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Efficacy of medications for the treatment of alcohol use disorder (AUD): A systematic review and meta-analysis considering baseline AUD severity

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ABSTRACT

Baseline severity of alcohol use disorder (AUD) is an influencing factor in the response to medications recommended for the treatment of AUD. The scarce efficacy of AUD medications partly justifies their limited uses. We were interested in evaluating the efficacy of approved and recommended AUD medications using generic inverse-variance, an analysis facilitating comparison between medications and placebo both at the end of the study and, concomitantly, to baseline values for the same participants. We conducted a systematic review to include randomized controlled trials (RCTs) comparing any medication to placebo providing, both at baseline and end of treatment, percent heavy drinking days (%HDD), percent drinking days (%DD), and/or drinks per drinking day (DDD). We searched PubMed, Embase, PMC, and three CT registers from inception to April 2023. A total of 79 RCTs (11,737 AUD participants; 30 different medications) were included: 47 RCTs (8465 participants) used AUD medications, and 32 RCTs (3272 participants) used other medications. At baseline, participants consumed on average approximately 12 DDD, and experienced 70 % DD, and 61 % HDD. Placebo halved or reduced these values to a third. Compared to placebo, AUD medications further reduced these outcomes (moderate to high certainty evidence). Other medications reduced the DDD without modifying other alcohol outcomes. AUD medications increased the risk of developing adverse events (high-certainty evidence). Despite the large placebo effects, our results support the benefits of providing AUD medications to people with AUD, helping them reduce alcohol consumption.

1. Introduction

Alcohol use is a major cause of death and disability [1–3]. The annual economic burden caused by the harmful consequences of alcohol is in the region of one trillion USD globally according to reported percentages of gross domestic production [4,5] and is expected to increase further [6]. Harmful consequences of excessive alcohol use were further manifested by increased mortality during the COVID-19 pandemic [7].

Alcohol use disorder (AUD) is a severe and widespread mental disorder characterized by an inability to control alcohol consumption, with frequent episodes of uncontrolled alcohol intake [8,9]. The natural course of AUD is characterized by spontaneous phases of remission and relapse [10], with many people with AUD improving without any medical intervention over sustained periods [11,12]. Critically, this disorder is associated with a high risk of developing a series of life-threatening diseases, including liver disease, cancers, hypertension,

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injuries, and death [1–3,13–18]. Medical treatment of AUD is aimed at helping people affected by AUD achieve and maintain abstinence, or at least reduce alcohol consumption and consequent harm [14,16,19]. It has been estimated that people with AUD feature a three to four-fold higher risk of mortality compared to people without AUD [20], with this risk being halved in AUD-affected subjects who receive medical treatments and reduce alcohol consumption compared to those who continue heavy use of alcohol [21].

Despite the high prevalence of the disorder and enormous consequences produced, AUD is one of the most frequently undiagnosed and untreated mental disorders [14,16]. A recent systematic review has estimated that globally only one in six people with AUD receives medical treatment [22]. The reasons underlying this low treatment rate include fear of stigmatization by affected subjects [23], inadequate education and training of physicians and health-care workers [24,25], and insufficient AUD screening in primary health care [14]. In addition, some characteristic features of the medical treatment involved contribute to its scarce use [14,16,19].

The more frequently used psychosocial interventions in AUD treatment comprise cognitive-behavioral therapies, motivational interviewing, and 12-step facilitation [26–28]. Other approaches developed in recent years include acceptance and commitment therapy [29] and mindfulness-based relapse prevention [30]. Despite evidence of the efficacy of psychosocial interventions [31], many health-care workers, particularly primary care physicians, are not familiar with psychosocial administration [14].

Pharmacological interventions comprise both approved and recommended medications for AUD treatment [14,16,19,32]. To date, disulfiram, naltrexone and acamprosate have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), nalmefene by the EMA, and baclofen by the French Medicines Agency [16,19,33–36]. Other medications, recommended for off-label uses, include gabapentin, topiramate, and varenicline [16,19]. Regrettably, despite meta-analytic evidence of their efficacies (disulfiram [37]; naltrexone and acamprosate [37]; nalmefene [38]; baclofen [39]; gabapentin [40]; topiramate [41]; varenicline [42]) on a global level, AUD medications are rarely used. A national survey conducted in the USA found that less than 2 % of people with AUD received approved AUD medications [43], with similar rates estimated in Canada (less than 0.4 % [44]) and Australia (less than 3 % [45]). In addition to the inadequate education and training of physicians, other reasons for the scarce use of AUD medications may lie in specific characteristics of these drugs [14,16]. As an example, some AUD medications are contraindicated in people with severe liver disease (e.g., naltrexone and disulfiram), kidney impairment (e.g., acamprosate), or cognitive impairment (e.g., disulfiram), or may be characterized by low adherence to treatment requiring the collaboration of a family member (e.g., oral naltrexone and disulfiram) [16,19]. In addition, some people with AUD may not obtain a satisfactory response to AUD treatments due to genetic factors [46] or in light of the limited evidence of the efficacy and safety of AUD medications in women [47,48]. These factors may complicate the use of AUD medications and contribute to their limited use.

