CCI JOURNAL CRITICAL CARE INNOVATIONS

REVIEW ARTICLE

Crit. Care Innov. 2021; 4(4):19-33

Effectiveness of the pharmacological interventions on abstinence of substance abuse disorder.

Akila R. Jayamaha [1] - A,D,G,N,O. ORCID www.orcid.org/0000-0002-3372-4537
Nimesha D.M. Herath [1] - B,G,M,N,O. ORCID www.orcid.org/0000-0001-6767-2678
Lahiru C. Nawarathne [1] - B,K,M,N,O. ORCID www.orcid.org/0000-0003-3279-1348
Nirmani A. W. Samarakoon [1] - H,K,N,O. ORCID www.orcid.org/0000-0003-2267-5925
Nadeeka D. K. Ranadeva [1] - H,K,O. ORCID www.orcid.org/0000-0002-6971-674X
Nishadi D. Dharmarathna [1] - H,K,O. ORCID www.orcid.org/0000-0001-5784-4253
Divithuragamage H. Buddhini [1] - D,N,O. ORCID www.orcid.org/0000-0003-0992-9628
Nirmala Priyadarshani [1] - D,N,O. ORCID www.orcid.org/0000-0002-4402-8342
Samanthi N. Senarath [1] - B,N,O. ORCID www.orcid.org/0000-0002-3069-6833
Piyumali S. Arachchi [1] - H,K,O. ORCID www.orcid.org/0000-0002-4622-3117
Kerstin L. Samarasinghe [1] - A,D,J,N,O. ORCID www.orcid.org/0000-0002-5699-9621
Neluka Fernando [2] - A,D,J,N,O. ORCID www.orcid.org/0000-0001-7551-8224

[1] *KIU, Colombo, Sri Lanka.*
[2] *Faculty of Medical Sciences, University of Sri Jayewardenepura, Colombo, Sri Lanka.*

Address for correspondence:
Nimesha D.M. Herath, MD - KAATSU International University Sri Lanka, 249/1 Malabe Road Thalangama North Koswatta, Battaramulla Colombo, 10120, Sri Lanka;
Tel: +94767063200; E-mail: HEI_SL_Cell@kiu.ac.lk

ISSN 2545-2533
Received: 17.10.2021
Accepted: 20.11.2021
Published: 31.12.2021

Author Contributions (CRediT Taxonomy):

Conceptualization - **A**
Data Curation - **B**
Formal Analysis - **C**
Funding Acquisition - **D**
Investigation - **E**
Methodology - **F**
Project Administration - **G**
Resources - **H**
Software - **I**
Supervision - **J**
Validation - **K**
Visualization - **L**
Writing (Draft Preparation) - **M**
Writing (Review & Editing) – **N**
Approved the final version - **O**

ABSTRACT

The abundance of pharmacological interventions to treat substance abuse disorder has solidified globally. Despite promising effects, use of pharmacological interventions in substance abuse disorder are limited in asian territories. This study aimed to identify and explore existing effective pharmacological interventions on abstinence of substance abuse disorder. A systematic review was conducted adhering to PRISMA guidelines. Google scholar, Pubmed, Hinari, and Cochrane databases were systematically searched and the topic and abstract of the articles were screened for eligibility. Articles of empirical studies on pharmacological interventions on abstinence of substance abuse disorder, which were published in peer-reviewed journals during 2010 to 2020, written in English, were included and articles on alcohol and smoking cessation were excluded from the review. Full papers were then assessed against eligibility criteria. Quality appraisal and data extraction of the selected articles were performed by two independent reviewers and discrepancies were discussed with another independent reviewer to reach consensus. Three hundred and seven research articles were identified through a comprehensive database search. After screening the topics and abstracts of the articles and assessing the relevant full texts for eligibility, 26 articles of the empirical studies were included in the systematic review. High doses of Buprenorphine, Methadone, Lofexidine, Naltrexone, SB-334867, Prazosin, and Baclofen were identified to be significantly effective in abstinence from substance abuse. It was concluded that empirical evidence of effective pharmacological interventions exists and its combination with existing non-pharmacological rehabilitation interventions are proposed as more effective in the treatment of substance abuse.

KEY WORDS: Substance abuse disorder, rehabilitation, pharmacological interventions, PRISMA, empirical.

INTRODUCTION

"Substance" is any psychoactive compound with the potential to cause health problems (physical, psychological, and social). According to the rules and regulations of the country, some of the substances may be legal (e.g., alcohol and tobacco) or illegal (e.g., heroin and cocaine). "Substance misuse" is defined as using any of these substances at high doses or in inappropriate situations. Repeated and prolonged misuse of any of these substances can cause substance use disorder which is significantly affecting the health and may require treatment. Substance use disorder (SUD) is a cluster of physiological, behavioral, and cognitive phenomena where the use of a substance(s) takes a higher priority in an individual than the other behaviors that once had a greater value [1]. SUD can range from mild, temporary to severe and chronic. Globally, it was estimated that around 269 million people misused various substances. Of them, 35.6 million people suffering from substance use disorders. Adolescents and young adults are the most accounted group and one out of three substance users is a woman. Furthermore, it has also been found that people who are socially and economically disadvantaged are more vulnerable to develop drug use disorders [2].

SUD has become a global crisis causing major problems in public health and law enforcement [3]. A hundred and sixty eight deaths per thousand population with an uncertainty range of 155-176, has been reported to WHO Global Health Estimates (GHE), in 2015. This accounts for 0.3% of all deaths reported within the WHO regions [3]. In addition, illicit drug dependence has contributed to many health problems, creating a substantial economic burden in countries by attributing to high expenses in healthcare. Expenses for health care involve prevention, diagnosis, treatment, and rehabilitation. There is an indirect cost where the productivity of these people is very low to the society and the workforce of a country [4].

