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The Association of Concurrent Psychotic Disorders with Outcomes of Opioid Agonist Therapy in Individuals with Opioid Use Disorder: A Systematic Review and Meta-Analysis of Observational Studies

Yangyang Li[1] · **Solja Niemelä**[1] · **Alexander Denissoff**[1]

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Abstract

Purpose of Review This systematic review examines the association between co-occurring psychotic disorders and Opioid Agonist Therapy (OAT) outcomes in Opioid Use Disorder (OUD).

Recent Findings We searched eight databases and reference lists up to March 20, 2024, for observational studies comparing OAT outcomes in patients with OUD with and without psychotic disorders. 21 studies with 17,623 participants were included, all exhibiting a low to moderate overall risk of bias. The results suggested that patients with OUD and psychotic disorders had significantly poorer OAT retention than those with OUD without psychotic disorders [odds ratio (OR) = 0.65; 95% confidence interval (CI): 0.57–0.74; $P < 0.05$]. Subgroup analysis identified study period as a source of heterogeneity, with no significant publication bias. No significant evidence suggested that co-occurring psychotic disorders were associated with illicit drug use, including opioids (OR = 1.05; 95% CI: 0.50–2.23; $P = 0.90$), amphetamines [relative risk (RR) = 1.09; 95% CI: 0.45–2.67; $P = 0.84$], cannabis (OR = 1.48; 95% CI: 0.99–2.21; $P = 0.06$), cocaine (RR = 1.19; 95% CI: 0.43–3.25; $P = 0.74$), and polydrug use (OR = 1.05; 95% CI: 0.40–2.72; $P = 0.93$). Sensitivity analysis confirmed the robustness of all pooled results except for cannabis use.

Summary Analyzing data from 21 studies involving 17,623 participants, we found that patients with OUD and psychotic disorders had significantly poorer OAT retention compared to those with OUD without psychotic disorders. However, no significant association was found between co-occurring psychotic disorders and illicit drug use.

Keywords Psychotic disorders · OUD · Comorbidity · OAT · Treatment retention · Illicit drug use

Introduction

OUD is more common among individuals with psychotic disorders [1, 2]. A study from Norway revealed that the prevalence of OUD in individuals with schizophrenia, bipolar disorder, depressive illness, and the general population was approximately 4.3%, 2.1%, 1.4%, and 0.5%, respectively [3]. OAT, primarily using methadone and buprenorphine, is the first-line treatment for OUD [4, 5], effectively alleviating withdrawal symptoms [6], reducing opioid-related harm, such as overdose and mortality [7], and improving treatment retention [8]. Nevertheless, there is concern about a treatment gap for patients with OUD and co-occurring psychotic disorders, who are often underutilizing OAT [9, 10]. The prevalence of co-occurring psychotic disorders among patients with OUD undergoing OAT varies. A survey of 193 OAT patients in the Netherlands reported that 37.8% had psychotic disorders [11]. In contrast, lower rates were observed in Nepal, Spain, and Canada, at 7.4%, 5.8%, and 3.07%, respectively [12–14]. Although psychotic disorders are relatively less prevalent in OAT populations according to some studies, they should not be overlooked due to the substantial burden they impose and their potential impact on treatment outcomes [15, 16]. However, people with concurrent psychotic disorders are often excluded from experimental studies evaluating the effectiveness of OAT among patients with OUD [17].

✉ Yangyang Li
yangyl@utu.fi

[1] Department of Psychiatry, Faculty of Medicine, University of Turku, Kiinamyllynkatu 10, Turku 20520, Finland

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In existing observational studies, there is an ongoing debate regarding the association between co-occurring psychotic disorders and OAT outcomes in patients with OUD. Some researchers have reported poorer OAT outcomes among patients with OUD and psychotic disorders compared to patients with OUD without psychotic disorders. For example, Pant et al. found significantly higher lifetime suicidality among individuals with OUD and psychotic disorders than those with OUD without psychotic disorders [13]. Similarly, studies by Gerra et al. and Shams et al. suggested poorer treatment retention and higher cannabis use among patients with OUD and psychotic disorders [18, 19]. On the other hand, conflicting findings have been reported by other researchers. For instance, Bouton et al. found no significant evidence that co-occurring psychotic disorders were related to illicit drug use [20]. Additionally, Lamont et al. reported no significant relationship between co-occurring psychotic disorders and treatment retention [17].

This research aimed to conduct a systematic review of observational studies to clarify the association between co-occurring psychotic disorders and critical outcomes, such as treatment retention and illicit drug use, as well as outcomes of limited importance, including depression, mortality, quality of life, cardiovascular safety, and adherence among patients with OUD receiving OAT.

Methods

This study adhered to and reported findings following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21, 22] and was registered on PROSPERO with the registration number CRD42024560560. The protocol for this systematic review was not published.

Information Sources and Search Strategy

We conducted comprehensive searches across eight databases—PubMed, EMBASE, Cochrane Library, Web of Science, PsycINFO, CINAHL, Scopus, and Google Scholar, retrieving the first 200 citations from the latter. No date restrictions were imposed on the searches, which covered articles up to March 2024. Additionally, we reviewed reference lists from relevant systematic reviews and observational studies to identify additional studies.

The search terms encompassed a broad spectrum of studies and primarily incorporated the following keywords: ((opiate OR opioid OR methadone OR buprenorphine OR naloxone OR "LAAM") AND (replacement OR "medication-assisted" OR substitution OR agonist OR maintenance) AND (therap* OR treatment* OR program*)) AND (psychotic OR psychos* OR schiz*). The specific search strategy is detailed in Online Resource 1.

