



## Psychosocially-Assisted Pharmacological Treatment of Opioid Dependent Adults: A Systematic Review

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### Abstract

**Background:** Opioid dependence is a conundrum that significantly contributes to global mortality, crimes, and transmission of diseases such as hepatitis (B and C), human immunodeficiency virus and perhaps, coronavirus disease 2019 (COVID-19). There are contradictory findings on the efficacy of psychosocially-assisted pharmacological treatment of opioid dependence in adults.

**Objective:** The overall objective of this research is to investigate if psychosocially-assisted pharmacological therapy has significantly better effect than pharmacological therapy with regards treatment outcomes of opioid dependent adults.

**Methods:** All methods employed in this study are in conformity with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) framework for systematic review which involve identification, screening, eligibility and inclusion. This systematic review involved PubMed literature search on randomized controlled trials published between 1st January 2015 to 1st October 2021.

**Results:** PubMed search yielded 5,216 articles which were screened using inclusion and exclusion criteria resulting in 19 articles being retained for data extraction. Of the 19 articles used in this study, 13 (68.4%) articles having a combined sample size of 1,928 (60.6%) showed that addition of psychosocial intervention to pharmacotherapy significantly improved abstinence from opioid abuse.

**Conclusion:** The outcome of evaluation of the overall evidences presented in the 19 articles used in this study is that psychosocially-assisted pharmacological therapy is significantly better than pharmacological treatment with respect to enhancement of abstinence from opioid abuse among opioid-dependent adults. Additionally, this study has provided specific combinations of psychosocial and pharmacological treatment that can produce significant beneficial effect on opioid abstinence. The huge downturn in randomized controlled trials on treatment of opioid dependence among adults has been highlighted in this study.

Keywords: Opioid dependence, Adults, Psychosocial intervention, Pharmacological treatment, Psychosocially-assisted pharmacological treatment

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### Introduction

#### *Opioid Dependence Conundrum*

Opioids are compounds which interact with opioid receptors of brain cells. Some are naturally occurring and can be obtained from the poppy seed

while others are synthetic or semisynthetic.<sup>1,2</sup> Although opioids are medically used to attenuate pain, long-term use, nonmedical use, misuse and usage without medical supervision can precipitate opioid dependence and attendant health issues.<sup>1</sup> As a sequel of worldwide use of opioids, addiction to opioids has become a global issue needing prompt and adequate attention. According to World Health Organization (WHO), the number of global death due to substance abuse was 500 000 as of 2017. Of this number of deaths, 70% were attributed to opioid misuse.<sup>1</sup> In addition to high mortality among opioid dependent individuals, addiction to opioid fosters spread of blood-borne viruses such as hepatitis B,C and human immunodeficiency virus.<sup>3</sup> Moreover, abuse of prescription opioids is inculcated in proliferation of crimes.<sup>4</sup> These data clearly show the humongous and devastating global impact of opioid dependence.

### ***Treatment of Opioid dependence***

Currently, there are three approved methods for treating opioid dependence. These are psychosocial, pharmacological and psychosocially-assisted pharmacological therapies. The objectives of psychosocial therapy are to guide addicted adults in controlling their desire for opioids, maintain abstinence and overcome emotional problems associated with opioid dependence.<sup>5</sup> There are empirical evidences supporting the beneficial effects of acceptance and commitment therapy, cognitive behavioral therapy,<sup>6,7</sup> motivational interviewing, twelve-step based therapy, contingency management, family therapy, and couples counseling.<sup>3</sup> Psychosocial intervention could be offered individually or in a group. The group approach is most widely used due to its ability to circumnavigate stigma and isolation while promoting supportive interactions among members of the group.<sup>8</sup>

Pharmacotherapy involves the use of drugs. Three medications are widely used for pharmacological treatment of opioid dependence. These are methadone, buprenorphine and naltrexone.<sup>3</sup> Methadone and buprenorphine are opioid agonists used both for detoxification and maintenance stages of treatment while naltrexone is an opioid antagonist used only for the maintenance stage after addictive opioids have been completely detoxified.