According to the National Dangerous Drug Control Board, Sri Lanka, a total number of 89321 drug-related arrests have been reported in 2019. As per the reports of the Drug Abuse Monitoring System, 3613 patients have been treated for SUD in the same year in Sri Lanka [5]. Moreover, as a developing country, Sri Lanka has faced serious social consequences due to SUD by its severe impact on public health, tendency to encourage crime, causes of diseases, poverty, and destruction of family life [6]. Therefore, many treatments and Preventive measures have been taken against SUD at national and global levels. Despite the efforts taken to treat SUD, relapse of drug use has become a major challenge. Therefore, different approaches for treating SUD are a paramount topic to be discussed to help people remain abstinent [7].

Treatment interventions deployed on abstinence of SUD are being conducted with both non-pharmacological and pharmacological interventions [8–11]. Among the different treatment methods used for SUD, pharmacotherapy is one of the treatment approaches proved to be effective and an abundance of scientific evidence are available in favor of its effectiveness. However, in Sri Lanka and Asian territories, non-pharmacological interventions are known to be more prominent. Despite the promising effects, limited use of pharmacological therapies is observed, which may be an alarming reason for the high relapse rates reported even after rehabilitation or treatment. Therefore, the identification and exploration of the pharmacological interventions reported on the abstinence of substance abuse disorder is a salient topic to be reviewed.

This review article brings upon the most effective pharmacotherapy for SUD where it also draws attention to the emerging drugs that are still in the preclinical phase that might be useful as a treatment intervention in the future.

MATERIAL AND METHODS

Study Selection

The systematic review was conducted and reported adhering to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12,13]. Four electronic research databases (Cochrane Library, Google Scholar, Hinari, and PubMed Central) were systematically searched to identify relevant articles. The concepts and keywords of “Substance-related disorder”, “Drug addiction”, Substance use”, “Therapy”, “Treatment” “Rehabilitation” (refer to Table 1 for the search equation) were used with Boolean algebras to identify the articles. All duplicate articles were removed using Mendeley desktop version 1.19.4. The reference lists of the retrieved articles were additionally examined to find more articles related to the topic of interest.

Table 1. Search equations and strategy used for identification of articles.

PubMed Central
MeSH descriptor: [Substance – Related Disorders] AND MeSH descriptor: [Rehabilitation] AND MeSH descriptor: [Treatment Outcome] OR MeSH descriptor [Residential Treatment] OR MeSH descriptor [Substance Abuse Treatment Centers] NOT Homeless NOT Alcoholic (words variations have been searched) NOT Smoking (words variations have been searched).
Cochrane Library
("substance related disorders"[MeSH Terms]) AND "substance related disorders/therapy"[MeSH Terms]) AND "substance related disorders/rehabilitation"[MeSH Terms])) NOT Alcoholic[MeSH Terms]) NOT smokers[MeSH Terms]) NOT homeless[MeSH Terms] AND ("last 10 years"[PDat]).
Hinari
("Substance related disorder") AND (rehabilitation) AND (methods) OR ("substance related disorder rehabilitation method") OR ("substance related disorder therapy") NOT (smok*) NOT (alcohol*) NOT (homeless).
Google Scholar
Substance related rehabilitation method "substance related disorders rehabilitation treatment" "substance related disorders rehabilitation" -"alcoholic smokers homeless".

The topic and abstract of the articles were screened for suitability by two independent reviewers. Disagreements were arbitrated by a third reviewer. Articles of empirical studies on pharmacological interventions on abstinence of substance abuse disorder which were published in peer-reviewed journals from 2010 to 2020, written in English, were included and articles on alcohol and smoking cessation were excluded from the review. Articles were excluded when the abstract and titles were mismatched. The full texts of the selected articles were retrieved and each retrieved article was critically appraised for quality using the English translation of the Critical Appraisal Skill Programme (CASP) [14] by the same independent

reviewers. Articles were appraised based on twelve questions that were used to understand the validity of the study, results, value, and relevance of the study outcomes. The question regarding local relevance was excluded since the articles were published worldwide.

The research articles obtaining a score between 9-11 were considered as excellent quality, 7-8 was good, 5-6 was fair quality and ≤ 4 was considered as poor quality, after the evaluation of studies utilizing the eleven questions related to CASP. Special attention was given to the articles of the preclinical studies and was discussed and reported separately. Those preclinical studies may reveal the emerging pharmacological treatments for substance use disorder.

Data Extraction

Data extraction was done using a data extraction form created by the investigators after a discussion with the research team. Outcomes of the retrieved articles were categorized under its study design, target drug, tested pharmacological drug, and its effectivity. Data extraction was conducted by two independent reviewers and the data were pooled into a table by another reviewer after discussing the discrepancies with reviewers to reach a consensus.

RESULTS AND DISCUSSION

Through a thorough, systematic search of the databases of Pubmed Central (114), Cochrane Library (118), Hinari (55), and Google scholar (20), 307 research records were identified and after removing the duplicate records, 305 research records were selected for screening. Hundred and eighty-two irrelevant records were excluded after screening the titles, abstracts, and date of publication, and narrowed it down to 123 articles. From the articles narrowed down, 73 were excluded as the articles were consisting only of non-pharmacological interventions utilized for SUD. The remaining articles were retained for assessing against the predetermined eligibility criteria for the systematic review. Upon assessment by CASP, 26 articles including current pharmacological interventions and emerging pharmacological interventions which scored more than 5 during appraisal were selected (figure 1).

Data of the 26 selected articles were extracted into a data extraction table that comprised the variables of author information, characteristics of the treatment group and control group, characteristics of the pharmacological intervention, effectiveness or statistical significance reported, and the conclusion of the study. Among the selected articles for the review, 20 articles included medications that are currently being utilized as a treatment for SUD, and six articles were related to the preclinical trials which are emerging pharmacological interventions for SUD.

The study revealed that the Buprenorphine, Disulfiram, Methadone, Naltrexone, Naloxone, Diazepam, Aripiprazole, Morphine, Topiramate, and Modafinil (Table 2) were currently utilized in the treatment regimens for the SUD. Half of the research articles included in the review belonged to the United States and other countries reported were Iran (8%), Singapore (4%), Sweden (4%), Netherland (4%), Switzerland (4%), and the United Kingdom (4%). Seventeen randomized control trials (65%), two comparison studies (7%), and one

case study have been included in the review. Six articles of preclinical trials related to the pharmacological interventions concluded that LY379268, Antalarmin, SB-334867, Prazosin, and Baclofen were proved to be effective against SUD (Table 3).