Eligibility Criteria

To qualify for inclusion, studies had to meet the following criteria: (i) Participants: Individuals with OUD receiving OAT, including methadone, buprenorphine, buprenorphine/naloxone, or levo-alpha-acetylmethadol (LAAM). Although LAAM is no longer approved by the FDA for the clinical treatment of OUD, we included it to provide a comprehensive analysis. (ii) Exposure Indicator: The presence of co-occurring psychotic disorders, which encompassed schizotypal personality disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance-induced psychotic disorder, and psychotic disorder due to another medical condition [23]. (iii) Study Design: Cohort, cross-sectional, or case-control studies. (iv) Comparison Group: Patients with OUD without psychotic disorders, including those with non-psychotic dual diagnoses or no dual diagnoses. (v) Outcomes of Interest: Critical Outcomes: illicit drug use, as quantified by the number of participants with positive urinalysis results, and treatment retention, defined by the number of participants remaining in the study at its conclusion. Outcomes of Limited Importance: Depression, as assessed by DSM or ICD criteria or validated scales; quality of life, as measured by established and reliable scales; death, indicated by the number of deceased or surviving participants or survival duration; cardiovascular safety, encompassing all relevant measures such as corrected QT interval (QTcF); and adherence or compliance, evaluated by how well participants followed healthcare provider recommendations. There were no restrictions regarding the language of publication or the publication date.

The exclusion criteria were as follows: (i) Studies exhibiting duplicate publication issues; (ii) Literature containing apparent errors; (iii) Literature lacking essential information, with no successful author contact.

Selection Process

Two researchers (YYL and SN) independently assessed titles and abstracts to identify which full-text articles needed screening. YYL and SN then independently acquired and evaluated the full texts of potentially relevant studies. If abstracts or articles were in languages other than Chinese or English, they were translated using "Zhiyun Document Translation" and Google Translate. Any uncertainties were resolved through discussion.

Data Extraction

YYL and SN randomly selected 10 studies from those included to develop and pilot-test a data extraction sheet. Subsequently, YYL collected the data, and SN verified its accuracy. Disagreements were resolved through discussion. The reviewers emailed the corresponding authors to confirm any ambiguous or missing data. For the same outcome, the latest, adjusted, intention-to-treat (ITT)-analyzed data and the largest sample sizes were prioritized. Subgroup data were combined if necessary. Extracted information included: (i) study characteristics (author, year, country); (ii) participant characteristics (age, sex, sample size, diagnosis); (iii) study design; (iv) exposed and control groups; (v) outcome measures; and (vi) OAT types.

Assessment of Risk of Bias

Two review authors (YYL, SN) independently used Newcastle-Ottawa Scale (NOS) to assess the quality of cohort and case-control studies [24]. NOS evaluates three aspects with 8 items: selection (0–4 points), comparability (0–2 points), and exposure or outcome (0–3 points) [25]. Based on their NOS scores, studies were categorized as low quality (0–3), moderate quality (4–6), and high quality (7–9) [26]. Cross-sectional studies were also independently assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria, which includes 11 items [27]. Each item is answered as "yes," "no," or "unclear," with "yes" scored as 1 and the others as 0 [28]. Studies were classified as low quality (0–3), moderate quality (4–7), and high quality (8–11) based on their AHRQ scores [29]. Any divergences were resolved through discussion to achieve consensus.

Data Analysis and Synthesis

A Meta-analysis was performed if at least two included studies addressed the same outcome, and significant heterogeneity, when present, could be explained through subgroup analysis or sensitivity analysis.

We conducted the meta-analysis using Stata version 17.0 and RevMan version 5.3. Dichotomous outcomes were analyzed by calculating the RR or OR for each study, accompanied by 95% CIs. For continuous data, the weighted mean difference (WMD) with 95% CI was used for studies utilizing the same scales, while the standardized mean difference (SMD) with 95% CI was applied for different scales. Effect sizes were combined using a fixed-effect model in the absence of significant heterogeneity [30], and a random-effects model when heterogeneity was present [31]. Statistical significance was assessed using a z-test, with a P-value less than 0.05 indicating significant results [32]. The meta-analysis results were presented in forest plots.

Heterogeneity among studies was evaluated using the Q-statistic and I^2 index. A P-value less than 0.05 indicated significant heterogeneity in the Q-test [33]. The I^2 index estimated the percentage of heterogeneity, interpreted as not important (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) [34–36]. Due to changes in OAT policies and the impact of the COVID-19 pandemic, a subgroup analysis based on study period was conducted to explain significant heterogeneity [37]. Sensitivity analysis explored the source of heterogeneity and assessed the robustness of the results by omitting studies one by one and observing changes in pooled effect sizes and heterogeneity [38]. Funnel plots were used to detect publication bias [32], and Egger's linear regression test and Begg's rank correlation test were conducted, with $P < 0.05$ indicating significant publication bias [39].

A narrative synthesis was conducted when data could not be pooled in a meta-analysis due to significant unexplained heterogeneity or the availability of only a single study. This involved summarizing, comparing, and qualitatively combining the results of each study on the same outcomes.

Results

Study Selection

A total of 7,044 records were identified from the electronic database search. After removing 1,779 duplicates, 5,265 records were screened, resulting in 5,217 exclusions. Of the remaining 48 full texts reviewed, 30 were further excluded for the following reasons: duplicates ($n=4$) [40–43], insufficient information ($n=6$) [10, 44–48], ineligible exposure factors ($n=14$) [43, 49–61], ineligible comparison ($n=1$) [62], and inaccessible full texts ($n=5$) [63–67]. Consequently, 18 articles were initially included. Additional searches of reference lists yielded 3 more articles [12, 68, 69]. Ultimately, 21 articles were included [11–14, 17–20, 41, 42, 68–78]. Details of the search and selection process are shown in the PRISMA flow diagram (Fig. 1).