This is due to the fact that interaction between naltrexone and the addictive opioid can result in withdrawal symptoms.<sup>3</sup> Overall data from several research show that pharmacological treatment is effective in abating opioid dependence.<sup>9,10</sup> However, certain studies have reported that two-thirds of adults who received pharmacological treatment do not attain long-term abstinence from opioid misuse.<sup>11,12</sup> Therefore, WHO and American Society of Addiction Medicine recommends concomitant treatment of opioid dependence using psychosocial and pharmacological therapies.<sup>5</sup>

Psychosocially-assisted pharmacological treatment involves the combined use of psychosocial and pharmacological interventions. There are contradictory findings on the efficacy of psychosocially-assisted pharmacological treatment of opioid dependence in adults. While some studies have identified significant effect of combining pharmacological and psychosocial interventions on treatment outcomes,<sup>3,13,14</sup> others observed opposite results.<sup>15,16</sup> Dugosh et al<sup>3</sup> conducted a systematic review to investigate the effectiveness of combining psychosocial intervention with pharmacotherapy. Although their findings showed overall significant beneficial effect of psychosocially-assisted pharmacotherapy on opioid dependence treatment outcome, the study analyzed empirical literatures between January 1, 2008 to December 31, 2014.<sup>3</sup> Findings of studies within the last seven years may have altered or corroborated the findings of Dugosh and colleagues. Therefore, a systematic review of studies spanning the last seven years became imperative.

### ***Research Question***

Does psychosocially-assisted pharmacological treatment of opioid dependent adults produce significantly better beneficial effects over pharmacological intervention with regards opioid abstinence and amount or frequency of opioid misuse?

### ***Overall Objective***

The overall objective of this research is to investigate if psychosocially-assisted pharmacological therapy has significantly better effect than pharmacological therapy with regards treatment outcomes of opioid dependent adults by

systematically reviewing articles on randomized controlled trials between 1<sup>st</sup> January 2015 to 1<sup>st</sup> October 2021.

## Methodology

### *Study Protocol*

All methods employed in this study are in conformity with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) framework for systematic review<sup>17</sup> which involve identification, screening, eligibility and inclusion.

### *Data source and Search Strategy*

Literature search was conducted in the PubMed database on 2<sup>nd</sup> October, 2021. The research question was divided into 4 concepts, psychosocial, pharmacological, opioid and opioid dependence (Table 1). The search employed controlled vocabulary (MeSH terms), keywords and their synonyms to systematically retrieve literatures that could address the research question.

### *Study Selection*

#### *Inclusion Criteria*

Randomized control trials (RCTs) that were conducted between 1<sup>st</sup> January 2015 to 1st October, 2021 were included in this research. Studies reported in English Language were included. Articles describing opioid dependence among adult population aged 18 years and above were included. Only studies in which pharmacological intervention was used as a control to measure the efficacy of psychosocially-assisted pharmacological intervention were included. Studies which measured the outcome of interventions in terms of abstinence, amount or frequency of opioid misuse and treatment retention were included. RCTs with sample size of at least 10 were included.

#### *Exclusion criteria*

Studies that are not RCTs and did not use pharmacological intervention as a control were excluded. Articles in which the sample size is less than 10 and those with insufficient information on methods used to evaluate the impact of psychosocially-assisted pharmacological treatment on opioid dependence were excluded.

### *Screening*

Titles of articles were screened to assess their relevance to the research question afterwards, screening of abstracts was carried out based on inclusion and exclusion criteria. Articles that passed the abstract screening stage were subjected to full text screening using inclusion and exclusion criteria.

### *Data Extraction and Analysis*

Data on effect size, sample size, age and gender of participants, country where study was conducted, duration of study, type of psychosocially-assisted pharmacological intervention, type of control used and outcomes of eligible studies were extracted. Due to the heterogeneous nature of included studies, only descriptive analysis of data was conducted. It has been reported that only studies with same intervention and control should be meta-analyzed.<sup>18</sup>

### *Risk of Bias*

Risk of bias of each eligible study was assessed using the Cochrane risk of bias tool which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.<sup>19</sup>

## Results

### *Search Results*

Literature search of each of the four concepts, psychosocial, pharmacological, opioid, opioid dependence resulted in 1 382 343, 9 565 477, 233 134 and 33 655 hits respectively. Upon combining the four concepts into a single query using "AND" as the Boolean operator, 5 216 hits were obtained. Initial screening of article titles using eligibility criteria resulted in exclusion of 5 060 articles while 156 were retained for further screening. Distribution of the 156 articles across the study period (1st January 2015 to 1st October 2021) is as follows, 36 (23.08%), 23 (14.74%), 30 (19.23%), 27 (17.31%), 17 (10.89%), 15 (9.62%) and 8 (5.13%) for 2015, 2016, 2017, 2018, 2019, 2020 and 2021 respectively.