People affected by mental disorders, including those with AUD [49], display strong responses to placebo [50]. Studies aimed at evaluating the efficacy and safety of medications used in the treatment of the above patients compare the results obtained at the end of treatment by participants who receive an experimental medication to those reported by participants who receive placebo [51]. Interestingly, the placebo response is influenced by a series of factors, including severity of the mental disorder at baseline [50,52]. Weimer and colleagues [50] analyzed 31 meta-analyses and systematic reviews of more than 500 randomized placebo-controlled trials (RCTs) and found that people affected by different mental disorders (e.g., depression, schizophrenia, including addiction) displayed higher responses to placebo when severity of symptoms at baseline was low. A recent systematic review confirmed this finding among people with AUD [52], investigating placebo response in a sample of 19 RCTs, comprising almost 20,000 participants with AUD divided into high or moderate severity groups according to alcohol consumption at baseline. The results showed that placebo response was higher among RCTs indicating a moderate severity of AUD at baseline than those reporting a high severity of AUD [52]. AUD severity at baseline also influences response to pharmacological treatments. For instance, response to varenicline was higher in people with less-severe AUD compared to those affected by more severe AUD [53], using alcohol use at baseline as measure of AUD severity [54]. Other factors capable of influencing response to AUD medications include genetic factors [46] and comorbid mental disorders [55].

We were interested in evaluating the efficacy and safety of AUD medications whilst excluding at least one potential influencing factor, namely AUD severity at baseline. To achieve this aim, we used the generic inverse-variance, an analysis that allowed comparison of medications and placebo at the end of the study and, concurrently, between baseline values of the same participants. We hypothesized that using this approach, medications approved and recommended for use in the treatment of AUD might be effective in reducing alcohol consumption despite the yielding of ineffective results by other medications.

2. Methods

This systematic review and meta-analysis was conducted according to the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions and by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 [56]. The study was registered in PROSPERO [57].

2.1. Search strategy and selection criteria

Our systematic review and meta-analysis adhered strictly to the PRISMA guidelines, with a search of PubMed, Embase, PMC, and three CT registers of USA (ClinicalTrials.gov), EU and WHO conducted between the start of the period through April 21, 2023; a total of 15,014 records were retrieved (see Supplemental content for the search strategy).

We searched RCTs that compared the efficacy of any medication to placebo in AUD treatment and provided both baseline and end of treatment information on at least one of the following three primary alcohol consumption measures: (1) percent heavy drinking days (% HDD), (2) percent drinking days (%DD), and (3) drinks per drinking day (DDD). In the protocol, outcome measures of alcohol consumption comprised the %HDD, DDD, and % of abstinent participants [57]. Before starting screening, the latter outcome measure was excluded as we realized that the rate of abstinent participants at baseline depended on inclusion criteria adopted by the studies (i.e. whether participants were required to be abstinent or not at baseline). Accordingly, this outcome was substituted by %DD. These outcomes, among the most frequently used by clinical trials on AUD [58], utilize a “standard drink” as a unit of measure of alcohol consumption. The content of a standard drink in grams of pure alcohol varies considerably between countries, ranging from 8 to 20 g [16,59,60]. In the present study, we reported the unmodified alcohol outcomes provided in the primary studies by adding the content in grams per standard drink in Table 1.

With regard to safety, the following secondary outcomes were selected: (1) number of dropouts, (2) number of participants who developed at least one adverse event, and (3) number of participants who developed at least one serious adverse event to evaluate potential differences between medication and control groups at the end of treatment.

Inclusion criteria were: AUD participants aged 18 years or older; RCTs comparing any medication to placebo; studies providing both baseline and end of treatment information of at least one of the three primary alcohol consumption measures; studies with at least 10 participants in both medication and placebo groups; and studies of at least

Table 1
List of the included studies divided according to the medications used.