Study Characteristics

As shown in Table 1, twenty-one included studies were observational studies, including 13 cohort studies, 7 cross-sectional studies, and 1 case-control study. These studies, published between 2001 and 2024, originated in North America ($n=9$), Europe ($n=7$), the Middle East ($n=3$), and Asia ($n=2$). A total of 17,623 patients were included, with mean ages ranging from 27 to 51 years. Most studies

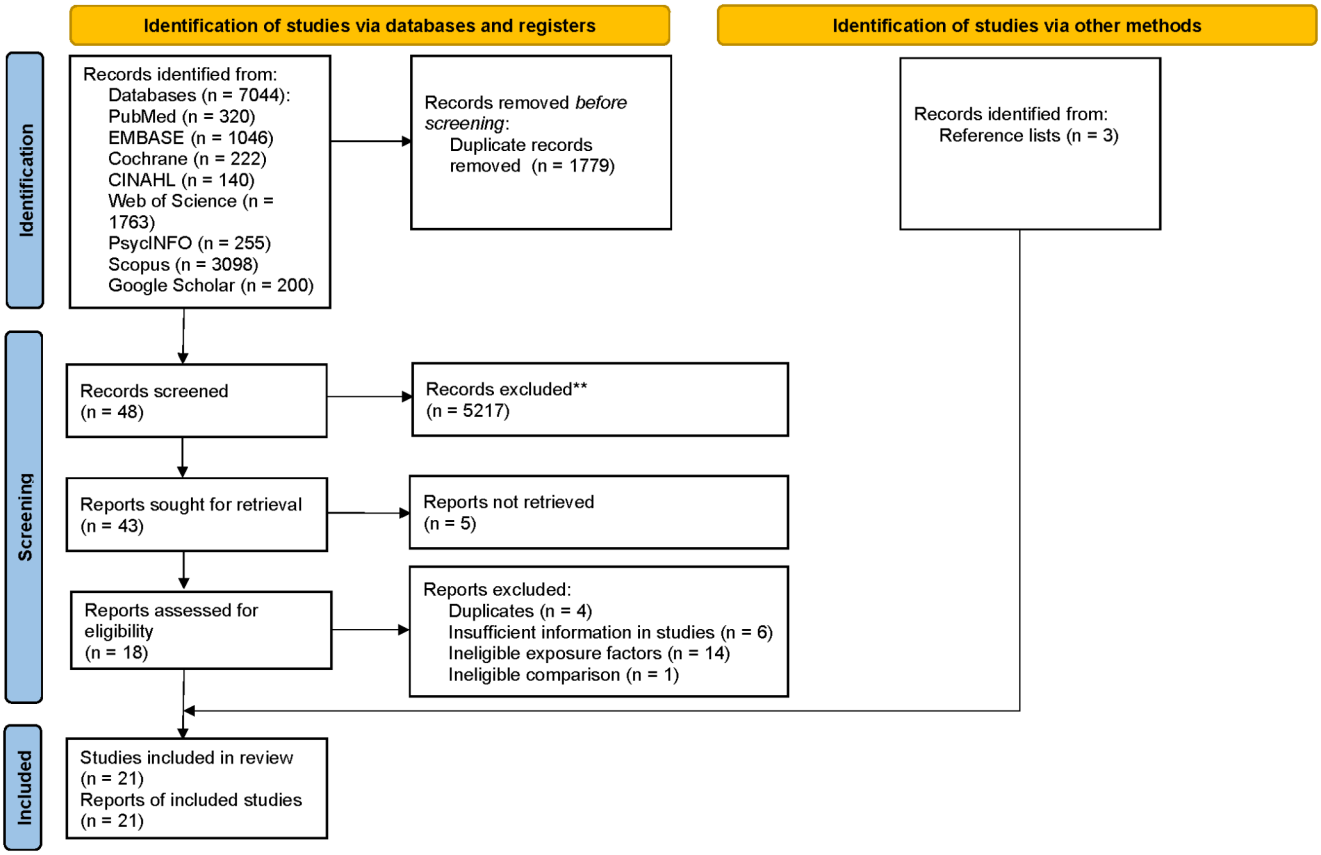

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

included both male and female patients, except for one that only included postpartum females.

Risk of Bias in Studies

All 13 included cohort studies had NOS scores above 3, suggesting moderate to high quality. In the selection domain, all studies included patients with a medical history or incident relevant to the outcomes at study initiation. In the comparability domain, 53.85% of the studies had limitations in controlling confounders. In the outcome domain, 3 out of 13 studies had follow-up rates below 80% and did not document those lost to follow-up.

Only one case-control study was included, which had an NOS score of 8, suggesting high quality. This study had no issues in the selection and comparability domains but lost 1 point in the exposure domain due to missing information on non-response rates for both the case and control groups.

The total AHRQ scores for the 7 included cross-sectional studies ranged from 4 to 9, suggesting moderate to high quality. These studies mainly had issues with subject selection, evaluator blinding, and follow-up completeness. Specifically, in subject selection, 57.14% of the studies either did not use consecutive or population-based sampling or did not mention this detail. None of the studies reported on evaluator blinding or follow-up completeness.

The detailed results of the risk of bias assessment are summarized in Online Resource 2.

The Association Between Co-Occurring Psychotic Disorders and Treatment Retention

Eight cohort studies with a total sample size of 11,232 were included in the meta-analysis evaluating treatment retention. The Q-test and I^2 index suggested moderate and non-significant heterogeneity ($I^2 = 47\%$; $P_{heterogeneity} = 0.07$), so a fixed-effect model was used for synthesis. The pooled OR for treatment retention was 0.65 (95% CI: 0.57–0.74; $P < 0.05$), suggesting significantly poorer OAT retention among patients with OUD and psychotic disorders compared to those with OUD without psychotic disorders (see Fig. 2). The sensitivity analysis suggested pooled OR values ranging from 0.59 (95% CI: 0.41–0.84) to 0.66 (95% CI: 0.58–0.75), confirming the robustness of the overall result. The funnel plot did not suggest significant asymmetry, suggesting no major publication bias (see Fig. 3). Additionally, Begg's test ($P = 0.71$) and Egger's test ($P = 0.63$) confirmed the absence of significant publication bias.