Results show that 107 (68.59%) of the 156 articles were obtained from studies carried out in the United

Table 1: Search Strategy

#	Concept	Query
1	Psychosocial	"Psychosocial Intervention"[Mesh] OR Psychosocial[tw] OR "Psychosocial treatment*" [tw] OR Behavioral[tw] OR Psychiatric[tw] OR Psychological[tw] OR "twelve step" [tw] OR "12 step" [tw] OR Counsel* [tw] OR Psychotherap* [tw]
2	Pharmacological	"Pharmacological Phenomena"[Mesh] OR Pharmacological[tw] OR Pharmaco* [tw] OR Treatment* [tw] OR Medication* [tw] OR Intervention* [tw] OR "Medication Assisted Treatment*" [tw] OR suboxone [tw] OR Subutex [tw] OR buprenorphine [tw] OR methadone [tw] OR naltrexone [tw] OR vivitrol [tw]
3	Opioid	"Analgesics, Opioid"[Mesh] OR Opioid* [tw] OR Opiate* [tw] OR Heroin [tw] OR Narcotic* [tw] OR Opium [tw] OR Codeine [tw] OR Morphine [tw]
4	Opioid dependence	"Opioid-Related Disorders"[Mesh] OR "Opioid dependence" [tw] OR "Opioid disorder" [tw] OR "Opioid misuse" [tw] OR "Opioid abuse" [tw] OR "Opioid Use Disorder" [tw]
1 AND 2 AND 3 AND 4	Psychosocial AND Pharmacological AND Opioid AND Opioid dependence	((("Psychosocial Intervention"[Mesh] OR Psychosocial[tw] OR "Psychosocial treatment*" [tw] OR Behavioral[tw] OR Psychiatric[tw] OR Psychological[tw] OR "twelve step" [tw] OR "12 step" [tw] OR Counsel* [tw] OR Psychotherap* [tw]) AND ("Pharmacological Phenomena"[Mesh] OR Pharmacological[tw] OR Pharmaco* [tw] OR Treatment* [tw] OR Medication* [tw] OR Intervention* [tw] OR "Medication Assisted Treatment*" [tw] OR suboxone [tw] OR Subutex [tw] OR buprenorphine [tw] OR methadone [tw] OR naltrexone [tw] OR vivitrol [tw])) AND ("Analgesics, Opioid"[Mesh] OR Opioid* [tw] OR Opiate* [tw] OR Heroin [tw] OR Narcotic* [tw] OR Opium [tw] OR Codeine [tw] OR Morphine [tw])) AND ("Opioid-Related Disorders"[Mesh] OR "Opioid dependence" [tw] OR "Opioid disorder" [tw] OR "Opioid misuse" [tw] OR "Opioid abuse" [tw] OR "Opioid Use Disorder" [tw]))

States of America (USA) while others were done in Malaysia (4; 2.56%), Canada (4; 2.56%), China (5; 3.21%), Iran (13; 8.33%), United Kingdom (7; 4.49%), Switzerland (4; 2.56%), Germany (2; 1.28%), Norway (1; 0.64%), Denmark (1; 0.64%), Singapore (1; 0.64%), Australia (1; 0.64%), Ireland (1; 0.64%), Russia (3; 1.92%), France (1; 0.64%) and Mexico (1; 0.64%). Further screening of the 156 articles using eligibility criteria resulted in the exclusion of 137 articles yielding a total of 19 articles which were used for data extraction.

