Review Article

Homoeopathic perspective in the management of Substance Use Disorders: A systematic review

ABSTRACT

Background: Substance abuse has become a widespread global issue. It includes abuse of illegal substances, namely marijuana, heroin, cocaine and methamphetamines, and legal substances, including alcohol, nicotine or prescribed medicines.

Aim of review: This review assesses the role of Homoeopathy in the therapeutic management of Substance use disorders (SUD) through a systematic web-based literature search.

Methods: A comprehensive search was conducted online and manually to identify homoeopathic research studies published between 1993 and 2022 on SUD in international databases and the Central Council of Research in Homoeopathy library. Relevant studies were categorised and assessed in terms of study designs, number of participants, evidence grades and clinical outcome parameters. A total of 21 full-text studies were screened and evaluated. Risk of bias (RoB) was assessed for all studies and model validity was appraised for the included RCTs'.

Results:.10 studies (3 Randomised Controlled Trials, 3 Observational studies, 1 Pilot study, 1 observational comparative study, 1 Retrospective cohort study and 1 case series) were included and 11 studies were excluded with reasons. 03 studies have a level of evidence of 1b with an 'A' grade of recommendation, which consists of the RCTs only. The most commonly prescribed medicines identified were: *Arsenic album, Nux vomica, Lycopodium, Pulsatilla, Sulphur, Staphysagria, Belladonna, Ipecac, Chamomilla, Rhustox, Phosphorus and Lachesis.*

A high risk of bias was elicited in most of the observational studies accentuating the need for more robust methodological studies.

Conclusion: The majority of the studies have a small number of recruitments. Pragmatic studies with larger sample sizes and validated outcome measures may be designed further to validate the promising role of homoeopathic medicines in SUDs and generate quality evidence.

Keywords: Substance use disorders, alcohol withdrawal, opioid withdrawal, Homoeopathy, Drug abuse.

INTRODUCTION

Alcohol, caffeine, cannabis, hallucinogens (phencyclidine and other similarly acting arylcyclohexylamines, as well as other hallucinogens, such as LSD), inhalants, opioids, sedatives, hypnotics, or anxiolytics; stimulants (including cocaine and other stimulants); tobacco; and other or unknown substances are the ten different drug classes that the DSM 5 identified for substance-related disorders. Substance use disorders and substance-induced disorders are the two categories of substance-related disorders. When a substance is persistently used despite issues, a pattern of symptoms develops called substance use disorders. Collaterally, substance-induced disorders such as intoxication, withdrawal and other substance/medication-induced mental disorders are also manifested. "Withdrawal is manifested by either a person having the characteristic withdrawal symptoms for the substance, or a person using the same or closely related substance to avoid the substance-specific withdrawal symptoms." [1]

Adverse effects on people's health are one of the main effects of illicit drug use on society. Drug use puts a heavy financial load on individuals, families and society. Socio-demographic trends are also influential such as the population's gender, age and the rate of urbanisation. Injecting drugs carries a high risk of infection with blood-borne viruses such as HIV, hepatitis B and hepatitis C and sharing contaminated needles and syringes is an important mode of transmission for those viruses.[2]

Substance abuse is one of the fields which needs special attention worldwide. For a long time, western countries have been in the limelight for drug abuse, but now it's been an ever-growing phenomenon among Indians for the past two decades. Increasing stress, economic burden, loss of moral and traditional values, also dwindling supportive bonds are the major causes of the Indian population to indulge in this area.[3] In June 2022, United Nations Office on Drugs and Crime (UNODC) presented a report in which Around 284 million people aged between 15-64 used illicit drugs worldwide in 2020, 30 percent more than in 2009 and 26 percent increases over the previous decade. Also, according to reports globally, 11.2 million people worldwide were injecting drugs. Out of these, approximately half were living with hepatitis C, 1.4 million were living with HIV and 1.2 million were living with both.[4] The fourth round of the National Family and Health Survey (NFHS-4), conducted in 2015–16, estimated the prevalence of tobacco and alcohol consumption among 112,122 men aged 15–54 years.[5]