Table 1 Characteristics of included studies

Study	Sample size(*n*)	Age (years), mean (SD)	Male (%)	Country	Psychiatric Comorbidity Diagnosis	OUD Diagnosis	Study Design	Exposed Group	Unexposed Controls	OAT Type	Outcome
Lamont et al., 2020 [17]	415	NA	44.58	Canada	MINI	DSM-IV	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD and non-psychotic psychiatric disorders	MMT	1. Illicit drug use (opioids, amphetamines, cannabis, and cocaine) 2. Treatment retention
Gerra et al., 2006 [18]	206	32.2 (8.9)	85.92	Italy	DSM-IV	DSM - IV	Cohort study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	BT	1. Illicit drug use (opioids) 2. Treatment retention
Volkov et al., 2022 [78]	877	39.55 (9.83)	74.57	Israel	DSM-IV-TR	DSM-IV-TR	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	1. Illicit drug use (opioids, amphetamines, cannabis, and cocaine) 2. Treatment retention 3. Survival
Rosic et al., 2017 [14]	652	38.93 (11.06)	54.14	Canada	MINI	DSM-IV	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Illicit drug use (opioids)
Miranda et al., 2001 [41]	132	27.9	88,6	Spain	GADS, IPDE	NA	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Illicit drug use (opioids and cocaine)
Maremmani et al., 2018 [42]	85	30.24 (6.34)	71.76	Italy	DSM-IV	DSM-IV	Cohort study	Patients with HUD and psychotic disorders	Patients with HUD without dual disorder	MMT	Treatment retention
Pant et al., 2022 [13]	231	33.8 (7.3)	92.20	Nepal	M.I.N.I.	NA	Cross-sectional study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	OAT	1. Suicidality 2. Depression
Maqoud et al., 2022 [75]	18	48.44 (9.41)	77.78	Italy	NA	NA	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	OAT	1. Illicit drug use (cannabis and cocaine) 2. Cardiovascular safety
Elkana et al., 2019 [71]	65	50.7 (9.9)	72.30	Israel	DSM-IV-TR	DSM-IV-TR	Cross-sectional study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	MMT	Illicit drug use (polydrug)
Bouton et al., 2017 [20]	62	45.15 (8.40)	77.42	France	DSM-5	DSM-5	Cross-sectional study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	OAT	Illicit drug use (opioids and polydrug)
Carpentier et al., 2009 [11]	193	40.3 (7.2)	83.40	Netherlands	MINI, SIDP-IV	NA	Cross-sectional study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Quality of life
Astals, 2008 [12]	175	32.66	75.43	Spain	DSM-IV	DSM-IV	Cross-sectional study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Quality of life
Litz et al., 2017 [74]	2,947	32.6 (11)	67.10	America	ICD-9	ICD-9	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD and non-psychotic psychiatric disorders	BT	Adherence
Gertner et al., 2022 [72]	7,956	35 (9.81)	25.74	America	ICD	ICD	cohort study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	BT	Treatment retention
Shadowen et al., 2022 [77]	138	28.9 (4.8)	0.00	America	NA	NA	Cohort study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	BT	Treatment retention

Table 1 (continued)

Study	Sample size(*n*)	Age (years), mean (SD)	Male (%)	Country	Psychiatric Comorbidity Diagnosis	OUD Diagnosis	Study Design	Exposed Group	Unexposed Controls	OAT Type	Outcome
Montalvo et al., 2019 [69]	321	38 (10)	62.00	America	NA	NA	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	BT	Treatment retention
Hui et al., 2017 [68]	1,234	38 (11)	62.10	America	NA	NA	Cohort study	Patients with OUD and schizophrenia	Patients with OUD without psychotic disorders	BT	Treatment retention
Shams et al., 2019 [19]	672	38.76 (11.10)	54.20	Canada	M.I.N.I., DSM-IV	DSM-IV	Cross-sectional study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Illicit drug use (cannabis)
Peles et al., 2007 [76]	90	41.6 (8.5)	55.60	Israel	DSM - IV	DSM-IV	Cross-sectional study	Patients with OUD and schizophrenia or paranoid disorders	Patients with OUD without psychotic disorders	MMT	Depression
Leece et al., 2015 [73]	1,048	38.94 (10.26)	62.21	Canada	NA	NA	Nested case-control study	Patients with OUD and psychotic disorders	Patients with OUD without psychotic disorders	MMT	Opioid-related deaths
Das et al., 2024 [70]	106	28.52 (4.57)	94.34	India	DSM-IV-TR	DSM-IV-TR	Cohort study	Patients with OUD and psychotic disorders	Patients with OUD and non-psychotic psychiatric disorders	BNMT	Compliance

Abbreviations: NA, not applicable; OUD, opioid use disorder; HUD, heroin use disorder; MMT, methadone maintenance treatment; BT, buprenorphine treatment; OAT, opioid agonist therapy; BNMT, buprenorphine-naloxone combination maintenance therapy; MINI, Mini-International Neuropsychiatric Interview; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; GADS, Goldberg Anxiety and Depression Scale; IPDE, International Personality Disorder Examination; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SIDP-IV, Structured Interview for DSM-IV Personality Disorders; ICD, International Classification of Diseases