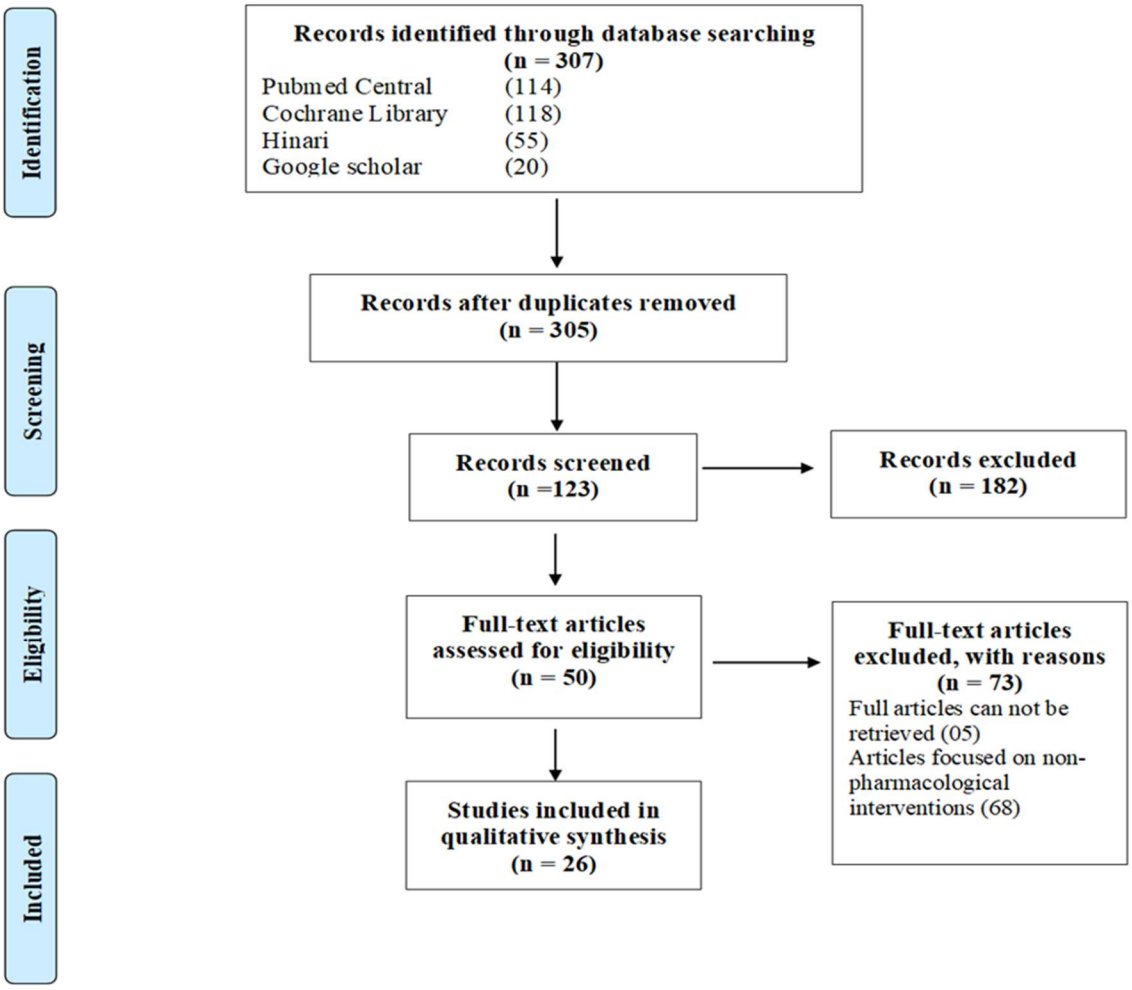

Figure 1. PRISMA Flow Diagram.

Current Pharmacological Interventions

Buprenorphine (BUP) is used to treat opioid abuse disorder and is found to be effective in most of the studies [15,16]. Tompkins et al. 2014 conducted a comparison study using BUP (total daily dose was 32 mg) and morphine (total daily dose was 120 mg) as a treatment for opioid abuse disorder [16]. Observer-rated, subject-rated, psychomotor, cognitive, performance, physiological, and sleep were the five types of opioid withdrawal measures evaluated in the study. The study revealed that morphine was accompanied by more withdrawal symptoms than BUP. In another study, three single high-dose BUP regimens of 32 mg, 64 mg, and 96 mg have been administered to eligible randomized participants. Higher effectiveness (having a rapid, effective, and safe means of opioid withdrawal), which has been observed within individuals at higher doses (64mg and 96 mg), maybe due to the higher occupancy of mu-opioid receptors [15]. An open randomized trial was conducted with BUP and methadone (MET) for a study period of 24 weeks.

Table 2. Current pharmacological interventions on substance abuse disorder.