Various emerging factors contribute to this epidemic which is rapidly spreading its legs in the society. Familial risk factors are the major contributors, including childhood maltreatment such as abuse and neglect, disturbed marital status of parents, parent's education status, child-parent relationship, socio-economic status of the family and negligence among youngsters. Physical, sexual and emotional abuse affected during childhood and adolescence is another crucial risk factor for substance misuse, increasing the likelihood of abuse by two to four times. Social risk factors like deviant peer relationships, popularity and bullying also contribute to increased incidences of substance abuse. Subjective risk factors like Attention-deficit hyperactivity disorder (ADHD) and depression are other major contributors to the pandemic of substance abuse in society. [6]

Cannabis, heroin and Indian-produced pharmaceutical drugs are the most frequently abused drugs in India. [3] Heroin has replaced natural opioids (opium and poppy husk) as the most commonly abused opioid. The usage of other synthetic drugs and cocaine have also increased significantly. [7] In India, alcohol has been consumed for centuries. However, recently, the sale and consumption of new alcoholic beverages with higher alcohol content—such as "strong beers" and "English liquors" like

whisky, scotch and brandy—has started to replace the more traditional libations. [8] India also faces a dual burden of tobacco use in the form of smoking and smokeless tobacco. The number of female tobacco users is still in trend in some northeastern states like Sikkim and Mizoram despite the implementation of the National tobacco eradication programs. [9]

Injecting drug use has become apparent among street children and so have inhalants. In alcohol dependence, high rates of depression, cluster B personality disorders and phobia have been demonstrated along with increased susceptibility to HIV/AIDS and other sexually transmitted diseases. Delirium and convulsions can also complicate opioid withdrawal states. Substance use among women and children is increasingly becoming the focus of attention and merits further research. [10]

Substance abuse should be treated as a chronic illness having behavioural components. Within the cycle of chronic addiction and recovery, there are also exacerbations of acute as well as chronic multiorgan system complications. Successful treatment of all chronic diseases requires a good relationship between patients and doctors and a non-judgmental approach. [11]

According to various research, standard treatments for substance abuse are still non-satisfying. The long-term use of these drugs leads to side effects, thereby poor compliance to medication, which always remains a challenge. [12] One of the studies among American Indians and Alaskan native communities revealed challenges in providing quality substance abuse treatment. The major challenges described were providing clinical services, the infrastructure of treatment settings and a greater service/treatment system. Also, substance abuse treatment services require a more integrated, individualised, comprehensive and longer-term approach to care. [13] Another study identified well-defined latent construct barriers for substance abuse. These are the Absence of Problem, Negative Social Support, Fear of Treatment, Privacy Concerns, Time Conflict, Poor Treatment Availability and Admission Difficulty.[14]

Another study highlighted that the psychosocial rehabilitation setting improved recruitment but was not sufficient to decrease dropout frequency among Brazilian cocaine treatment seekers. [15]

Keeping in view these limitations posed in the treatment of SUDs and owing to the varying degree of associated side effect profiles in standard treatment for SUDs, there has always been a need for a supporting and alternate intervention for SUDs. The current web-based systematic review is undertaken to underline the potential and promising role of homoeopathic medicines in SUDs through assessment of the underlying homoeopathic approaches followed in the past conducted studies to expand more viable management strategies in varied types of drugs abused. This review is undertaken to identify the gaps, deficiencies and trends followed for homoeopathic treatment in SUDs. The objective is to formulate robust research designs by addressing the inadequacies of the previously concluded studies and framing advanced clinical homoeopathic guidelines in SUDs. The current review not only reflects upon the homoeopathic approaches followed in previously completed studies in the light of modern science but also aims to enable clinicians to effectively treat SUD patients in reducing the drug menace in society by breaking the chain of addiction through timely management of cases.

Materials and Methods

The following criteria were adopted for undertaking this review:

Types of studies

The present review included studies where the homoeopathic interventions aimed to treat or manage substance abuse. All types of Randomised Controlled Trials (RCTs) and observational studies undertaken in programmed setting entailing the abuse of alcohol, cocaine, heroin, marijuana, nicotine or any other medically prescribed drug, etc., were included in the review. Well-documented and peer-reviewed case reports and case series were also included. Studies related to exclusively allopathic and complementary modes of therapeutics (Ayurveda, Unani, Siddha, Yoga and Naturopathy) without homoeopathy, Postgraduate and PhD dissertations on substance abuse, animal experiments, letters

from editorials, any duplicate articles, conference proceedings, correspondences, personal experiences/viewpoints and review articles were excluded from this review.