**Risk of Bias**

With respect to random sequence generation and allocation concealment, 7 (37%) studies had low risk of bias while 12 (63%) studies had unclear risk of bias (Table 2). For allocation concealment, the risk of bias was as follows, 6 (32%; low risk), 1 (5%; high risk) and 12 (63%; unclear risk). In the domain of blinding of participants and researchers, 1 study

(5%) had low risk of bias while 11 (58%) and 7 studies (37%) were observed to have unclear and high risk of bias respectively (Table 2). In 1 study (5%) blinding of outcome assessment was reported (low risk of bias) while 13 studies (69%) and 5 studies (26%) were deemed to have unclear risk and high risk of bias respectively. All studies have low risk of bias in the domain of incomplete outcome data and other bias. One study (5%) had unclear risk of bias and 18 (95%) had low risk of bias with respect to selective reporting.

**Psychosocial interventions used in conjunction with buprenorphine-naloxone**

**Distress tolerance**

Stein and colleagues evaluated the effectiveness of a novel adjunctive distress tolerance psychosocial intervention in the USA. This study was a randomized controlled trial among opioid

Table 2: Outcomes of risk of bias analysis

Study	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Stein 2015	?	?	?	?	+	+	+
Cochran 2015	?	?	-	?	+	+	+
Zhong 2015	?	?	?	?	+	+	+
Pan 2015	+	+	+	?	+	+	+
Saunders 2015	?	?	?	?	+	+	+
Kim 2016	?	?	-	-	+	+	+
Moore 2016	?	?	?	?	+	+	+
Schwartz 2017	+	+	?	?	+	+	+
Weiss 2017	?	?	?	?	+	+	+
Coffin 2017	?	+	?	?	+	+	+
Rezapour 2017	?	?	?	?	+	+	+
Day 2018	+	+	-	-	+	+	+
Barry 2019	?	?	?	?	+	+	+
Shi 2019	+	?	?	?	+	+	+
Marsden 2019	+	?	-	-	+	+	+
Cochran, 2019	+	?	-	+	+	+	+
Harvey 2020	+	-	-	-	+	+	+
Schottenfeld 2021	?	+	-	-	+	+	+
Cooperman 2021	?	+	?	?	+	?	+

Low risk

High risk

Unclear risk

dependent individuals aged 18 to 65 years who requested for buprenorphine intervention and were willing to remain in treatment for 3 months. Twenty-five (25) of the 49 participants were randomized to receive distress tolerance (DT) in conjunction with buprenorphine-naloxone while 24 received treatment as usual (TAU) which involved administration of buprenorphine-naloxone and brief counselling (health education) by a physician.<sup>20</sup> The DT psychosocial intervention was developed using the concepts of exposure and

acceptance. Primary outcomes of treatment were self-reported illicit opioid use and opioid positive urine analysis. They determined a priori that an effect difference of 10% would be considered significant. Intent to treat urine toxicology analysis of the DT and control groups at 3 months of treatment revealed values of 62.5% and 72% respectively at confidence interval of -16.7, 35.7. This was indicative of a statistically non-significant difference between the DT and control group.

### **Therapeutic education system**

In another study carried out in the USA by Cochran et al,<sup>21</sup> therapeutic education system (TES) was used in conjunction with buprenorphine. Although the multisite randomized controlled trial involved a total of 497 substance use disorder patients, only 108 were opioid-dependent. It was a 12 week-study, participants were at least 18 years old and involved more males than females.<sup>21</sup> Participants were randomized to receive treatment as usual (TAU) or TES. The TAU arm received buprenorphine while the TES group were subjected to a cognitive behavioral therapy designed using the framework of community reinforcement in addition to buprenorphine. The primary outcome of this study was abstinence from opioid misuse measured by urine toxicology and self-report of opioid abuse. Cochran and colleagues found out that adjunctive TES had no significant effect on abstinence from opioid misuse.

### **Cognitive-behavioral therapy**

The effect of adjunctive cognitive behavioral therapy (CBT) on opioid abstinence was reported by Moore et al.<sup>22</sup> This study was conducted in the USA. Participants (n = 140) were at least 18 years of age and 71% were male. Outcome was abstinence from illicit opioid use measured by self-report and urine toxicology. Participants were randomized to receive CBT or treatment as usual.<sup>22</sup> The CBT group had significantly higher proportion of opioid-negative urine toxicology test (7.6) compared to the control (3.6).