Author/Year	Study design	Country	Sample size	Pharmacological drug/s	Mechanism of action	Targeted substance	Effectiveness
(Ahmadi *et al*., 2018)	Double blind randomized trial	Iran	90	Buprenorphine (BUP)	Partial agonist at mu-opioid receptors, an antagonist at delta- and kappa-opioid receptors	Opioids	Maximal treatment retention (64 mg, 96 mg doses group)
(Tompkins *et al*., 2014)	Double blind comparison study	USA	12	BUP /Morphine	Bind to opioid receptors (mu, Kappa, Delta) [48]	Heroin	Minimal withdrawal symptoms after BUP cessation
(Hser *et al*., 2014)	Multi-site, open-label, randomized trial	USA	1269	BUP/ Methadone (MET)	A long-acting opioid analgesic [49]	Opioids	Higher completion and retention rates in MET high doses compared to BUP.
(Potter *et al*., 2013)	Multi-site, open-label, randomized trial	USA	1250	BUP combined with Naloxone/ MET	Mu-opioid antagonists (MOA) [50]	Opioids analgesics (OA), Heroin	BUP appear to have no superiority over MET on OA users versus heroin users
(Moran *et al*., 2017)	Randomized double-blind clinical trial	USA	18	Aripiprazole/ MET	Partial agonist at dopamine D2, serotonin 5-HT1A receptors and an antagonist at 5-HT2A receptors	Cocaine, Opioids	Aripiprazole is not effective and slightly increase the craving on those who have achieved abstinence
(Lofwall *et al*., 2014)	Double blind, randomized, placebo-controlled mixed-design study.	USA	7	Aripiprazole	Agonist in hypodopaminergic states, functional antagonist in hyperdopaminergic states	Cocaine	No attenuation in reinforcing of cocaine and relieving withdrawal effects
(Oliveto *et al*., 2011)	Double blind, randomized, placebo-controlled clinical trial	USA	155	Disulfiram/ MMT	Dopamine-b-hydroxylase Inhibitors [51]	Cocaine	Ccontraindicated for cocaine dependence at doses <250 mg/day
(Carroll *et al*., 2016)	Randomized double blind clinical trial	USA	99	Disulfiram	Dopamine-b-hydroxylase Inhibitors (Forray & Sofuoglu, 2014)	Cocaine	No added benefit to the CBT in reducing the cocaine use. Appeared as a safe medication within the sample
(Hermes *et al*., 2019)	Randomized, double-blind placebo controlled, 12-week relapse prevention study.	USA	57	Lofexidine (LFX) combined therapy Naltrexone (NTX)	a2- adrenergic agonists	Opioids	Significant improvement in opioid craving due to the use of LFX/NTX NTX may have limited the ability to detect the positive effects of LFX.

(Guo *et al*., 2018)	Randomized, double blind placebo-controlled trial	Singapore	108	LFX/ Diazepam	Stimulate the inhibitory GABA-signaling pathways [52]	Heroin	Withdrawal symptoms and opiate craving were lower in the Lofexidine group relative to the Diazepam group
(Hiltunen, Eklund & Borg, 2011)	Fifteen years follow-up study (Cohort Study)	Sweden	38	Methadone Maintenance Treatment (MMT)	A long-acting opioid analgesic [49]	Opiates	Proper termination of MMT have improved the life situation of the subjects
(Law *et al*., 2017)	Randomized double-blind controlled trial	UK	80	BUP/Naloxone (NLX) vs MET/LFX	(Described individually)	Opiates	Craving was greater in BUP/NLX group than MET/LFX. However withdrawal symptoms were earlier in the MET/LFX group.
(Rich *et al*., 2015)	Randomized, open-label trial	USA	223	Methadone	A long-acting opioid analgesic [49]	Opioid	Adherence to treatment was reported even after dismissal from in-house treatment among the subjects continued MMT during incarceration. Engagement of risk behaviors and the risk of death from overdose have been reduced
(Hämmig *et al*., 2014)	International, multi-center, two-phase cross over study	Switzerland	276	MET/ Slow releasing Oral Morphine	(Described individually)	Opioid	SROM was more effective in long-term treatment maintenance and reducing craving
(Mannelli *et al*., 2011)	Double-blind, randomized trial	USA	174	Very Low Dose NTX (VLNTX)	Competitive binding at the opioid receptors in the brain [53]	Opioids	Reduction of withdrawal symptoms and better completion treatment rates have been reported. Safe and effective for treatment retention and for reducing withdrawal severity
(Pirnia *et al*., 2018)	Single-center placebo-controlled Trial	Iran	54	Topiramate/ MMT	Enhances the GABAergic system, antagonizes the glutamatergic system	Cocaine and opioids	Reduced the craving no effect on the durability of the treatment
(Umbricht *et al*., 2014)	Randomized double-blind controlled clinical trial	USA	171	Topiramate/ MMT		Cocaine	No significant increase or decrease in cocaine craving or abstinence
(Kampman *et al*., 2015)	Double-blind placebo-controlled trial	USA	94	Modafinil	Alpha-adrenergic/glutamate agonist	Cocaine and alcohol	Significantly blunting the cocaine craving and improve the abstinent from cocaine

(Dackis *et al*., 2012)	Randomized double-blind, placebo-controlled trial	USA	210	Modafinil	Cocaine	Negative outcomes, though further research is warranted
(Nuijten *et al*., 2015)	Open-label, randomised feasibility trial.	Netherland	65	Modafinil	Cocaine	Further research is warranted

Table 3. Emerging pharmacological interventions.

Author/Year	Study Design	Pharmacological agent	Mechanism of action	Outcomes
(Justinova *et al*., 2016)	Pre-clinical trial	LY379268	Group II metabotropic glutamate receptor agonist [51]	May have an effect on nicotine seeking behavior, but there is no effect on cocaine seeking behavior
(Mello *et al*., 2006)	Pre-clinical trial	Antalarmin	Corticotrophin-releasing factor 1 receptor [51]	Produced sedation, though there were no significant reduction in Cocaine reinforcement or self-administration was reported
(Erami *et al*., 2012)	Pre-clinical trial	SB-334867	Orexin-1 receptor antagonist [51]	Protect against physical withdrawal and bars the development of morphine tolerance
(Ranjbar-Slamloo *et al*., 2012)	Pre-clinical trial	SB-334867	Orexin-1 receptor antagonist [51]	Development of tolerance to morphine is attenuated however no effect on already developed tolerance
(Greenwell *et al*., 2009)	Pre-clinical trial	Prazosin	α1-Adrenergic receptor agonist [51]	Decreased the heroin self-administration in rats with long access (12h) rats and reversed the impaired food intake and duration of meals
(Spano *et al*., 2007)	Pre-clinical trial	Baclofen	GABAB receptor agonist [51]	Block reinforcement of heroin seeking behavior dose dependently; (0.625 and 1.25 mg/kg)

The study revealed that the treatment completion and treatment retention were higher in the MET group (74%) and positive urine results of opioids were higher in the MET group than the BUP ($p<0.01$). The use of higher doses proved to be associated with better retention in treatment with respect to both medications. However, BUP high doses proved to be lowering the Opiate use among continued Opiate users [17]. In contrast to that, treatment with opioid analgesics and heroin abuse was targeted in a study done by Potter et al. 2013, and as the treatment method, BUP in combination with Naloxone alongside with the Methadone Maintenance Treatment (MMT) were compared [18]. The findings of Potter et al. 2013 were surprising as BUP was not indicated as a superior treatment method to MET in comparison [18].