Search methods for identification of studies

Electronic searches

A systematic literature search was conducted in the leading national/international search databases and advanced search engines (PubMed, Medscape, Science Direct, Google Scholar) and CCRH Homoeopathic Archives of India and AYUSH portal for all clinical studies published between the years 1993 to April 2022. The keywords used to search this literature review are substance abuse, opioid withdrawal, alcohol dependence, homoeopathy, alcohol withdrawal, cocaine, heroin and drugs.

Manual searching

A manual search was undertaken at CCRH, an apex body undertaking homoeopathic research in India. The CCRH library publishes Current Health Literature Awareness Services (CHLAS), indexing the Journals/titles available in the library on a quarterly basis.

Online and manual literature searches were carried out by one researcher (US). The second researcher (SS) and third researcher (HR) checked all searches for their appropriateness. Screening of all articles (at titles/abstract and full-text level) was carried out by the first and second researchers. A total 21 number of articles were identified, of which 11 were excluded and 10[12,15,19-25] articles were included. Review articles, animal experimentations, thesis/dissertations, annual meeting reports and case reports are excluded from the studies.

Data analysis

The first (US) and second researchers (SS) extracted, appraised and analysed data. The studies were assessed manually by the researcher (SS) and details of the studies were also added manually. The data of studies was re-examined and cross-checked for entries by the first researcher (US) and third

researcher (HR). A consensus was also reached for all studies after analysis for assessment of Risk of bias (RoB) and model validity [16] was also appraised for the included RCTs. RoB was assessed according to the Cochrane Collaboration guidelines [17] and the details of searches of studies, excluded and included studies are tabulated in Table 1 and reported according to PRISMA. [18]

(Table.1 Overview of Homoeopathic Studies on Substance Abuse Disorders)

RESULTS

Number of articles

A total of 21 articles were searched related to SUD and Homoeopathy in the review. Out of 21 articles, 11 were excluded (01 case report, 01 dissertation, 02- animal experimentation, 03- annual reports, 04- review articles). 10 articles related to homoeopathic treatment or management of SUD were included, out of which 01 case series [23], 01 pilot study [22], 01 Retrospective cohort study[26], 03 RCT[12,15,21] and 04 observational studies were present. [19,20,24,25]. [FIGURE NO. 1]

Number of participants

01 case series included 30 patients [23], 01 pilot study included 10 patients [22], 01 retrospective cohort study had recruited 53 patients [26], 03 included RCTs had 80, 54 and 169 patients respectively [12,15,21] and the remaining 03 observational studies included 40,112 and 261 subjects [24,20,25]. 01 comparative observational study had not specified the number of participants and was found inconclusive [19].

Duration of Treatment

The studies showed a variation in the duration of treatment ranging between a minimum of 28 days to a maximum of 12 months [13-24]

Homoeopathic treatment approach

05 studies included in the current review followed a constitutional homoeopathic approach [12,20,21,25,26] and 04 studies followed a symptomatic approach [15,19,22,23], while one study did not have any specific approach [24].

Medicines prescribed frequently

The most commonly prescribed medicines identified under the review are *Arsenic album, Nux vomica, Lycopodium, Pulsatilla, Sulphur, Staphysagria, Belladonna, Ipecac, Chamomilla, Rhustox, Phosphorus and Lachesis.* In one of the studies, Q potencies of *Opium and E. Coca* were given [15]. The potencies most commonly used were 30[12,21,22,25] and 200[12,19,22,25]. In some of the studies 3X[23] and 6X[25] potencies were used and in some of the studies 1M[12,25], 10M[25], 50M[25] potencies were used.

Assessment/ outcome parameters

In the current review of included studies, authors used various questionnaires, scores and scales. These scores were 12- Item Short-Form Health Survey scores [15] and Severity of alcohol dependence scores [12].

Some studies used observational scales like the Clinical Institute Withdrawal Assessment Scale of Alcohol-Revised [20] and the Minnesota Cocaine Craving Scale [15].

Questionnaires used in the highlighted studies under review were the Severity of Alcohol Dependence Questionnaire [12], WHO QOL-BREF [12,20], Validated Standardised Questionnaire and interview explicitly developed for the study. [24].