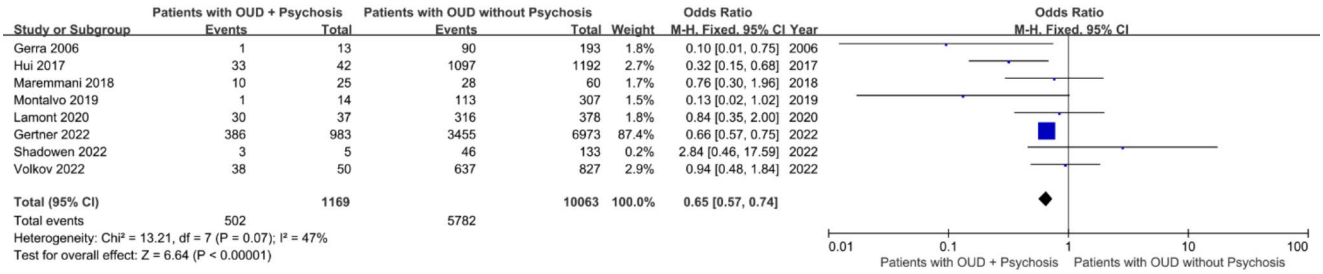

Fig. 2 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: treatment retention. OUD = opioid use disorder

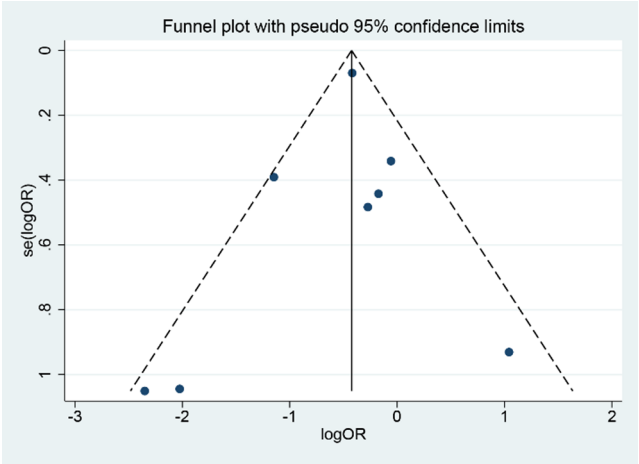

Fig. 3 Funnel plot for assessing publication bias in studies on opioid agonist therapy retention. OR = odds ratio, SE = standard error

We conducted a subgroup analysis based on study period to explore heterogeneity. The analysis revealed a significant subgroup effect ($I^2 = 84.5\%$; $p = 0.01$), suggesting that study period statistically significantly changes the OAT effects in patients with OUD and psychotic disorders in comparison to those with OUD without psychotic disorders (see Fig. 4). Treatment retention was better in patients with OUD without psychotic disorders compared to patients with OUD and psychotic disorders both before and after 2017. However, the pooled OR was higher for studies published in 2017 and after (OR = 0.68; 95% CI: 0.59–0.77; $P < 0.05$) compared to those before 2017 (OR = 0.33; 95% CI: 0.19–0.56; $P < 0.05$). Therefore, the subgroup effect was quantitative. There was higher heterogeneity within the "before 2017" subgroup (42%) than the "2017 and after" subgroup (19%). However, the heterogeneity was lower within the subgroups than overall (47%), suggesting that the subgroup analysis interpreted the heterogeneity. With only eight studies in the meta-analysis and an uneven number of patients between the "before 2017" subgroup (1,846 patients) and the "2017 and after" subgroup (9,386 patients), further investigation is needed to confirm the reliability of these subgroup effects.

The Association Between Co-Occurring Psychotic Disorders and Illicit Drug Use

Opioid Use

Illicit opioid use was reported in six studies. Two of these studies, involving 746 participants, could not be synthesized due to differences in reporting formats and did not find a

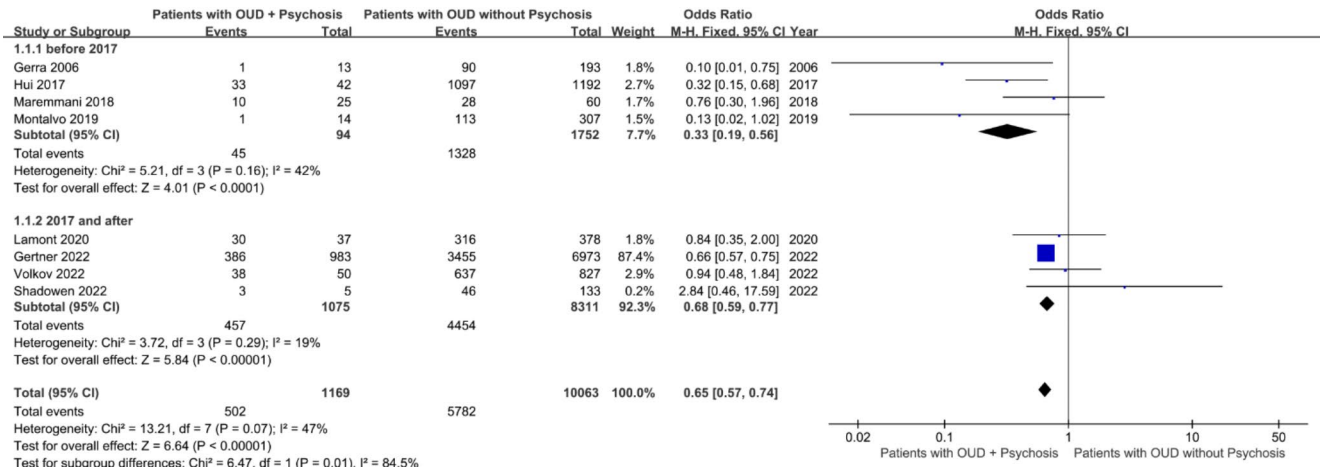

Fig. 4 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: treatment retention, subgroup: study period. OUD = opioid use disorder