Lofwall et al., 2014, revealed that no diminishing or positive reinforcement was reported among the participants (intravenous cocaine and nicotine) who received aripiprazole as a treatment and no attenuating effect on nicotine withdrawal as well [19]. The results were against Aripiprazole as an effective treatment method for cocaine abuse and nicotine withdrawal and cessation. A double-blind clinical trial with randomization to either Aripiprazole or placebo reported similar cocaine craving rates among the participants in both groups and aripiprazole was also reported to be increasing cocaine craving in those who had achieved

abstinence previously [20]. Current literature is not supportive enough for the effectiveness of Aripiprazole as a pharmacological intervention for cocaine abuse and nicotine abuse.

Oliveto et al., 2011 conducted a double-blind, randomized, placebo-controlled clinical trial to assess the dose-related efficacy of Disulfiram for treating individuals with cocaine dependence using three different Disulfiram (62.5 mg, 125 mg, 250 mg) groups with a placebo group [21]. Thrice-weekly urine samples and self-reported opioid use were assessed as the primary outcomes. Cocaine-positive urine samples increased over time in Disulfiram groups which were treated with 62.5mg and 125mg and decreased over time in the 250mg Disulfiram and placebo groups. Self-reported cocaine use increased in the 125mg Disulfiram group than the other three treatment groups. Another study was conducted by Carroll et al., 2016, to compare the effectiveness of Disulfiram (250 mg/d) therapy with placebo in combination with cognitive behavior therapy (CBT) [22]. The study revealed that the Disulfiram has no added benefit to the CBT in reducing cocaine use.

Lofexidine (LFX), is a non-opiate, nonaddictive, alpha 2-adrenergic agonist. A randomized, double-blind placebo-controlled trial was conducted to assess the effectiveness of lofexidine on opioid use outcomes and treatment compliance in combination with naltrexone. The study revealed significant improvement in opioid craving, delayed return to opioid use, and improved treatment compliance and treatment completion rates among individuals who received naltrexone and lofexidine combination therapy [9]. Guo et al., 2018, conducted a double-blind, Placebo-controlled trial to examine the safety and efficacy of Lofexidine in assisting opioid detoxification against diazepam [23]. According to the study, withdrawal symptoms and opiate craving were lower in the lofexidine group relative to the diazepam group. Evidence is suggesting the use of lofexidine in combination with other treatments enhanced opioid relapse prevention.

Methadone (MET) is a commonly used treatment against substance use disorder [17,18,25,27,28]. Hiltunen, Eklund, and Borg, 2011, conducted a 15-year followed-up study among patients who underwent methadone maintenance treatment (MMT) [27]. The study confirmed that the patients' life situation and subjective well-being seem to be higher after successful termination of MMT. Confirming that, a randomized, controlled trial conducted among incarcerated participants showed the benefits of the continuation of MMT, which could reduce the engagement of risk behaviors and the risk of death from overdose [26]. BUP with Naloxone (NLX) and MET with LFX were administered separately to two groups of opiate-dependent individuals. Withdrawal symptoms were earlier in the MET/ LFX group, although the craving for opiates was greater in the BUP/ NLX group [24]. This further confirmed the effectiveness of MET as a combination therapy. In contrast to that, Hämmig et al., 2014, conducted a multi-center, two-phase study to investigate the efficacy and safety of slow-release oral morphine to methadone [25]. Findings of this study showcased that slow-releasing oral morphine was rated as high in treatment satisfaction, fewer cravings for heroin, and lower mental stress than the MET.

Alcohol use is a major drawback that affects opioid dependence treatment. Naltrexone in very low doses (VLNTX) was used to treat problem drinking opioid detoxification, which is safe and is associated with reduced withdrawal symptoms and higher treatment completion rates [28].

Pirnia et al., 2018, conducted a randomized control trial to evaluate the effectiveness of topiramate for treating opiate and cocaine abuse [29]. The cocaine-dependent individuals with MET were randomized to the topiramate group or placebo group. Topiramate was not more effective than placebo in reducing cocaine use, and the study suggested that the efficacy of topiramate is limited as a treatment for cocaine abuse. A similar study (double-blind controlled clinical trial) has been conducted among patients with cocaine dependence on MMT, which has proven that topiramate is ineffective on cocaine craving or abstinence [30].

Kampman et al., 2015, revealed that Modafinil was significantly blunting cocaine craving and improve the abstinent from cocaine based on the results of a double-blind, placebo-controlled clinical trial [31]. In contrast to that, Nuijten et al., 2015, conducted a randomized feasibility trial and revealed the Modafinil did not improve cocaine abstinence, cocaine craving, health, social functioning, and patient satisfaction, and treatment adherence to modafinil was low as well [32]. Confirming the findings, Dackis et al., 2005, found that there were no significant differences in cocaine abstinence, craving, cocaine withdrawal, retention, and tolerability between Modafinil and placebo patients based on a randomized, double-blind, placebo-controlled study. Evidence suggests that Modafinil may not demonstrate favorable clinical outcomes as a treatment for cocaine dependence [33].

Emerging Pharmacological Treatments

Numerous preclinical trials have been conducted to explore the possibilities of alternative pharmacological interventions which can be utilized to treat SUD. LY379268, Antalarmin, SB-334867, Prazosin, and Baclofen were found to be the new emerging treatment methods that were identified in the current systematic review.