	Study by first author and year	Sample size (drug/ placebo)	Country	Average age	Gender %male	Race % white	Comorbidity	Dose (mg)	Route	Duration (week)	% HDD	DDD	% DD	Standard drink content
Medications approved or reccomded for the tretment of alcohol use disorder														
Acamprosate	Anton 2006 [66] arm 2	229 (151/78)	US	44.3	70.7	73.95	No	3000	os	16			X	14 g
	Anton 2006 [66] arm 4	228 (152/76)	US	44.1	68.2	79.35	No	3000	os	16			X	14 g
	Morley 2006 [111] arm 2	86 (55/31)	Australia	43.8	70.2	NA	No	1998	os	12		X		10 g
	Namkoong 2003 [116]	142 (72/72)	S. Korea	44.3	95.8	0 (95.8 % Koreans)	No	1332/ 1998	os	8	X	X	X	NA
	Ralevski 2011 [129]	23 (12/11)	US	50.73	82.6	34.8	Yes (Schizophrenia 39.1 %; schizoaffective: 43.5 %; cocaine and cannabis dependence: 26.1 %	1998	os	12	X	X	X	14 g
	Tolliver 2012 [137]	33 (16/17)	US	42.25	63.9	86.2	Bipolar disorder	1998	os	14	X		X	14 g
Disulfiram	Petrakis 2005 [122] arm 2	98 (66/32)	US	46	98.5	79.3	Different disorders	250	os	12	X		X	14 g
Nalmefene	Gual 2013 [85]	718 (358/ 360)	Spain	44.75	72.7	98.9	No	18	os	24	X		X	10–16 g
	Mann 2013 [105]	604 (306/ 298)	Europe	51.6	67.3	99.9	No	18	os	24	X			10–14 g
	Mason 1999 [106]	105 (70/35)	US	41.8	65.8	82.15	No	20–80	os	12		X	X	14 g
	Miyata 2019 [109] arm 1	306 (184/ 122)	Japan	48.7	68.8	100 Japanese	No	10	os	24	X			10 g
	Miyata 2019 [109] arm 2	371 (248/ 123)	Japan	48.5	66.7	100 Japanese	No	20	os	24	X			10 g
Naltrexone	Anton 1999 [64]	131 (68/63)	US	42.5	71	85.5	No	50	os	12		X	X	14 g
	Anton 2005 [65] arm 1	80 (39/41)	US	44.5	76	83.5	No	50	os	12		X	X	14 g
	Anton 2005 [65] arm 2	80 (41/39)	US	43	75	85	No	50	os	12		X	X	14 g
	Anton 2006 [66] arm 1	233 (155/78)	US	44.2	69.4	76.25	No	100	os	16			X	14 g
	Anton 2006 [66] arm 3	231 (154/77)	US	44.3	67.8	74.25	No	100	os	16			X	14 g
	Balldin 2003 [70] arm 1	55 (25/30)	Sweden	50	80.5	NA	No	50	os	24	X	X	X	12 g
	Balldin 2003 [70] arm 1	63 (31/32)	Sweden	49.5	89	NA	No	50	os	24	X	X	X	12 g
	Collins 2021 [73]	152 (74/78)	US	47.9	86	29	Not detailed	380	im	12			X	14 g
	Foa 2013 [80] arm 1	80 (40/40)	US	42.4	67.5	21.25 (Black = 72.5 %)	PTSD	100	os	24			X	14 g
	Foa 2013 [80] arm 2	85 (42/43)	US	43.1	63.5	21.25 (Black = 72.5 %)	PTSD	100	os	24			X	14 g
	Guardia 2002 [86]	192 (93/99)	Spain	41.5	74.5	NA	No	50	os	12		X		10 g
	Hersh 1998 [91]	64 (31/33)	US	35.5	92.2	76.6	Cocaine dependence	50	os	8		X	X	14 g
	Killeen 2004 [95]	97 (54/43)	US	36.7	57	78.5	35 % Polysubstance	50	os	12	X	X	X	14 g
	Kranzler 2000 [98] arm 1	93 (61/32)	US	40.7	77.5	93.6	12 % Dysthymic; 5.5 % depression	50	os	12	X	X	X	14 g
	Kranzler 2004 [99]	315 (158/ 157)	US	43.85	65.1	82.2	No	150–300	im	12	X			14 g

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Table 1 (*continued*)

	Study by first author and year	Sample size (drug/ placebo)	Country	Average age	Gender %male	Race % white	Comorbidity	Dose (mg)	Route	Duration (week)	% HDD	DDD	% DD	Standard drink content
	Krystal 2001 [100]	627 (418/ 209)	US	49.1	98.1	63.3	No	50	os	12		X	X	14 g
	Morley 2006 [111] arm 1	83 (53/30)	Australia	45	67.9	NA	No	50	os	12		X		10 g
	O'Malley 2008 [118]	68 (34/34)	US	40.4	63.5	68 % Alaska Natives	50 % Tobacco smokers	50	os	16	X	X	X	14 g
	Oslin 2008 [119]	240 (120/ 120)	US	41	72.9	72.9	No	100	os	24	X		X	14 g
	Petrakis 2004 [121]	31 (16/15)	US	46	100	80.6	Schiphrenia	50	os	12	X		X	14 g
	Petrakis 2005 [122] arm 1	91 (59/32)	US	47	97.5	75.4	Different disorders	50	os	12	X		X	14 g
	Pettinati 2008 [125] arm 1	116 (58/58)	US	39	100	26.7	Cocaine dependence	150	os	12	X	X	X	14 g
	Pettinati 2008 [125] arm 2	48 (24/24)	US	39.2	0	16.7	Cocaine dependence	150	os	12	X	X	X	14 g
	Pettinati 2014 [126]	80 (39/41)	US	47.9	81.3	African Americans 81.3 %	Cocaine dependence	380	im	8	X	X	X	14 g
	Schmitz 2004 [131] arm 1	40 (20/20)	US	35.3	87.5	35	Cocaine dependence	50	os	12			X	14 g
	Schmitz 2004 [131] arm 2	40 (20/20)	US	36.7	80	20	Cocaine dependence	50	os	12			X	14 g
	Toneatto 2009 [138]	52 (27/25)	Canada	40	93	NA	Gambling	up to 250	os	11		X	X	14 g
	Volpicelli 1997 [139]	97 (48/49)	US	38.45	77.8	37.35	No	50	os	12			X	14 g
Baclofen	Addolorato 2011 [63] arm 1	21 (14/7)	Italy	44.4	82	100	No	30	os	12		X		12 g
	Addolorato 2011 [63] arm 2	21 (14/7)	Italy	43.1	71	100	No	60	os	12		X		12 g
	Garbutt 2010 [82]	80 (40/40)	US	48.9	55	96	No	30	os	12	X		X	14 g
	Garbutt 2021 [83] arm 1	63 (43/20)	US	46.6	50.6	88.05	No	30	os	16	X		X	14 g
	Garbutt 2021 [83] arm 2	57 (37/20)	US	46.1	52.1	85.6	No	75	os	16	X		X	14 g
	Hauser 2017 [89]	180 (88/92)	US	57	98.3	57.3	Chronic hepatitis C	30	os	12	X	X	X	14 g
	Leggio 2015 [101]	30 (15/15)	US	46.3	70	43	No	80	os	12	X			14 g
	Morley 2014 [112] arm 1	21 (14/7)	Australia	46.9	57	NA	No	30	os	12	X			10 g
	Morley 2014 [112] arm 2	21 (14/7)	Australia	46.3	42.5	NA	No	60	os	12	X			10 g
	Morley 2018 [113] arm 1	53 (36/17)	Australia	47.21	71	NA	Liver diseases	30	os	12		X	X	10 g
	Morley 2018 [113] arm 2	51 (35/16)	Australia	47.21	71	NA	Liver diseases	75	os	12		X	X	10 g
	Müller 2015 [115]	56 (28/28)	Germany	46.5	69.7	NA	No	30–270	os	20			X	12 g
	Ponizovsky 2015 [128]	64 (32/32)	Israel	43.65	75	NA	No	50	os	12	X		X	12 g
Gabapentin	Anton 2020 [68]	90 (44/46)	US	49.6	77	94	No	1200	os	16	X	X	X	14 g