The remaining studies assessed symptomatic improvements like Alcohol withdrawal syndrome, delirium tremens symptoms, sleep improvement, mood on waking, abstinence rate and average abstinence [19,21,22,23,25].

Treatment outcomes

All the studies evaluated under this review showed encouraging and favourable effects for homoeopathic treatment in SUD.

Type of Publication:

All studies were published in peer-reviewed national and international journals.

Level of evidence and grades of recommendation

Out of 10 studies, 03 studies had a level of evidence of 1b with an 'A' grade of recommendation, which included 3 RCTs [11,12,20], while 05 studies had a 2b level of evidence with 'B' grades of recommendation which included 03 observational studies [19,23,24], 01 retrospective cohort study[25] and 01 observational comparative study[18], 01 case series[22] and 01 pilot/empirical study[21] had level 4 of evidence with 'C' grades of recommendation.

DISCUSSION

Management of any condition in Homoeopathy is based on proper interrogation of the patient, followed by the formation of the totality of symptoms considering both the psychological and physical state of the patient. Studies reviewed in the current article primarily followed the constitutional approach [11,19,20,24,25], which includes patients' mental and physical makeup based on individuality. Each sufferer of substance abuse has different circumstances, emotional symptoms and physical sensations that need to be understood carefully. [27,28,29]. The current review explored and outlined the supporting and integrated role of holistic homoeopathic treatment in the management of withdrawal states of SUDs.

The most commonly prescribed drugs found effective were *Arsenicum album, Nux vomica, Sulphur, Phosphorus, Lycopodium, Staphysagria, Lachesis, Chamomila, Ipecac and Pulsatilla*. *Arsenicum album* was one of this review's most indicated symptomatic and constitutional remedies.

The current review underlined the methodological flaws in some of the included studies as they lacked the usage of standardised, validated scales and questionnaires for outcome assessment. Apart from this,

in most of these studies, no specified diagnostic criteria, investigations and lab markers were used as a practical, measurable endpoint for the analyses. These may be incorporated for designing future-controlled studies and the results may be documented as evidence.

The majority of the studies have a small number of recruitments at inclusion. A high risk of bias was elicited in most of the observational studies accentuating the need for studies with comprehensive, robust methodological designs to generate more consistent evidence about the effects of homoeopathic interventions. (Table 3, figure 3). Pragmatic studies having larger sample sizes strengthened with validated outcome measures may be designed for further validating the promising role of homoeopathic medicines in SUDs and the generalisation of the results in a controlled setting.

The present review showed that since several Homoeopathic studies were conducted on the smaller side, more large-scale studies need to be planned and designed to corroborate the supporting and scientific role of homoeopathy in drug addiction through its holistic application.

SUDs are commonly associated with a high relapse rate; hence it is difficult to conclude the long-term and sustained role of homoeopathic medicines for the condition from the included studies in this review. These may be explored in further studies with concrete designs. The included studies did not have a more extended follow-up period. Keeping a considerably longer follow-up for the recruits might help evaluate a definitive relapse and compliance rate through homoeopathic medicines. The role of other auxiliary measures and supporting treatment which might pose as known and unknown confounders were also not adequately elucidated in the included studies during the treatment and consequent follow-ups as they might influence the quality of life of recovering patients.

An important question when assessing research evidence is whether individual studies provide the "best possible" outcome that could be expected with the tested intervention in the particular field of research. For appraising the internal validity and analysing the extent to which the studies had minimised biases, the RCTs included in this review were assessed for their model validity, Risk of bias (table 2, figure 2) and the degree to

which the design and setting corresponded with "best practice" [30], as per recommendations put forth by *Mathie et al.* [13]. (Table 4, Figure 4)

Substance abuse patients are associated with other medical conditions and comorbidities. Any indirect change in such conditions may be explored further through homoeopathic interventions. Socio-economical, psychological and other environmental factors may also hamper the recovery of patients. These factors also must be further investigated by conducting controlled observational studies and robust trials.