LY379268 is an agonist that acts on group II metabotropic glutamate receptors 2 and 3 (mGluR2/mGluR3) which act as a mediator of drug-reinforced behaviors and are involved in the mechanisms underlying the relapse of SUD [34]. Justinova et al., 2016, conducted a pre-clinical study to assess the effects of LY379268 on nicotine and cocaine-seeking behavior in abstinent squirrel monkeys [34]. Study showcased that LY379268 may influence nicotine-seeking behavior, but there is no effect on cocaine-seeking behavior.

Corticotropin-releasing factor (CRF_1) agonist, Antalarmin had reported attenuating effects on alcohol/ethanol self-administration in pre-clinical study literature [35,36]. Mello et al., 2006, evaluated the effect of antalarmin on cocaine self-administration and cocaine discrimination in rhesus monkeys [37]. Study revealed that Antalarmin did not significantly decrease the self-administration of cocaine and the reinforcing or the discriminative stimulus effects of cocaine. Also, Antalarmin in combined administration with BUP and NLX was found to be reversing the place aversion produced by precipitated opioid withdrawal in morphine-dependent rats [38].

Erami et al., 2012, evaluated the effects of pretreatment with SB-334867 (Orexin receptor type-1 (OX1R) antagonist) on the development of morphine tolerance and physical signs of dependence in rats [39]. Study demonstrated that pre-treatment of SB-334867 delayed the development of morphine tolerance and

significantly decreased the somatic signs of withdrawal including diarrhea, teeth chattering, jumping, and defecation. Confirming that Ranjbar-Slamloo et al., 2012, revealed microinjection of SB-334867 prior to morphine injection inhibited the development of tolerance in rats [40].

Prazosin is a promising treatment used in alcohol dependence [41–43]. Greenwell et al., 2009, revealed that Prazosin was effective in decreasing heroin self-administration in rats [44]. Baclofen is a γ-aminobutyric acid GABAB receptor agonist which showed promising results against alcohol abuse disorder [45,46]. A study was conducted to examine the effect of baclofen on the reinstatement of extinguished heroin-seeking behavior in abstinent rats. Results revealed that Baclofen reduced the tendency to resume heroin-seeking behavior in rats [47].

Limitations

Due to the limited availability of the literature, 03 articles related to emerging pharmacological interventions for SUD were included, which were not within the range of 2010 – 2020 as mentioned in the inclusion criteria. The current review only included articles written in English language, hence a significant number of articles written in other languages might not have been grasped. Limited access to the databases were also a limitation.

CONCLUSIONS

Various pharmacological interventions are existing to treat substance abuse disorder and have solidified globally. Present Systematic review revealed that Buprenorphine, Disulfiram, Methadone, Naltrexone, Naloxone, Diazepam, Aripiprazole, Morphine, Topiramate, and Modafinil are the currently utilizing pharmacological interventions to treat the substance use disorder. Buprenorphine, Methadone, Lofexidine, and Naltrexone were found to be significantly effective in abstinence from substance abuse, mainly for opiate-seeking behavior. With the aim of filling the vacuum of alternative pharmacological interventions against the substance use disorder, numerous pre-clinical trials have been conducted using LY379268, SB-334867, Antalarmin, Prazosin, and Baclofen. SB-334867, Prazosin, and Baclofen were the effective emerging pharmacological interventions for SUD. However, human trials based on pre-clinical trials are still controversial due to the lack of literature. Empirical evidence of effective pharmacological interventions exists and the combination of treatment with existing non-pharmacological rehabilitation interventions is considered more effective in the treatment of substance abuse.

SUPPLEMENTARY INFORMATION

Funding: *This research received no external funding.*
Institutional Review Statement: *The study was conducted according to the guidelines of the Declaration of Helsinki.*
Informed Consent Statement: *Informed consent was obtained from all subjects involved in the study.*
Data Availability Statement: *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
Conflicts of Interest: *The authors declare no conflicts of interest.*
Acknowledgements: *This research was supported by the Accelerating Higher Education Expansion and Development (AHEAD) Operation of the Ministry of Higher Education funded by the World Bank.*

REFERENCES

[1] Wakeman SE, Saitz R. Alcohol and Drug Use Disorders. Chronic Illness Care. 2018: 83-94.
doi: https://doi.org/10.1007/978-3-319-71812-5_7

[2] UNODC World Drug Report 2020: Global drug use rising; while COVID-19 has far reaching impact on global drug markets. United Nations: Office on Drugs and Crime. 2021.
[WWW]: https://www.unodc.org/unodc/press/releases/2020/June/media-advisory---global-launch-of-the-2020-world-drug-report.html
(accessed 23 October 2021)

[3] World Drug Report 2018: Opioid crisis, prescription drug abuse expands; cocaine and opium hit record highs. United Nations: Office on Drugs and Crime. 2021.
[WWW]: https://www.unodc.org/unodc/en/frontpage/2018/June/world-drug-report-2018_-opioid-crisis--prescription-drug-abuse-expands-cocaine-and-opium-hit-record-highs.html
(accessed 23 October 2021)

[4] Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Costs of disorders of the brain in Europe. Eur J Neurol. 2005; Suppl 1: 1-27.
doi: https://doi.org/10.1111/j.1468-1331.2005.01202.x

[5] NDDCB. Drug Abuse Monitoring System 2019 Annual Report.
[WWW]: http://www.nddcb.gov.lk/Docs/research/Annual%20Report%202019.pdf
(accessed 23 October 2021)

[6] Mahir IL, Wazeema TM. Social aspects of drug addiction in Sri Lanka. J. Polit. Law. 2020; 13(2): 54.
doi: https://doi.org/10.5539/jpl.v13n2p54

[7] Reichel CM, Bevins RA. Forced abstinence model of relapse to study pharmacological treatments of substance use disorder. Curr. Drug Abuse Rev. 2009; 2(2): 184-194.
doi: https://doi.org/10.2174/1874473710902020184

[8] Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, et al. Efficacy of Disulfiram and Cognitive Behavior Therapy in Cocaine-Dependent Outpatients: A Randomized Placebo-Controlled Trial. Arch. Gen. Psychiatry. 2004; 61(3): 264-272.
doi: https://doi.org/10.1001/archpsyc.61.3.264