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Table 1 (*continued*)

	Study by first author and year	Sample size (drug/ placebo)	Country	Average age	Gender %male	Race % white	Comorbidity	Dose (mg)	Route	Duration (week)	% HDD	DDD	% DD	Standard drink content
	Falk 2019 [77]	346 (173/ 173)	US	50.05	66	69.2	No	1200	os	24	X	X	X	14 g
Topiramate	Johnson 2007 [93]	371 (183/ 188)	US	47.25	73.1	84.9	No	300	os	14	X	X	X	14 g
	Likhitsathian 2013 [102]	106 (53/53)	Thailand	41.5	100	Thai	No	100–300	os	12	X	X	X	NA
	Pennington 2020 [120]	32 (15/17)	US	46.6	93.7	49.8	Traumatic brain injury	25–300	os	12	X	X	X	14 g
	Rubio 2009 [130]	63 (31/32)	Spain	42.285	100	NA	No	250	os	12	X	X	X	10 g
Varenicline	de Bejczy 2015 [75]	171 (86/85)	Sweden	55.1	62	100	No	2	os	12	X	X		13 g
	Hurt 2018 [92]	33 (16/17)	US	39.5	64	91	Smokers	2	os	12	X	X	X	14 g
	Pfeifer 2019 [127]	28 (15/13)	US	45	85.7	NA	Nicotine dependence	1	os	12		X		14 g
Other medications														
Aripiprazole	Anton 2008 [67]	295 (149/ 146)	US	47.3	68.4	84.4	No	30	os	12		X	X	14 g
Bromocriptine	Dongier 1991 [76]	84 (43/41)	Canada	41.2	78.5	NA	No	7	os	8		X	X	14 g
Bupropion	Grant 2007 [84]	58 (30/28)	US	39.6	84	58	Various psychiatric disorders	300	os	8		X	X	14 g
Buspirone	Fawcett 2000 [78] arm 2	74 (48/26)	US	39.4	100	83	Depression	10	os	24	X	X	X	14 g
	Kranzler 1994 [96]	61 (31/30)	US	39.45	77.1	95	Anxiety	20	os	12		X	X	14 g
	Malec 1996 [104]	57 (28/29)	Canada	41.635	72.3		No	20	os	12		X	X	14 g
Carbamazepine	Mueller 1997 [114]	29 (13/16)	US	38.75	59.5	90	41 % Other SUDs; 34 % affective disorders	200	os	48		X		14 g
Citalopram	Naranjo 1995 [117]	62 (53/46)	Canada	45.25	56.5	NA	No	40	os	12		X	X	14 g
Divalproex	Brady 2002 [71]	39 (19/20)	US	40.3	38.8	46.25	No	1500	os	12		X		14 g
Doxazosin	Back 2023 [69]	141 (70/71)	US	45.7	84	45	PTSD	16	os	12	X	X	X	14 g
	Kenna 2016 [94]	41 (20/21)	US	42.1	70.5	49	No	16	os	10	X			14 g
Fluoxetine	Cornelius 1995 [74]	21 (11/10)	US	33.8	66.7	38.1	Depression	20	os	12			X	14 g
	Kranzler 1995 [97]	101 (51/50)	US	40.1	80	95	No	up to 47	os	12		X	X	14 g
GHB	Gallimberti 1992 [81]	82 (41/41)	Italy	37.45	66.2	100	No	50/Kg	os	12	X	X	X	12 g
	Guiraud 2021 [88] arm 1	128 (102/26)	Europe	47.7	72.8	NA	No	0.75	os	12	X			10–14 g
	Guiraud 2021 [88] arm 2	129 (104/25)	Europe	47.9	71.8	NA	No	1.25	os	12	X			10–14 g
	Guiraud 2021 [88] arm 3	126 (101/25)	Europe	48.2	72.8	NA	No	1.75	os	12	X			10–14 g
	Guiraud 2021 [88] arm 4	128 (103/25)	Europe	48	71.9	NA	No	2.25	os	12	X			10–14 g
Glycine	Serrita 2019 [132]	20 (10/10)	US	48.9	100	45	Schizophrenia	0.8/kg	os	12	X		X	14 g
Imipramine	McGrath 1996 [107]	69 (36/33)	US	37.4	49.1	81.5	Primary depression	300	os	12	X	X	X	14 g
Leviracetam	Fertig 2012 [79]	130 (64/66)	US	44.3	76.2	64.5	No	2000	os	14	X	X	X	14 g
Lithium	Fawcett 2000 [78] arm 1	82 (56/26)	US	40.5	100	83.5	Depression	300	os	24	X	X	X	14 g