CONCLUSION

The studies evaluated under the review showed encouraging effects for homoeopathic treatment in SUDs. The majority of the studies had a small number of recruitments at inclusion. Pragmatic studies having larger sample sizes strengthened with validated outcome measures may be designed for further validating the promising role of homoeopathic medicines in SUDs. A high risk of bias was elicited in most of the observational studies accentuating the need for studies with comprehensive, robust methodological designs. Further, the review outlined the importance of generating quality levels of evidence and appraising validity of the studies on the subject under research and inferencing future augmented results in terms of homoeopathic treatment administered. Studies were also evaluated for their grades of recommendation, as embracing stronger grades of recommendation will aid in better clinical decision-making for SUD patients and add strength to studies. Future studies may also address the long-term and sustained role of homoeopathic medicines to demonstrate relapse and compliance rates.

This review, with the approach outlined in the included studies, will refresh the homoeopathic literature for SUDs in light of modern science for a comprehensive clinician understanding. The review findings may be further applied to arrive an improved clinical outcome for effectively managing SUDs cases.

NOTE:

The study highlights the efficacy of " Homoeopathic " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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Table.1 Overview of Homoeopathic Studies on Substance Abuse Disorders

S.No.	Author's name	Year of Publication	Study design	Study Name	Number of participants	Intervention	Type of Homoeopathy	Assessment/ outcome parameters	Summary of results	Medicine used and potency	Levels of Evidence[31]	Grades of Recommendation[31]
1.	Butehorn *et a.l* [19]	2017	Observational Comparative study	Use of Homeopathic Nux Vomica in Reducing PAWS (Post acute withdrawal syndrome) in Early Recovering Addicted Women	3 separate cohorts with numbers not specified in cohorts. Women in the cohorts are between the ages of 18 to 60 with varied ethnicity and all multiple drug users with addiction.	Homoeopathy	Therapeutic	Successful completion of substance abuse treatment program (6 months for 2 cohorts, 28 days for 3rd cohort.)	Two separate cohort groups showed that women who choose the homeopathic protocol the program at a percentage of 66% (for first cohort) and 63% (for second cohort) versus 33% and 37% for those who did not choose homeopathy	Drug-Nux Vomica Potency-200	2b	B
2.	Nayak, *et al.*[20]	2014	Prospective, observational, multicentre exploratory study	Managing acute alcohol withdrawal with Homoeopathy: A prospective, observational, multicentre exploratory study	112	Homoeopathy	Constitutional	Clinical assessment through Clinical Institute Withdrawal Assessment Scale of Alcohol-Revised (CIWA-Ar) and quality of life through World Health Organisation	Significant decrease in CIWA-Ar mean scores and increase in quality-of-life score ($P < 0.001$).	Drug-Arsenicum album, Lycopodium clavatum , Belladonna , Nux vomica, Pulsatilla. Potency- Not mentioned	2b	B

								Quality of Life(WHOQOL)-BREF				
3.	Ajay Grover, *et al*.[21]	2009	Double blind placebo-controlled trial	Double blind placebo-controlled trial of Homoeopathic medicines in the management of withdrawal symptoms in Opium addicts and its alkaloid derivatives-dependents	169 (85 on drug and 84 on placebo)	Homoeopathy and Placebo	Constitutional	Disappearance of symptoms after the 3rd day of starting the treatment.	Action of each individual Homoeopathic Medicine in relieving symptoms is significantly better than that of placebo in each group under the study	Drug-Arsenic album, Nux-vomica, Ipecac, Chamomilla, Rhus tox, Pulsatilla Potency- 30	1b	A
4.	Manchanda, *et al.*[12]	2016	Randomised controlled, open-label, comparative trial	A randomised comparative trial in the management of Alcohol Dependence: Individualised Homoeopathy versus standard Allopathic Treatment	80 (Individual Homoeopathy Group =40 and Standard AllopathiGroup= 40)	Homoeopathy and Allopathy	Constitutional	• Severity of Alcohol Dependence Questionnaire [SAD] • Quality of life through WHO QOL-BREF • Withdrawal Assessment for Alcohol Scale (CIWA-Ar)	80% (n = 32) of the patients in Homoeopathy and 37.5% (n = 15) of the patients in the Allopathy responding to Confidence Interval before 2.4 treatment with absolute difference was 42.5% (42.5 [95% confidence interval [CI]: 23.0,	Drug-Sulphur, Lycopodium clavatum, Arsenic album, Nux vomica, Phosphorus and Lachesis Potency-30,200,1M	1b	A

