weeks	SPQ	↑2.7 scores For gabapentin (p=0.023)	Not reported Not reported
Ansoms 1991	RCT, cross-over	Zopiclone 7.5mg PO HS; Lormetazepam 1mg PO HS	Placebo x 2 days (same patients)	54	8 days	Spiegel Sleep Questionnaire	NSS except time to fall asleep for lormetazepam (p=0.013)	NSS Not reported
Ramdrug 2014	Case-control	Amitriptyline	No treatment	30	4 weeks	Total scores (Pittsburgh insomnia rating scale, distress sleep parameters, QoL)	Cases (↓50.3) Control (↓9.1) No analysis	Not reported Not reported

PC: placebo-controlled. DB: double blinded. OL: open-label. RCT: randomized controlled trial. ADE: adverse event
 PSG: polysomnograph. PSQI: Pittsburgh Sleep Quality Index. SPQ: Sleep Problems Questionnaire. ISI: Insomnia Severity Index.
 SEI2%: sleep efficiency after sleep onset. WASO: wake time after sleep onset. QoL: quality of life. NSS: not statistically significant. SAE: serious adverse events

Table 3: Summary of Included Studies & Outcomes

Discussion

- Studies were limited to patients with alcohol or opioid use disorders
- No study on cannabis or stimulant was found
- Low quality evidence - small number of placebo-controlled RCTs, small sample size, unclear and high risk of bias, and short duration of therapy
- 60% of studies reported safety and 30% of studies reported abstinence data

Conclusions

- No study was found for cannabis or stimulant dependent patients with insomnia
- Current evidence does not support the use of pharmacological treatments for insomnia in SUD patients
- Further studies are needed to assess the efficacy and safety of pharmacological treatments