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Table 1 (*continued*)

	Study by first author and year	Sample size (drug/ placebo)	Country	Average age	Gender %male	Race % white	Comorbidity	Dose (mg)	Route	Duration (week)	% HDD	DDD	% DD	Standard drink content
Mecamylamine	Petrakis 2018 [123]	136 (68/68)	US	48.5	85.9	48.5	No	10	os	12	**X**	**X**	**X**	14 g
Nefazodone	Hernandez-Avila 2004 [90]	41 (21/20)	US	42.9	48.8	NA	Depression	200–600	os	10	**X**	**X**	**X**	14 g
	Kranzler 2000 [98] arm 2	90 (59/31)	US	41.6	76.3	91	12 % Dysthymic; 5.5 % depression	100	os	12	**X**	**X**	**X**	14 g
	Wetzel 2004 [140] arm 1	103 (53/50)	Germany	43.1	100	NA	No	up 600	os	12		**X**	**X**	NA
	Wetzel 2004 [140] arm 2	97 (50/47)	Germany	42.9	100	NA	No	up 600	os	12		**X**	**X**	NA
Olanzapine	Guardia 2004 [87]	60 (29/31)	Spain	43.41	76.8	NA	No	15	os	12		**X**	**X**	10 g
Oxytocine	Melby 2021 [108]	38 (19/19)	Norway	47.4	71.1	NA	No	24 IU	in	4		**X**		12.8 g
Prazosin	Simpson 2009 [134]	24 (12/12)	US	45.5	79.2	83.3	No	8	os	6	**X**	**X**	**X**	14 g
	Simpson 2015 [135]	30 (15/15)	US	43.3	63.4	40	PTSD	16	os	6	**X**		**X**	14 g
	Simpson 2018 [136]	92 (48/44)	US	48.2	79.5	56.55	No	16	os	12	**X**	**X**	**X**	14 g
	Wilcox 2018 [141]	33 (17/16)	US	39.615	63.9	47.2	42 % Marijuana use	16	os	6	**X**	**X**	**X**	14 g
Quetiapine	Brown 2008 [72]	102 (52/50)	US	38.3	62.6	60.7	Bipolar disorder	600	os	12	**X**		**X**	14 g
	Litten 2012 [103]	218 (105/ 113)	US	45.45	80.4	82.3	No	400	os	12	**X**	**X**	**X**	14 g
Sertraline	Moak 2003 [110]	82 (38/44)	US	41.5	61	98.78	Depression	200	os	12		**X**	**X**	14 g
	Pettinati 2001 [124] arm 1	53 (26/27)	US	43	49.1	77.4	Lifetime depression	200	os	14			**X**	14 g
	Pettinati 2001 [124] arm 2	47 (24/23)	US	46.4	55.3	83	No	200	os	14			**X**	14 g
Tiapride	Shaw 1987 [133]	32 (13/19)	UK	NA	100	NA	Anxiety	100	os	24			**X**	NA

Legend: Some of the 79 included studies provided more than two arms each, for a total of 101 datasets. Medications approved for the treatment of alcohol use disorder (AUD) comprise acamprosate, disulfiram, nalmefene, and naltrexone. Medications recommended for AUD treatment comprise baclofen, gabapentin, topiramate, and varenicline. Other medications comprise medications not approved nor recommended for AUD treatment. Abbreviations: DDD: number of drinks per drinking day; %DD: rate of drinking days; %HDD: rate of heavy drinking days.

4-week duration.

Zuzana Mitrova conducted the searches; RA and ZL independently screened all abstracts and screened all full-text articles. Discrepancies were discussed with a third author, HL-P. The risks of bias for the included RCTs were assessed independently using the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* [61].

2.2. Bias and quality analysis

Two authors (RA and ZL) used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* [61] to evaluate the risk of bias for each RCT. The Cochrane risk of bias tool includes the following seven risks of bias due to: (1) random sequence generation, (2) selection, (3) deviations from intended interventions, (4) measurement of outcomes, (5) incomplete outcome data, (6) selection of the reported result, and (7) from other sources. After data extraction, the two authors independently judged the risk for each domain as low, high, or unclear. Disagreements were resolved with the third author (HL-P).

The quality assessment of this study followed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework. Based on the risk of bias, the quality of evidence was graded as very low, low, moderate, or high [62].