									61.6]) and estimated effect: 6.6 (95% C.I: 2.4, 18.2), P = 0.0002. A significant difference favouring Homoeopathy was also observed in three out of four domains of WHO QOL-BREF. Statistically significant difference was found in the number of drinking days (median difference: −24.00; CI: −39.0–−8.0; P = 0.001) and number of drinks per drinking day (median difference: −6.3 [95% CI: −11.3–−1.9]; P = 0.004)			
5.	Adler, *et al.*[15]	2018	Randomised Double-blind,	Double-blind evaluation of homeopathy	54 (51 Homoeopathy Group and 53	Homoeopathy and Placebo	Therapeutics	• Percentage of cocaine-using days	• Mean percentage of	Q-potencies of Opium and E. coca	1b	A

			placebo-controlled, parallel-group, pilot trial	on cocaine craving: a randomised controlled pilot study	placebo group)			• Minnesota Cocaine Craving Scale • 12- Item Short-Form Health Survey scores	cocaine-using days in the homeopathy group was 18.1% (standard deviation (SD): 22.3%), compared to 29.8% (SD: 30.6%) in the placebo group (P < 0.01) • Analysis of the Minnesota Cocaine Craving Scale scores showed no between-group differences in the intensity of cravings, but results significantly favored homeopathy over			

									placebo in the proportion of weeks without craving episodes and the patients' appraisal of treatment efficacy for reduction of cravings. • Analysis of 12-Item Short-Form Health Survey scores found no significant differences			
6.	Gopinadhan.S, *et al*.[22]	1994	Pilot/Empirical Study	A pilot study on effect of Arsenicum Album in Alcohol Dependents	10	Homoeopathy	Therapeutics	• Development of aversion to alcoholic drinks • Relief of symptoms and signs of long	• Out of 10 cases, 8 developed definite aversion to alcoholic drinks. 1 develope	Drug-Arsenic album Potency-30,200	4	C

								continued intake of alcohol	d decreased affinity towards alcoholic drinks and other one developed reduction in amount and frequency of alcoholic intake but most of behavioural and physical symptoms were completely relieved with Arsenic album. • Out of 5 cases with raised ESR, 2 had showed reduction; 4 cases with raised serum bilirubin and 3 cases			

									with raised SGOT and SGPT also showed reduction.			
7.	Milewska, *et a.l*[23]	1993	Case series	Homoeopathic treatment of alcohol withdrawal	30	Homoeopathy	Therapeutics	Alcohol withdrawal syndrome and delirium tremens symptoms improvement	Results favourable	Drug-Sulphur Potency-3X	4	C
8.	B.Sylvian *et a.l*[24]	2022	Cross-sectional observational study	Complementary and alternative medicines in patients with alcohol or tobacco use disorder: Use, expectations and beliefs	40	Complementary and Alternative medicine	Not Specified	Standardised and validated questionnaire used (CAMBI28) and interview with standardised questions developed specifically for the study.	Of 40 patients recruited, 62.5% used or had used CAM, at least half for comorbid disorders and not specifically for their SUD. Almost all wanted the integration of CAM into the health system and believed that their general practitioner should be able to	-	2b	B

									redirect them to a CAM specialist if indicated. (4 (10%) Patients used homoeopathy)			
9.	Yogendra Rai[25]	1994	Clinical observational study	Treatment of Drugs Dependent's with Homoeopathy-An attempt	261	Homoeopathy	Constitutional	Improvement index	209 (80.08%)-Improved 32 (12.26%) did not improved and 20 (7.66%) were dropped out of the study	Drug-Rhustox, Avena sativa, Nux Vomica, Arsenic album, Bryonia alba, Chamomilla Potency used-30,200,1M,10M, 50M, 6X	2b	B
10.	Bhuvaneswari R, et al.[26]	2020	Retrospective cohort study	Homoeopathic Management of Acute Alcohol Withdrawal Syndrome: A Retrospective Cohort Study	53	Homoeopathy	Constitutional	• Severity of Alcohol Dependence Questionnaire (SADQ) • Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar)	• Out of the 53 cases chosen for the study, 32 cases were of moderate withdrawal and 21 cases were of severe withdrawal • Statistically significant	Drug-Arsenicum album, Ranunculus bulbosus, Nux vomica and Sulphur	2b	B

									difference in the Mean CIWA score (t=7.76, p<0.001) after 12 hours of treatment, with a mean difference of 5.96±5.59 with CI (4.42,7.5). Among the 53 cases, Delirium Tremens (DTs) was present in 12 (22.6%) cases. Seizures were absent in all 53 cases and all cases were treated only by homoeopathic medications and method			