### **Opioid drug counselling**

A study conducted by Weiss et al.<sup>23</sup> examined the effect of counselling when used in combination with buprenorphine-naloxone in the treatment of opioid dependence. In this study conducted in the USA, 653 opioid-dependent adults were randomized to receive usual care or adjunctive counselling and buprenorphine-naloxone.<sup>23</sup> Outcome measure was self-reported illicit opioid use and urine toxicology analysis of opioid misuse. They observed that opioid drug counselling produced no significant improvement of treatment outcome compared to usual care.

### **Repeated dose motivational interviewing intervention**

In a study conducted by Coffin et al.<sup>24</sup> in the USA, repeated dose motivational interviewing intervention (REBOOT) was used in conjunction with naloxone to investigate its effect on treatment of opioid-dependent adults.<sup>24</sup> A total of 63 patients aged 18-65 years were enrolled for the study. The REBOOT arm had 43 participants randomized to it while the control arm had 20. Most of the participants recruited into this study were male (n = 42). Outcome measure was number of overdose events. Results showed that the REBOOT group had significantly lower experience of overdose events compared to the control with confidence interval of 0.24-0.90.

### **Web-based cognitive-behavioral therapy**

The effectiveness of adjunctive web-based cognitive-behavioral therapy (CBT4CBT) in buprenorphine treatment of opioid-dependent adult was investigated by Shi et al.<sup>25</sup> in the USA. This 12-week study was designed to evaluate the effect of CBT4CBT used as an adjunct to office-based buprenorphine treatment. Individuals were at least 18 years in age and majority were male. Of the 20 participants, 10 each were randomized to receive CBT4CBT and standard buprenorphine care.<sup>25</sup> The primary outcome of this study was abstinence from illicit opioid use assessed by urine toxicology test. Results of urine toxicology showed that the CBT4CBT group had significantly higher percentage of opioid-negative urine samples (91%) than the standard care arm (64%).

### **Brief motivational intervention-medication therapy management**

Brief motivational intervention-medication therapy management (BMI-MTM) was used as adjunct to naloxone in a study conducted by Cochran et al.<sup>26</sup> in the USA. BMI-MTM comprises of drug counselling, a session of motivation and 8 weeks of navigation sessions. Adult naloxone patients (n = 32) were assigned to receive BMI-MTM (n = 15) or standard medication counselling (SMC) who served as the control. Primary outcome of this study was abstinence from opioid misuse measured by prescription opioid misuse index and urine screens.<sup>26</sup> The BMI-MTM group reported a

significantly greater reduction in opioid misuse than the SMC group with a confidence interval value of 0.05, 0.35.

### **Behavioral counselling**

This study conducted in Malaysia by Schottenfeld et al.<sup>27</sup> They investigated the effect of addition of behavioral counselling to buprenorphine-naloxone treatment of adult opioid dependent patients. This study involved 234 participants who were randomly assigned to receive physician management without abstinence-contingent buprenorphine-naloxone (ACB) or behavioral counseling (n = 58), physician management with ACB without behavioral counseling (n = 60), physician management with behavioral counseling without ACB (n = 59) and physician management with behavioral counseling and ACB (n = 57). Primary outcome was abstinence from illicit opioid use measured by urine screens.<sup>27</sup> Participants assigned to behavioral counselling groups were found to have significantly higher rates of opioid-negative urine test results than those in groups that did not involve behavioral counselling.

### **Psychosocial interventions used in conjunction with methadone**

#### **Comprehensive psychosocial intervention**

Zhong et al.<sup>28</sup> evaluated the effect of adjunctive comprehensive psychosocial intervention in the treatment of opioid-dependent adults resident in China. Majority of study participants (n = 141) were male. Urine test and self-reported opioid use were used to measure opioid abstinence. The authors reported that there was no significant difference between the 2 arms of treatments with regards opioid abstinence.<sup>28</sup>

#### **Cognitive behavioral therapy**

Two studies were conducted to investigate the impact of cognitive behavioral counselling when used as an adjunct to methadone treatment of opioid dependence. These randomized controlled trials were conducted by Pan et al.<sup>29</sup> and Barry et al.<sup>30</sup> in China and the USA respectively.