[9] Hermes G, Hyman SM, Fogelman N, Kosten TR, Sinha R. Lofexidine in combination with oral naltrexone for opioid use disorder relapse prevention: a pilot randomized, double-blind, Placebo-Controlled Study. Am. J. Addict. 2019; 28(6): 480-488.
doi: https://doi.org/10.1111/ajad.12942

[10] Axelrod SR, Perepletchikova F, Holtzman K, Sinha R. Emotion regulation and substance use frequency in women with substance dependence and borderline personality disorder receiving dialectical behavior therapy. Am. J. Drug Alcohol Abuse. 2011; 37(1): 37-42.
doi: https://doi.org/10.3109/00952990.2010.535582

[11] Chan YY, Lo WY, Li TC, Shen LJ, Yang SN, Chen YH, et al. Clinical efficacy of acupuncture as an adjunct to methadone treatment services for heroin addicts: a randomized controlled trial. Am. J. Chin. Med. 2014; 42(3): 569-586.
doi: https://doi.org/10.1142/S0192415X14500372

[12] Liberati A, Altman D, Tetzlaff J, Mulrow C, Tzsche P, Loannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009; 6(7): e1000100.
doi: https://doi.org/10.1371/journal.pmed.1000100

[13] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7): e1000097.
doi: https://doi.org/10.1371/journal.pmed.1000097

[14] Brice R. CASP CHECKLISTS - CASP - Critical Appraisal Skills Programme [Internet]. CASP - Critical Appraisal Skills Programme. 2021.
[WWW]: https://casp-uk.net/casp-tools-checklists/
(accessed 13 December 2020)

[15] Ahmadi J, Jahromi MS, Ghahremani D, London ED. Single high-dose buprenorphine for opioid craving during withdrawal. Trials. 2018; 19(1): 1-7.
doi: https://doi.org/10.1186/s13063-018-3055-z

[16] Tompkins DA, Smith MT, Mintzer MZ, Campbell CM, Strain EC. A double blind, within subject comparison of spontaneous opioid withdrawal from buprenorphine versus morphine. J Pharmacol Exp Ther. 2014; 348(2): 217-226.
doi: https://doi.org/10.1124/jpet.113.209478

[17] Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction 2014; 109(1): 79-87.
doi: https://doi.org/10.1111/add.12333

[18] Potter JS, Marino EN, Hillhouse MP, Nielsen S, Wiest K, Canamar CP, et al. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). J Stud Alcohol Drugs. 2013; 74(4): 605-613.
doi: https://doi.org/10.15288/jsad.2013.74.605

[19] Lofwall MR, Nuzzo PA, Campbell C, Walsh SL. Aripiprazole effects on self-administration and pharmacodynamics of intravenous cocaine and cigarette smoking in humans. Exp Clin Psychopharmacol. 2014; 22(3): 238-247.
doi: https://doi.org/10.1037/a0035165

[20] Moran LM, Phillips KA, Kowalczyk WJ, Ghitza UE, Agage DA, Epstein DH, et al. Aripiprazole for cocaine abstinence: a randomized controlled trial with ecological momentary assessment. Behav Pharmacol. 2017; 28(1): 63-73.
doi: https://doi.org/10.1097/FBP.0000000000000268

[21] Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, et al. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. Drug Alcohol Depend. 2011; 113(2-3): 184-191.
doi: https://doi.org/10.1016/j.drugalcdep.2010.07.022

[22] Carroll KM, Nich C, Petry NM, Eagan DA, Shi JM, Ball SA. A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. Drug Alcohol Depend. 2016; 160: 135-142.
doi: https://doi.org/10.1016/j.drugalcdep.2015.12.036

[23] Guo S, Manning V, Yang Y, Koh PK, Chan E, de Souza NN, et al. Lofexidine versus diazepam for the treatment of opioid withdrawal syndrome: a double-blind randomized clinical trial in Singapore. J Subst Abuse Treat. 2018; 91: 1-11.
doi: https://doi.org/10.1016/j.jsat.2018.04.012

[24] Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. J Psychopharmacol. 2017; 31(8): 1046-1055.
doi: https://doi.org/10.1177/0269881117711710

[25] Hämmig R, Köhler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. J Subst Abuse Treat. 2014; 47(4): 275-281.
doi: https://doi.org/10.1016/j.jsat.2014.05.012

[26] Rich JD, McKenzie M, Larney S, Wong JB, Tran L, Clarke J, Noska A, et al. Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: a randomised, open-label trial. Lancet 2015; 386(9991): 350-359.
doi: https://doi.org/10.1016/S0140-6736(14)62338-2

[27] Hiltunen AJ, Eklund C, Borg S. The first 38 methadone maintenance treatment patients in Stockholm: 15-year follow-up with a main focus on detoxification from methadone. Nord J Psychiatry. 2011; 65(2): 106-111. doi: https://doi.org/10.3109/08039488.2010.503904

[28] Mannelli P, Peindl K, Patkar AA, Wu LT, Tharwani HM, Gorelick DA. Problem drinking and low-dose naltrexone-assisted opioid detoxification. J Stud Alcohol Drugs. 2011; 72(3): 507-513. doi: https://doi.org/10.15288/jsad.2011.72.507

[29] Pirnia B, Soleimani AA, Malekanmehr P, Pirnia K, Zahiroddin A. Topiramate for the treatment of dually dependent on opiates and cocaine: A single-center placebo-controlled trial. Iran J Public Health. 2018; 47(9): 1344-1352.