S. No	Bias domain	Source of bias	Ajay Grover et al 2009[21]	Manchanda et al 2016[12]	Adler et al 2018[15]
1	Selection bias	Random Sequence Generation	+	+	+
		Allocation concealment	+	+	+
2	Performance bias	Blinding of participants and personnel	+	-	+
3	Detection bias	Blinding of outcome assessment	+	-	+
4	Attrition bias	Incomplete outcome data addressed	+	+	+
5	Reporting bias	Selective reporting	+	+	+
6	Other bias	other Risk of bias	+	?	+

Table 2: Risk of bias of RCTs
(Lower Risk of bias +, Higher Risk of bias -, Uncertain Risk of bias?)

S. No	Bias domain	Source of bias	Nayak et al 2014[20]	Gopinadhan et al 1994[22]	Milewska et al 1993[23]	Syndi D et al 2022[24]	Rai Y 1994 [25]	wari et al. 2020 [26]	Butenorn et al 2017[19]
1.	Selection bias	Random Sequence Generation	-	-	-	-	-	-	-
		Allocation concealment	-	-	-	-	-	-	-
2.	Performance bias	Blinding of participants and personnel	-	-	-	-	-	-	-
3.	Detection bias	Blinding of outcome assessment	-	-	-	-	-	-	-
4.	Attrition bias	Incomplete outcome data addressed	+	-	-	+	-	+	-
5.	Reporting bias	Selective reporting	+	-	-	+	-	+	-
6.	Other bias	other Risk of bias	-	-	-	-	-	-	-

(Lower Risk of bias +, Higher Risk of bias -, Uncertain Risk of bias?)

Table 3: Risk of bias of Observational/uncontrolled studies

S. No	Bias domain	Ajay Grover et al 2009[21]	Manchanda et al 2016[12]	Adler et al 2018[15]
1.	Rationale for intervention	+	+	+
2.	Principles consistent with intervention	+	+	+

3.	Practitioner qualified and experienced	+	+	+
4.	Outcome measure reflects expected main effect	-	+	+
5.	Outcome measure sufficiently sensitive of detecting change	-	+	?
6.	Follow up length appropriate to detect intended effect of intervention	+	+	-

Table 4: Model Validity of RCTs

(Acceptable MV +, Inadequeate MV -, Uncertain MV ?)