2.3. Data analysis

For each study, in addition to primary and secondary outcomes, the following information was extracted: number of participants, age, gender, ethnicity, comorbidity, detoxification before treatment, name of medication, dose, route of administration, and duration of treatment. Information was collected in an Excel file (available on request). When discrepancies occurred in published data or outcome measures of alcohol consumption were missing, corresponding authors were contacted (ZL) for corrections, clarifications, or requests.

We placed data relating to approved AUD medications (disulfiram, naltrexone, acamprosate, and nalmefene) and off-label medications (i.e., baclofen, gabapentin, topiramate, and varenicline) together in the group named "AUD medications". Data relating to other medications neither approved for AUD treatment nor suggested as off-label medications were then compiled in the group "other medications". On including RCTs with more than a single arm in the meta-analyses (e.g. two different doses of the same medication or two different medications compared to placebo), we divided the control group into two different groups, each group comprising half the participants of the original group to avoid counting participants in the control group twice.

Cochrane RevMan software [Review Manager (RevMan) Version 5.4 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] was used for our analyses. In detail, we evaluated the efficacy of medications analyzing the three primary alcohol consumption measures by calculating the generic inverse-variance "e" effect as mean difference (MD) for each outcome between baseline and end of treatment values of both medication and placebo groups. The uncertainty in each result was expressed with a 95 % confidence interval (CI). We considered a significant difference between medication and placebo when CIs excluded 0 (P-values <0.05) and the lack of difference in cases where CIs included 0 (P-values ≥ 0.05).

For the secondary dichotomous safety outcomes (i.e., dropout, adverse events, and serious adverse events), we calculated the risk ratio (RR), with 95 % CI comparing medication and control groups at the end of treatments. We considered a significant difference between medication and placebo when CIs excluded 1 (P-values <0.05) and the lack of difference in cases where CIs included 1 (P-values ≥ 0.05). Heterogeneity was expressed by means of I^2 [61]. The presence of significant heterogeneity was defined as I^2 value > 50 %; for I^2 value > 50 %, possible reasons were investigated by visually inspecting the funnel plots to identify RCTs that might be contributing to the heterogeneity [61]. Meta-analyses were conducted using a random effect model for all analyses.

Standard error (SE) for e was estimated by the square root of the sum of the squared standard deviations (SD) divided by n, in the absence of information about the correlation between baseline and end of treatment assessments of the outcomes. We noted that this implied an assumption of zero correlation and yielded a conservative estimate of SE.

The number of participants recruited by the selected RCTs did not always correspond to the number of participants who received medications or placebo at baseline and end of treatment. We reported the number provided by the primary RCTs.

2.4. Missing data recovery

All randomized participants were included in statistical analyses, without any imputation of missing data. To collect the greatest amount of data, authors of those studies that met our inclusion criteria but did not provide sufficient data were contacted: two authors (HL/PB) sent an email to the corresponding authors of the studies published from 2000 onwards asking for any missing values of %HDD, DDD and %DD at baseline and/or at the end of the treatment. We did not contact the corresponding authors of studies published prior to 2000, considering that it would have been difficult to obtain data collected more than 20 years ago.

3. Results

3.1. Results of the search

As indicated by the PRISMA flow diagram in Fig. 1, the searches conducted yielded a total of 15,014 articles. After duplicate screening, 4693 articles were excluded. Of the 10,321 remaining, 9937 were excluded based on titles and abstracts, and the other 384 were assessed for eligibility. One record was not retrieved, and 21 records identified through reference searches were added for a total of 404 studies that were full-text assessed for eligibility independently by two authors. A third author was asked to review uncertain articles.

3.2. Excluded studies

Globally, we excluded 325 articles for the following reasons: 75 were different publications (e.g., conference abstracts); 164 provided insufficient data (e.g., alcohol outcomes were not provided both at baseline and end of treatment); 80 articles had different design (e.g., duration < 4 weeks); 5 articles were not in English; and one article provided discrepant data (see Fig. 1).

3.3. Included studies

We included a total of 79 RCTs (involving 11,737 participants) which met our inclusion criteria [63–141]. These 79 RCTs investigated the efficacy of 30 medications: 4 approved medications (acamprosate, disulfiram, nalmefene, and naltrexone), 4 off-label medications (baclofen, gabapentin, topiramate, and varenicline) and 22 other medications neither approved nor recommended for AUD treatment (like aripiprazole and bromocriptine). Sixteen of the 79 included studies provided data of two arms each as they compared two medications to placebo [78,98,111,122], two doses of the same medication to placebo [63,83,109,112,113], added different psychological treatments to the same medication [65,70,80,131,140], evaluated efficacy dividing participants according to male-female gender [125], or to the presence of absence of comorbid mental disorders [124]. Two other studies [66,88] provided data of four arms each. Together, we collected a total of 101 datasets. Table 1 shows the characteristics of these 101 datasets divided according to medications used.