[30] Umbricht A, DeFulio A, Winstanley EL, Tompkins DA, Peirce J, Mintzer MZ, et al. Topiramate for cocaine dependence during methadone maintenance treatment: a randomized controlled trial. Drug Alcohol Depend. 2014; 140: 92-100. doi: https://doi.org/10.1016/j.drugalcdep.2014.03.033

[31] Kampman KM, Lynch KG, Pettinati HM, Spratt K, Wierzbicki MR, Dackis C, et al. A double blind, placebo controlled trial of modafinil for the treatment of cocaine dependence without co-morbid alcohol dependence. Drug Alcohol Depend. 2015; 155: 105-110. doi: https://doi.org/10.1016/j.drugalcdep.2015.08.005

[32] Nuijten M, Blanken P, van den Brink W, Hendriks V. Modafinil in the treatment of crack-cocaine dependence in the Netherlands: Results of an open-label randomised controlled feasibility trial. J Psychopharmacol. 2015; 29(6): 678-687. doi: https://doi.org/10.1177/0269881115582151

[33] Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology. 2005; 30(1): 205-211. doi: https://doi.org/10.1038/sj.npp.1300600

[34] Justinova Z, Le Foll B, Redhi GH, Markou A, Goldberg SR. Differential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on nicotine versus cocaine self-administration and relapse in squirrel monkeys. Psychopharmacol. 2016; 233(10): 1791-1800. doi: https://doi.org/10.1007/s00213-015-3994-y

[35] Chu K, Koob GF, Cole M, Zorrilla EP, Roberts AJ. Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF1 receptor antagonist antalarmin and by CRF1 receptor knockout. Pharmacol Biochem Behav. 2007; 86(4): 813-821. doi: https://doi.org/10.1016/j.pbb.2007.03.009

[36] Marinelli PW, Funk D, Juzytsch W, Harding S, Rice KC, Shaham Y, et al. The CRF 1 receptor antagonist antalarmin attenuates yohimbine-induced increases in operant alcohol self-administration and reinstatement of alcohol seeking in rats. Psychopharmacology (Berl). 2007; 195(3) :345-355. doi: https://doi.org/10.1007/s00213-007-0905-x

[37] Mello NK, Negus SS, Rice KC, Mendelson JH. Effects of the CRF1 antagonist antalarmin on cocaine self-administration and discrimination in rhesus monkeys. Pharmacol Biochem Behav. 2006; 85(4): 744-751. doi: https://doi.org/10.1016/j.pbb.2006.11.008

[38] tinus L, Cador M, Zorrilla EP, Koob GF. Buprenorphine and a CRF 1 antagonist block the acquisition of opiate withdrawal-induced conditioned place aversion in rats. Neuropsychopharmacology 2005; 30(1): 90-98. doi: https://doi.org/10.1038/sj.npp.1300487

[39] Erami E, Azhdari-Zarmehri H, Rahmani A, Ghasemi-Dashkhasan E, Semnanian S, Haghparast A. Blockade of orexin receptor 1 attenuates the development of morphine tolerance and physical dependence in rats. Pharmacol Biochem Behav. 2012; 103(2): 212-219. doi: https://doi.org/10.1016/j.pbb.2012.08.010

[40] Ranjbar-Slamloo Y, Azizi H, Fathollahi Y, Semnanian S. Orexin receptor type-1 antagonist SB-334867 inhibits the development of morphine analgesic tolerance in rats. Peptides 2012; 35(1): 56-59. doi: https://doi.org/10.1016/j.peptides.2012.02.023

[41] Rasmussen DD, Kincaid CL, Froehlich JC. Prazosin+ naltrexone decreases alcohol drinking more effectively than does either drug alone in P rats with a protracted history of extensive voluntary alcohol drinking, dependence, and multiple withdrawals. Alcohol Clin Exp Res. 2015; 39(9): 1832-1841.
doi: https://doi.org/10.1111/acer.12828

[42] Simpson TL, Malte CA, Dietel B, Tell D, Pocock I, Lyons R, et al. A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 2015; 39(5): 808-817.
doi: https://doi.org/10.1111/acer.12703

[43] Simpson TL, Saxon AJ, Stappenbeck C, Malte CA, Lyons R, Tell D, et al. Double-blind randomized clinical trial of prazosin for alcohol use disorder. Am J Psychiatry. 2018; 175(12): 1216-1224.
doi: https://doi.org/10.1176/appi.ajp.2018.17080913

[44] Greenwell TN, Walker BM, Cottone P, Zorrilla EP, Koob GF. The α1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. Pharmacol Biochem Behav. 2009; 91(3): 295-302.
doi: https://doi.org/10.1016/j.pbb.2008.07.012

[45] Mirijello A, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Caputo F, et al. Identification and management of alcohol withdrawal syndrome. Drugs 2015; 75(4): 353-365.
doi: https://doi.org/10.1007/s40265-015-0358-1

[46] Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. Alcohol Alcohol. 2005; 40(2): 147-150.
doi: https://doi.org/10.1093/alcalc/agh130

[47] Spano MS, Fattore L, Fratta W, Fadda P. The GABAB receptor agonist baclofen prevents heroin-induced reinstatement of heroin-seeking behavior in rats. Neuropharmacology 2007; 52(7): 1555-1562.
doi: https://doi.org/10.1016/j.neuropharm.2007.02.012

[48] Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database Syst Rev. 2016; 4(4): CD003868.
doi: https://doi.org/10.1002/14651858.CD003868.pub4

[49] Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2003; (2): CD002209.
doi: https://doi.org/10.1002/14651858.CD002209

[50] Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P, et al.. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Database Syst Rev. 2018; (6): CD006332.
doi: https://doi.org/10.1002/14651858.CD006332.pub3

[51] Forray A, Sofuoglu M. Future pharmacological treatments for substance use disorders. Br J Clin Pharmacol. 2014; 77(2): 382-400.
doi: https://doi.org/10.1111/j.1365-2125.2012.04474.x

[52] Weintraub SJ. Diazepam in the treatment of moderate to severe alcohol withdrawal. CNS Drugs. 2017; 31(2): 87-95.
doi: https://doi.org/10.1007/s40263-016-0403-y

[53] Pharmacokinetics of Naltrexone Following Intravenous and Oral Routes of Administration in Healthy Volunteers. Clinicaltrials.gov. 2020.
[WWW]: https://clinicaltrials.gov/ct2/show/NCT00714584
(accessed 23 December 2020)