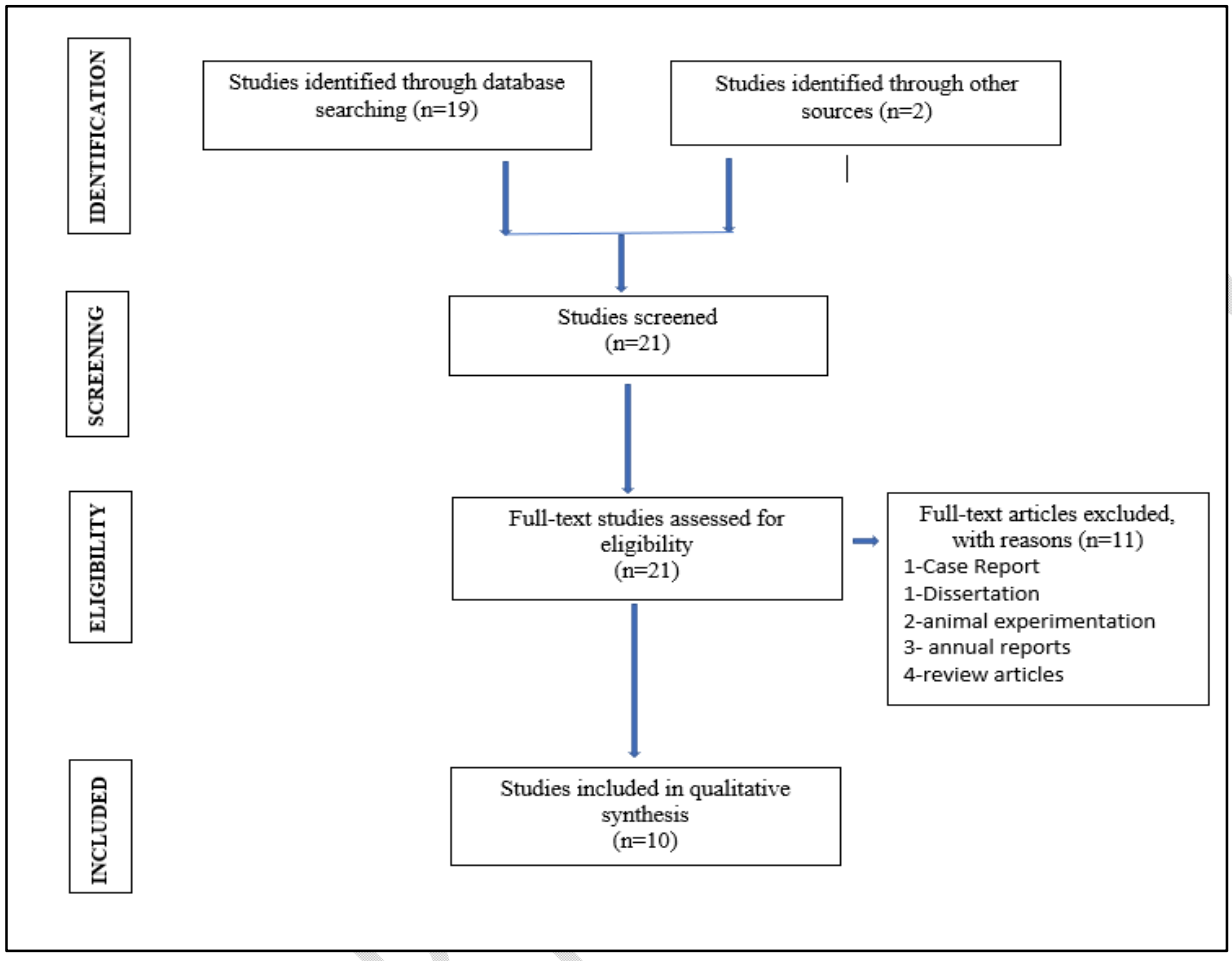

Figure 1 Study flow chart - search strategy

Bias domain	Ajay Grover et	Manchanda et al	Adler et al 2018[15]
Random Sequence Generation	+	+	+
Allocation concealment	+	+	+
Blinding of participants and personnel	+	-	+
Blinding of outcome assessment	+	-	+
Incomplete outcome data addressed	+	+	+
Selective reporting	+	+	+
other Risk of bias	+	?	+

Figure 2: Risk of bias of RCTs

(Lower Risk of bias +, Higher Risk of bias -, Uncertain Risk of bias?)

Source of bias	Nayak et al 2014[20]	Gopinadhan et al 1994[22]	Milewska et al 1993[23]	Sylian B et al 2022[24]	Rai Y 1994[24]	hwari et al 2020[26]	Butehorn et al 2017[19]
Random Sequence Generation	−	−	−	−	−	−	−
Allocation concealment	−	−	−	−	−	−	−
Blinding of participants and personnel	−	−	−	−	−	−	−
Blinding of outcome assessment	−	−	−	−	−	−	−
Incomplete outcome data addressed	+	−	−	+	−	+	−
Selective reporting	+	−	−	+	−	+	−
other Risk of bias	−	−	−	−	−	−	−

(Lower Risk of bias +, Higher Risk of bias -, Uncertain Risk of bias?)

Figure 3: Risk of bias of Observational/uncontrolled studies

Bias domain	Ajay Grover et al 2009[21]	Manchanda et al 2016[12]	Adler et al 2018[15]
Rationale for intervention	+	+	+

Principles consistent with intervention	+	+	+
Practitioner qualified and experienced	+	+	+
Outcome measure reflects expected main effect	-	+	+
Outcome measure sufficiently sensitive of detecting change	-	+	?
Follow up length appropriate to detect intended effect of intervention	+	+	-

Figure 4: Model Validity of RCTs

(Acceptable MV +, Inadequeate MV -, Uncertain MV ?)