The duration of RCTs varied from 4 [108] to 48 weeks [114] with a

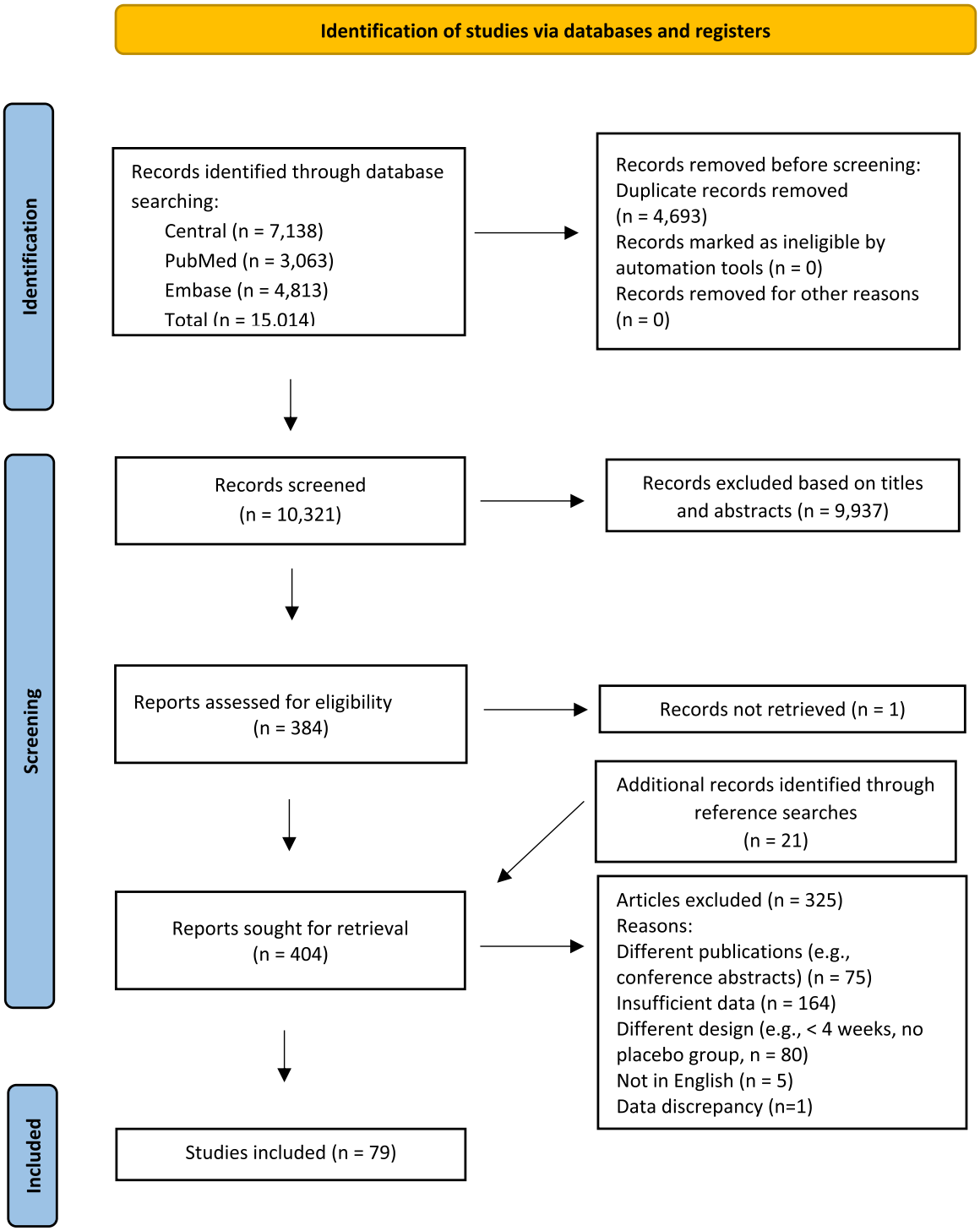

Fig. 1. PRISMA study flow diagram. Legend: PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-analyses.

mean of 13.9 (5.7) weeks. Most RCTs were of a 12-week duration (60.8 %). In all RCTs, medications were orally administered, with the exception of three RCTs in which participants received intramuscular injection of naltrexone [73,99,126] and intranasal oxytocin [108].

Studies ranged in size from 20 [132] to 718 participants [85], with a mean size of 149 participants per RCT. Participants were aged approximately 44 years, with the majority of RCTs recruiting mainly men at rates up to 100 % of participants [78,102,121,130,132,133,140]. Only four RCTs recruited higher rates of women than men [71,90,107,112] and one RCT provided the results divided by female and male participants [125]. The majority of RCTs were conducted in the USA (54 out of 79, equal to 72.2 %), four each in Canada and Spain (5.1 %), three in Australia (3.8 %), two in different European countries, Germany, Italy, and Sweden (2.5 %), and one each in Israel, Japan, Norway, South Korea, Thailand, and UK each (1.3 %).

Thirty-five out of 101 datasets (34.7 %) reported the presence among participants of comorbid mental disorders: mood disorders (i.e., depression, bipolar disorders, dysthymic; 11 datasets, 26.8 %), disorders not described in detail (6 datasets, 14.6 %), cocaine dependence (6 datasets, 14.6 %), schizophrenia (2 datasets, 4.9 %), post-traumatic stress disorder (PTSD; 4 datasets, 9.8 %), anxiety (2 datasets, 4.9 %), gambling (1 dataset, 2.4 %), marijuana use (1 dataset, 2.4 %), and

traumatic brain injury (1 dataset, 2.4 %).