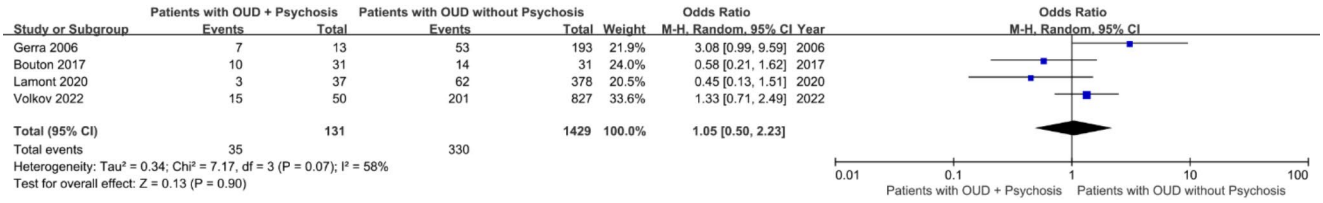

Fig. 5 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: illicit opioid use. OUD = opioid use disorder

Fig. 6 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: amphetamine use. OUD = opioid use disorder

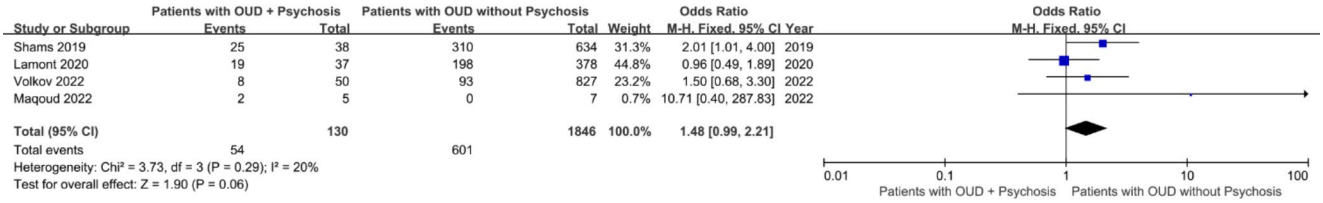

Fig. 7 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: cannabis use. OUD = opioid use disorder

significant association between co-occurring psychotic disorders and illicit opioid use among patients with OUD receiving OAT (Rosic et al.: estimated β: -4.31; 95% CI: -16.48, 7.87; $P = 0.49$).

Four studies, encompassing 1,560 participants, were included in the meta-analysis. Given the substantial heterogeneity ($I^2 = 58\%$; $P_{heterogeneity} = 0.07$), a random-effects model was used. The analysis suggested no significant association between co-occurring psychotic disorders and illicit opioid use among patients with OUD receiving OAT (OR = 1.05; 95% CI: 0.50–2.23; $P = 0.90$) (see Fig. 5). The sensitivity analysis confirmed stability, with pooled OR values ranging from 0.81 (95% CI: 0.40, 1.65) to 1.30 (95% CI: 0.59, 2.90). Removing the study by Gerra et al. reduced the I^2 index from 58 to 43%, potentially due to its early publication year and high male proportion. Subgroup analysis and publication bias assessment were not conducted due to the small number of studies.

Amphetamine Use

Two prospective cohort studies with 1,292 patients investigated amphetamine use in patients with OUD receiving OAT. Given the low heterogeneity ($I^2 = 33\%$; $P_{heterogeneity} = 0.22$), a fixed-effect model was applied, suggesting no significant relationship between co-occurring psychotic disorders and amphetamine use (RR = 1.09; 95% CI: 0.45–2.67; $P = 0.84$) (see Fig. 6). The sensitivity analysis suggested that the RR value ranged from 0.46 (95% CI: 0.06–3.28) to 1.70 (95% CI: 0.62, 4.64), confirming the pooled result's reliability.

Cannabis Use

Four studies examined cannabis use among 1,976 patients with OUD receiving OAT. The fixed-effects meta-analysis suggested a pooled OR of 1.48 (95% CI: 0.99–2.21; $P = 0.06$), suggesting no clear evidence of a significant link between co-occurring psychotic disorders and cannabis use (see Fig. 7). Heterogeneity was low ($I^2 = 20\%$; $P_{heterogeneity} = 0.29$). The sensitivity analysis suggested that excluding the study by Lamont et al. increased the OR from 1.48 (95% CI: 0.99–2.21) to 1.90 (95% CI: 1.15–3.14), highlighting the study's substantial impact on the results. Consequently, the findings on cannabis use are not robust due to the small number of studies and should be interpreted with caution until more evidence is available.

Cocaine Use

Four studies compared cocaine use between patients with OUD and psychotic disorders and those with OUD without psychotic disorders undergoing OAT. One study with 94

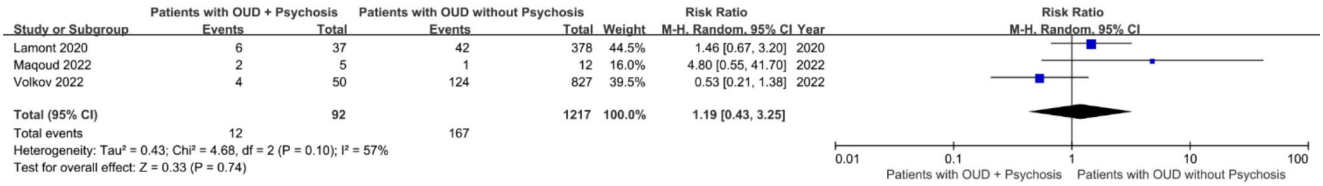

Fig. 8 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: cocaine use. OUD = opioid use disorder

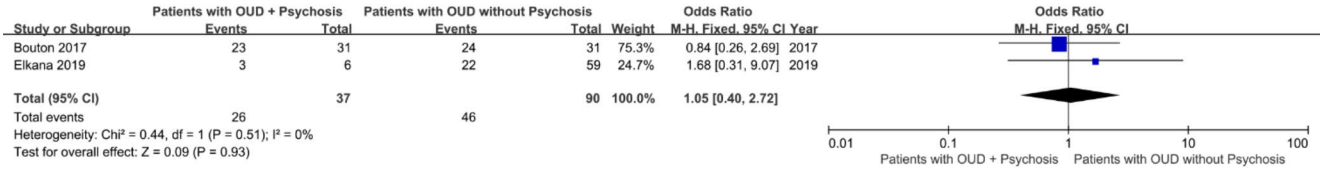

Fig. 9 Forest plot of comparison: patients with psychotic versus patients with non-psychotic OUD receiving opioid agonist therapy, outcome: polydrug use. OUD = opioid use disorder

participants reported cocaine use differently from the others and found no significant association with co-occurring psychotic disorders.