#### **Pan et al.<sup>29</sup>**

Pan and colleagues conducted a randomized controlled trial to investigate the effect of cognitive

behavioral therapy (CBT) in conjunction with methadone on opioid abstinence among opioid-dependent adults. The 26-week study randomized 120 participants to the CBT arm and 120 to the control.<sup>29</sup> Male participants were more (n = 186) than female participants. The primary outcome of this study was opioid abstinence measure through urine screens to detect and quantify illicit opioid. Proportion of opioid-negative urine test at week 26 were 73% and 63% for the CBT and control group respectively. These values were significantly different.

#### **Barry et al.<sup>30</sup>**

In another study carried out by Barry et al.,<sup>30</sup> cognitive behavioral therapy was used in conjunction with methadone in the treatment of 40 opioid-dependent individuals. Participants were at least 18 years old and 63% of them were male. Primary outcome of this study was abstinence from opioid misuse measured by weekly urine toxicology analysis. Study participants (n = 21) were randomized to receive cognitive behavioral therapy (CBT) and methadone drug counselling (MDC, n = 19) which served as the control.<sup>30</sup> Results of primary outcome measure for the CBT group was significantly higher than the MDC arm (Wald  $\chi^2(1) = 5.47, p = 0.019$ ).

#### **Therapeutic Education System**

A study by Kim et al.<sup>31</sup> investigated the impact of adding therapeutic education system to methadone treatment of opioid dependence in the USA. A total of 160 participants who were at least 18 years of age were used in this study. Of the 160 participants, 75% were male.<sup>31</sup> Participant were randomized to receive TES or treatment as usual. There was a significant difference between both groups with regards odds of having opioid-positive urine screen with confidence interval value of 1.48–1.85.

#### **Patient-centered methadone**

The effect of patient-centered methadone (PCM) treatment of opioid dependence was investigated by Schwartz and colleagues in the USA. It was a randomized trial in which participants were at least 18 years old and 59% were males. A total of 300 participants were involved and 149 were randomized to PCM while a 151 to standard care.

The primary outcome of this study was number of opioid-positive urine screens at 12 months. Schwartz et al.<sup>32</sup> found no significant difference between the 2 groups with respect to the primary outcome measured at confidence interval value of 0.61, 1.56.<sup>32</sup>

#### ***Cognitive rehabilitation therapy***

Rezapour et al.<sup>33</sup> investigated the effect adding cognitive rehabilitation therapy (CRT) to methadone treatment of opioid dependence in Iran. In this study 120 males were randomized to 2 treatment groups, CRT and standard care. Abstinence from opioid misuse was the outcome of study.<sup>33</sup> The CRT arm showed significantly lower frequency of opioid misuse than the control.

#### ***Mindfulness-Oriented Recovery Enhancement (MORE)***

A study conducted by Cooperman et al.<sup>34</sup> investigated the effect of using mindfulness-oriented recovery enhancement (MORE) as an adjunct to methadone in the treatment of opioid-dependent adults resident in the USA. Mean age of participants (n = 30) was 50.4 years comprising of 15 each of male and female. Abstinence from opioid misuse was the outcome, and was measured through urine toxicology. Results showed that the MORE arm had significantly lower opioid misuse than the control group.<sup>34</sup>

#### ***Psychosocial interventions used in conjunction with buprenorphine-naloxone, methadone or naltrexone***

##### ***Integrated cognitive behavioral therapy***

Saunders et al.<sup>35</sup> evaluated the effect of adjunctive integrated cognitive behavioral therapy (ICBT) on opioid dependence in the USA.<sup>35</sup> A total number of 126 adult participants at least 18 years of age with co-occurring opioid dependence and post-traumatic stress disorder were randomized to receive ICBT or usual care. They observed participants who received ICBT had significantly lower odds of opioid-positive urine test compared to those who received usual care with confidence interval value of 0.01, 0.81.

##### ***Brief Social Behavior and Network Therapy***

A randomized controlled trial was conducted in the UK by Day et al.<sup>36</sup> They investigated the effect of addition of brief social behavior and network therapy (BSBNT) to methadone or buprenorphine treatment. This 12-month study involved 83 participants that are at least 18 years in age. Participants were randomized to receive BSBNT (n = 26), personal goal setting (PSG, n = 27) and treatment as usual with methadone or buprenorphine (n = 30). The primary outcome of the study was number of days of abstinence from opioid misuse.<sup>36</sup> Day and colleagues found out that there was no significant difference in primary outcome between the 3 arms of the study.