Three studies, encompassing 1,309 participants, were included in the meta-analysis. Due to substantial heterogeneity ($I^2 = 57\%$; $P_{heterogeneity} = 0.10$), a random-effects model was utilized. Results suggested that co-occurring psychotic disorders were not significantly associated with cocaine use (RR = 1.19; 95% CI: 0.43–3.25; $P = 0.74$) (see Fig. 8). The sensitivity analysis suggested the result was robust, with RR values ranging from 0.91 (95% CI: 0.33–2.53) to 1.70 (95% CI: 0.78–3.71). Excluding the study by Volkov et al. reduced the I^2 from 57 to 3%, suggesting that the large sample size and long follow-up duration in that study may have contributed to the heterogeneity.

Polydrug Use

Two studies investigated polydrug use among 127 patients with OUD undergoing OAT. With no detected heterogeneity ($I^2 = 0\%$; $P_{heterogeneity} = 0.51$), a fixed-effect model was used. The results did not suggest a significant association between co-occurring psychotic disorders and polydrug use (OR = 1.05; 95% CI: 0.40–2.72; $P = 0.93$) (see Fig. 9). The sensitivity analysis suggested that the pooled OR ranged from 0.84 (95% CI: 0.26–2.69) to 1.68 (95% CI: 0.31–9.07), suggesting that the result was steady.

The Association Between Co-Occurring Psychotic Disorders and Outcomes of Limited Importance

Depression

Two cross-sectional studies investigated depression among 305 patients with OUD receiving OAT. Depression was measured using the Mini International Neuropsychiatric Interview (M.I.N.I.) in the study by Pant et al. and the 21-item Hamilton Rating Scale for Depression (21-HAM-D) in the study by Peles et al., respectively. Due to differences in definitions and data formats, the results were summarized qualitatively. Both the study by Pant et al. (adjusted OR = 0.95, 95% CI: 0.25–3.56) and Peles et al. (WMD = 2.32; 95% CI:-4.60, 9.24; $P = 0.51$) suggested there was no significant association between psychotic disorders and depression.

Death

Three studies with 2,156 participants compared death or survival outcomes between patients with OUD and psychotic disorders and those with OUD without psychotic disorders receiving OAT, each using different definitions. Due to these differences, a narrative synthesis was used. Volkov et al. found significantly poorer survival among patients with OUD and psychotic disorders (WMD = -2.40, 95% CI: -4.63, -0.17; $P = 0.04$). Similarly, Pant et al. reported significantly higher lifetime suicidality in patients with OUD and psychotic disorders (adjusted OR = 5.94; 95% CI = 1.66–21.34; $p = 0.01$). However, Leece et al. found no significant association between co-occurring psychotic disorders and opioid-related deaths (adjusted OR = 0.21; 95% CI: 0.02–2.02).

Quality of Life

Two cross-sectional studies conducted in Europe reported quality of life using different tools: Carpentier et al. employed the EuroQol-5D (EQ-5D), while Astals et al. used the 12-item Short-Form (SF-12). Due to the small number of studies and high heterogeneity among them ($I^2 = 80\%$; $P = 0.03$), a meta-analysis was not feasible. Therefore, we

conducted a narrative synthesis of the two studies involving 368 patients with OUD receiving OAT. Carpentier et al. found significantly poorer quality of life among patients with OUD and psychotic disorders compared to those with OUD without psychotic disorders (WMD = -0.27; 95% CI: -0.45, -0.09; $P=0.003$). However, Astals et al. found that co-occurring psychotic disorders were not significantly related to quality of life (WMD=2.75; 95% CI: -6.20, 11.70; $P=0.55$).

Adherence or Compliance

Two cohort studies with 3,053 participants assessed adherence or compliance with OAT among patients with OUD. A narrative synthesis of the studies was conducted due to varying definitions. Litz et al. found no clear evidence of a significant difference between patients with psychotic disorders and those with other psychiatric disorders, including major depressive disorder/bipolar disorder (MDDBP) (unadjusted OR=0.93; 95% CI: 0.54–1.62; $P=0.81$), anxiety disorders (unadjusted OR=0.82; 95% CI: 0.48–1.41; $P=0.47$), or personality disorders (unadjusted OR=1.19; 95% CI=0.31–4.58; $P=0.80$) in terms of adherence. However, Das et al.'s study suggested that patients with psychotic disorders had significantly poorer compliance than those with mood and anxiety disorders but better compliance than those without Axis I disorders.

Cardiovascular Safety

A cohort study conducted in Italy examined cardiovascular safety in 18 patients with OUD undergoing OAT using an electrocardiogram. The study suggested that no significant link between co-occurring psychotic disorders and the QT interval corrected by the Fridericia formula (QTcF) (WMD=15.15; 95% CI: -35.04, 65.34; $P=0.55$).

Discussion

To the best of our knowledge, our systematic review and meta-analysis is the first to synthesize the association between co-occurring psychotic disorders and outcomes among patients with OUD undergoing OAT. Analyzing data from 21 studies involving 17,623 participants, we found that patients with OUD and psychotic disorders had significantly poorer OAT retention compared to those with OUD without psychotic disorders. However, co-occurring psychotic disorders were not significantly associated with illicit opioid use, amphetamine use, cannabis use, cocaine use, polydrug use, and depression among patients with OUD undergoing OAT. The findings related to cannabis use were inconclusive due to a limited number of studies. Narrative synthesis was required for outcomes such as depression, death, quality of life, and adherence or compliance due to inconsistent definitions and data formats, while cardiovascular safety could not be synthesized as it was reported in only one study.