##### ***Integrated psychological intervention***

In this UK study conducted by Marsden et al.,<sup>37</sup> an integrated psychological intervention (ISI) was used in conjunction with methadone or buprenorphine. ISI involved cognitive-behavioral therapy, contingency management and 12-step group method. Study participants were at least 18 years old and comprise of 205 males and 68 females making a total of 273 individuals. All participants were randomly assigned to either ISI (n = 136) or usual care (n = 137). Primary outcome of the study was abstinence from illicit opioid use evaluated by opioid urine screens.<sup>37</sup> The ISI group had significantly higher percentage of opioid-negative urine test (16%) compared to the control group (7%) with confidence interval of 0.01–2.37.

##### ***Individual counselling, group counselling and 12-step participation***

Harvey et al.<sup>5</sup> evaluated the effect of 3 psychosocial interventions namely, individual counselling (IC), group counselling (GC) and 12-step participation (TS) when used in conjunction with buprenorphine-naloxone or extended-release naltrexone in the treatment of opioid-dependent individuals resident in the USA.<sup>5</sup> Individuals of at least 18 years of age (n = 570) were recruited into the study. Abstinence from illicit opioid use was the primary outcome measure and urine screens was employed to ascertain it. Participants were randomized to IC, GC, TS and treatment as usual. IC and TS had significant effect on abstinence from illicit opioid use with confidence interval value of 0.42, 0.74



## Discussion

### *Search results*

From the search results of this study, it was observed that between 1<sup>st</sup> January 2015 to 1st October 2021, research on treatment of opioid dependence using adjunctive psychotherapy experienced a downturn despite the fact that opioid dependence is very much prevalent. Decreased funding of randomized control trials may have contributed to this situation. The sharp drop in research between 2018 to 2021 can be attributed to coronavirus disease 2019 (COVID-19) pandemic. However, it is important to give opioid use disorder adequate attention because opioid-dependent individuals are less likely to adhere to COVID-19 protocols or accept vaccination. Consequently, they could hamper the global fight against the pandemic. This systematic review has established that United States of America had given the most attention to randomized controlled trials (RCT) of psychosocially-assisted pharmacotherapy. It is pertinent to note there is no published article on the RCT of psychosocially-assisted pharmacotherapy in Africa which suggests that such study has not been conducted in the African continent.

### *Psychosocial interventions used in conjunction with buprenorphine-naloxone*

Addition of distress tolerance to standard buprenorphine-naloxone treatment did not significantly improve abstinence from opioid misuse.<sup>20</sup> Adjunctive therapeutic education system was also not found to significantly improve treatment outcome.<sup>21</sup> Additionally, opioid drug counselling used as an adjunct to buprenorphine-naloxone did not significantly improve abstinence from illicit opioid use.<sup>23</sup> A study reported that adjunctive cognitive behavioral therapy significantly increased abstinence from opioid misuse.<sup>22</sup> The efficiency of buprenorphine-naloxone treatment apropos of reduction in frequency of opioid misuse was significantly enhanced by the addition of repeated dose motivational interviewing intervention.<sup>24</sup> A web-based cognitive-behavioral therapy has been demonstrated to significantly increase abstinence from opioid abuse.<sup>25</sup> It is worthy of note that treatment of opioid-dependent adults using buprenorphine-naloxone became

significantly improved when adjunctive brief motivational intervention-medication therapy management was used.<sup>26</sup> Moreover, behavioral counselling significantly improved the outcome of buprenorphine-naloxone treatment.<sup>27</sup>

### *Summary of findings on psychosocial interventions used in conjunction with buprenorphine-naloxone*

Of the 8 articles reviewed in this study, 3 of them with a combined sample size of 810 showed that using psychosocial interventions in conjunction with buprenorphine-naloxone do not significantly improve abstinence from opioid abuse while the remaining 5 articles having a combined sample size of 489 are in favor of psychosocially-assisted pharmacological interventions. On the basis of number of articles, addition of psychosocial interventions to buprenorphine-naloxone improves treatment outcome while on the basis of total sample size adjunctive psychosocial interventions do not improve outcome of buprenorphine-naloxone treatment.