Poorer retention among patients with OUD and co-occurring psychotic disorders receiving OAT may be due to illicit benzodiazepine use, worse cognitive performance, and challenges with family relationships and employment. First, patients with OUD and psychotic disorders have a significantly higher prevalence of illicit benzodiazepine use compared to those with OUD without psychotic disorders [78], which is associated with poorer retention [14, 69, 78, 79]. Second, they exhibit significantly worse cognitive performance compared to patients with OUD without psychotic disorders [71], affecting their eligibility for take-home doses, which require a certain level of cognitive function and are associated with higher retention [80–82]. Third, family relationships and employment are significant predictors of OAT retention [83, 84]. However, patients with OUD and psychotic disorders are about three times more likely to live alone and have significantly worse employment status compared to patients with OUD without psychotic disorders [48, 78].

Individuals with comorbid substance use disorders and psychotic disorders often face challenges related to low motivation for change, such as diminished self-esteem, reduced tolerance for frustration, and impaired social skills, all of which can hinder treatment progress [15]. However, our findings did not provide significant evidence to suggest that co-occurring psychotic disorders were associated with illicit drug use (including opioids, amphetamines, cannabis, cocaine, and polydrug use) or depression among patients with OUD receiving OAT. This result contrasts with previous research, which has shown an association between substance use and psychotic disorders. For example, Myran et al., Schoeler et al., and Gowin et al. have highlighted growing concerns about the increasing prevalence of cannabis use, as it can elevate the incidence of psychotic disorders and cause cognitive problems [85–87]. One potential explanation for the discrepancy in findings is the common use of combination medications in OAT, such as antipsychotics and opioid agonists. Opioid agonists like methadone and buprenorphine not only possess anti-craving [42] and antidepressant [18, 69, 88] properties but also exhibit antipsychotic effects [42, 89, 90], which may mitigate the association between psychotic disorders and both illicit drug use and depression. Recently, two systematic reviews have suggested that genotypes involved in dopamine function can moderate the relationship between cannabis use and the risk of psychosis [91, 92]. Cannabis and stimulant use (e.g., cocaine and amphetamines) are known to exacerbate psychotic symptoms by

elevating synaptic dopamine concentrations, which is associated with positive psychotic symptoms [93–95]. However, the synaptic action of dopamine can be disrupted by opioid agonists with antidopaminergic activity, which affect opioid receptors in the brain and regulate dopamine transmission and release [96, 97].

Our subgroup analysis suggested that study period could account for the heterogeneity in OAT retention studies. More recent studies may reflect the impact of advancements in OAT policies and care models. Increased incidence and risk of OUD-related diseases have prompted governments to remove unnecessary regulations and innovate OAT care models to improve accessibility [98]. Since 2016, the U.S. and Canadian governments have expanded access to OAT by issuing more methadone and buprenorphine waivers, funding OAT services, and including OAT in healthcare insurance [98, 99]. Similar actions to reduce restrictions and improve access to OAT also occurred in other countries, such as Austria, Germany, and Switzerland [100]. The COVID-19 pandemic in 2020 further accelerated the adoption of supportive OAT policies and patient-centered care models globally [101, 102]. Supportive policies and care models, which offer easier, more efficient, and affordable access to OAT, have proven more effective for OAT entry and retention than punitive approaches [80, 103].

This systematic review comprehensively assessed the association between co-occurring psychotic disorders and OAT outcomes among patients with OUD. It suggested that co-occurring psychotic disorders were not significantly associated with illicit drug use among patients with OUD receiving OAT, so researchers should consider including individuals with co-occurring psychotic disorders in relevant experimental studies. Additionally, poorer retention in patients with co-occurring psychotic disorders reminded healthcare providers to offer special care to improve retention, such as family and employment support. Moreover, patients with dual diagnoses also need careful management for safety [104]. These patients often require higher doses of opioid agonist medications and are more likely to be prescribed multiple psychotropic medications, including antipsychotics and benzodiazepines [17]. Therefore, healthcare providers must carefully monitor for potential safety risks and ensure that prescriptions are appropriate and safely managed.

However, our review has several limitations. First, despite including all available observational studies, the smaller-than-expected number limited our ability to conduct subgroup analyses, meta-regression, and publication bias tests. Second, patients with concurrent psychotic disorders are often excluded from experimental studies evaluating the effectiveness of OAT among patients with OUD. As a result, the included studies were observational, with inherent limitations in evidence quality. Additionally, unadjusted data were used due to constraints in the available data. Third, the population of patients agreeing to participate in the original studies of OAT may have less severe comorbidities compared to the general population of individuals with OUD and co-occurring psychotic disorders. Lastly, most studies included were from developed countries in North America and Europe, with few studies from developed countries in the Middle East and developing countries in Asia, restricting the generalizability of our findings.

Conclusion

This study provides evidence that co-occurring psychotic disorders are negatively associated with OAT retention, suggesting poorer retention among patients with OUD and psychotic disorders compared to those with OUD without psychotic disorders. The study also provides evidence regarding illicit drug use, including opioids, amphetamines, cannabis, cocaine, and polydrug use, suggesting no significant association between co-occurring psychotic disorders and illicit drug use.

In the future, researchers should consider including participants with OUD and psychotic disorders in experimental studies investigating the effectiveness of OAT. In future studies, the effects of antipsychotic treatment on the outcomes of OAT should also be thoroughly examined. Additionally, there is a pressing need for high-quality original studies conducted outside of Europe and North America, especially in developing countries, to improve the generalizability of existing findings and strengthen the evidence base. Moreover, healthcare providers should consider offering additional care, such as employment and family support, to patients with OUD and psychotic disorders to help them remain in OAT.

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Declarations

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