### *Psychosocial interventions used in conjunction with methadone*

Comprehensive psychosocial intervention used as an adjunct to methadone has been shown to have an insignificant effect on abstinence from opioid abuse.<sup>28</sup> Additionally, patient-centered methadone used in conjunction with methadone does not improve treatment outcome.<sup>32</sup> Contrary to the aforementioned psychosocial interventions, addition of cognitive behavioral therapy to methadone significantly improves treatment outcome.<sup>29,30</sup> There is empirical evidence on the significant impact of therapeutic education system in methadone treatment of opioid dependence.<sup>31</sup> Moreover, addition of cognitive rehabilitation therapy to methadone treatment has been demonstrated to significantly enhance abstinence from illicit opioid use.<sup>33</sup> A psychosocial intervention called mindfulness-oriented recovery enhancement has been shown to improve methadone treatment outcome.<sup>34</sup>

### *Summary of findings on psychosocial interventions used in conjunction with methadone*

With regards methadone treatment, 7 articles were

reviewed. Out of which 2 with a combined sample size of 441 reported that addition of psychosocial intervention to methadone treatment did not produce significant effect on treatment outcome while 5 having a combined sample size of 470 provided empirical evidences on the significant effect of adjunctive psychotherapy in methadone treatment of opioid-dependent adults. Based on combined sample size and number of articles, addition of psychosocial interventions to methadone treatment could significantly improve abstinence from opioid abuse.

Psychosocial interventions used in conjunction with buprenorphine-naloxone, methadone or naltrexone Adjunctive brief social behavior and network therapy has been demonstrated to have non-significant effect on opioid abstinence in medication-assisted opioid treatment.<sup>36</sup> On the contrary, adjunctive integrated cognitive behavioral therapy have been reported to have significant beneficial effect on abstinence from opioid abuse.<sup>35</sup> Furthermore, addition of an integrated psychological intervention to medication-assisted opioid treatment significantly improved treatment outcome.<sup>37</sup> A study by Harvey and colleagues reported the significant effect of adding individual counselling or 12-step participation to medication-assisted treatment of opioid-dependence.

### ***Summary of findings on psychosocial interventions used in conjunction with buprenorphine-naloxone, methadone or naltrexone***

The 4 articles which met the inclusion criteria of this study had mixed reports on psychosocially-assisted pharmacological treatment of opioid use disorder. One (1) of the articles which involved 83 participants reported that adjunctive psychosocial intervention did not significantly improve treatment outcome. On the other hand, 3 of the articles having a combined sample size of 969 demonstrated that addition of psychotherapy to medication-assisted opioid treatment significantly improved abstinence from opioid abuse. On the basis of number of articles and combined sample size, addition of psychosocial intervention to medication-assisted treatment of opioid-dependent adults could significantly enhance abstinence from opioid abuse.

### ***Overall summary of findings***

A total of 19 articles with a combined sample size of 3,180 were used in this study. Six (31.6 %) of them with a combined sample size of 1,252 (39.4%) reported that adjunctive psychosocial intervention when used in conjunction with pharmacological treatment did not have any significant effect on abstinence from opioid abuse. The remaining 13 (68.4%) articles having a combined sample size of 1,928 (60.6%) showed that addition of psychosocial intervention to pharmacotherapy significantly increased abstinence from opioid abuse. This finding is congruent with that of Dugosh et al. (2016) and Amato et al. (2011).<sup>3,13</sup>

### **Conclusion**

This research employed a rigorous approach to systematically review psychosocially-assisted pharmacological treatment of opioid-dependent adults. The effect of adding psychosocial intervention to pharmacological treatment of opioid dependence is not consistent. Some randomized controlled trials reported that it had no significant benefit while others reported the contrary. However, the outcome of evaluation of the overall evidences presented in the 19 articles used in this study suggest that psychosocially-assisted pharmacological therapy is significantly better than pharmacotherapy with respect to enhancement of abstinence from opioid abuse among opioid-dependent adults. Additionally, this study has provided specific combinations of psychosocial and pharmacological treatment that can produce beneficial effect on opioid abstinence. Despite the huge negative global impact of opioid abuse, it has been observed that there is a significant downturn in randomized controlled trials (RCT) on treatment of opioid dependence among adults. More research efforts are needed to develop effective combinations of psychosocial and pharmacological interventions.

### **Conflict of interest**

The authors declare that they have no competing interest.

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