3.4. Types of medications

Among the 79 RCTs included, 47 RCTs (62 datasets; 8465 participants) used approved and off-label medications for AUD treatment (AUD medications). In detail, 32 RCTs (40 datasets; 6507 participants) used approved AUD medications: acamprosate (5 RCTs; 6 datasets; 741 participants), disulfiram (one RCT; one dataset; 98 participants), nalmefene (4 RCTs; 5 datasets; 2104 participants), and naltrexone (22 RCTs; 28 datasets; 3564 participants); 18 RCTs (22 datasets; 1958 participants) used off-label medications recommended for AUD treatment: baclofen (9 RCTs; 13 datasets; 718 participants), gabapentin (2 RCTs; 2 datasets; 436 participants), topiramate (4 RCTs; 4 datasets; trials; 572 participants), and varenicline (3 RCTs; 3 datasets; 232 participants).

The other 32 RCTs (39 datasets; 3272 participants) used the following medications which were neither approved nor recommended for the treatment of AUD (other medications): aripiprazole (1 RCT; 1 dataset; 295 participants), bromocriptine (1 RCT; 1 dataset; 84 participants), bupropion (1 RCT; 1 dataset; 58 participants), buspirone (3 RCTs; 3 datasets; 192 participants), carbamazepine (1 RCT; 1 dataset; 29 participants), citalopram (1 RCT; 1 dataset; 99 participants), divalproex (1 RCT; 1 dataset; 39 participants), doxazosin (1 RCT; 1 dataset; 41 participants), fluoxetine (2 RCTs; 2 datasets; 122 participants), gamma hydroxybutyric acid (GHB; 2 RCTs; 5 datasets; 593 participants); glycine (1 RCT; 1 dataset; 20 participants), imipramine (1 RCT; 1 dataset; 69 participants), leviracetam (1 RCT; 1 dataset; 130 participants), lithium (1 RCT; 1 dataset; 82 participants), mecamylamine (1 RCT; 1 dataset; 136 participants), nefazadone (2 RCTs; 4 datasets; 331 participants), olanzapine (1 RCT; 1 dataset; 60 participants), oxytocin (1 RCT; 1 dataset; 38 participants), prazosin (4 RCTs; 4 datasets; 179 participants), quetiapine (2 RCTs; 2 datasets; 320 participants), sertraline (2 RCTs; 3 datasets; 182 participants), and tiapride (1 RCT; 1 dataset; 32 participants).

3.5. Risk of bias

3.5.1. Selection bias: random sequence generation

We judged 49 RCTs to be at low risk of bias, one RCT at high risk of bias, and the remaining 29 RCTs at unclear risk of bias as they provided no information about the method used for random sequence generation (see Supplement content: S Figs. 1 and 2).

3.5.2. Selection bias: allocation concealment

We judged 39 RCTs at low risk of bias, two RCTs at high risk of bias, and the other 38 RCTs at unclear risk of bias as they did not provide methods of allocation concealment.

Blinding: Performance bias

We judged 67 RCTs at low risk of bias, two RCTs at high risk of bias, and 10 RCTs at unclear risk of bias as information on blinding of participants and researchers was missing or unclear.

3.5.3. Blinding: detection bias

We considered 25 RCTs at low risk of bias, one RCT at high risk of bias, and the other 53 RCTs at unclear risk of bias as they failed to provide enough information to make a judgement.

3.5.4. Attrition bias: incomplete outcome data

We deemed 58 RCTs at low risk of bias, 2 RCTs at high risk of bias, and the remaining 19 RCTs at unclear risk of bias as information about numbers of and reasons for dropouts, or other data for each group was unclear or missing.

3.5.5. Reporting bias: selective reporting

We considered 51 RCTs at low risk of bias, five RCTs at high risk of bias, and the other 23 RCTs at unclear risk of bias as they provided insufficient information to assign risk of bias.

3.5.6. Other potential sources of bias

We considered 56 RCTs at low risk of other sources of bias, one at high risk of other sources of bias, and the other 22 RCTs at unclear risk of other sources of bias as they provided insufficient information to assign potential risk of other sources of bias.

3.6. Alcohol use outcomes

3.6.1. %HDD

3.6.1.1. All medications: baseline and end of treatment values. We identified 54 datasets (44 RCTs) that provided the %HDD at both baseline and end of treatment. At baseline (see Table 2), participants reported approximately 60 % of HDD. At the end of treatment, %HDD had been reduced to approximately one third.

3.6.1.2. AUD medications: baseline and end of treatment values. In 36 of the above 54 datasets (66.7 %; 30 RCTs), participants received AUD medications or placebo (see Tables 2 and 3). Both AUD medications and placebo reduced %HDD to approximately one third.

3.6.1.3. AUD medications: E effect. The results of the meta-analysis, including baseline values of alcohol use (e effect) revealed that, compared to placebo, AUD medications further reduced the %HDD of 3.57 % (moderate-certainty evidence); see Table 3 and Fig. 2. Visual inspection of the funnel plot (see Supplement content: S Fig. 3; asymmetry not suggestive of potential bias) did not show potential publication bias.

3.6.1.4. Other medications: baseline and end of treatment values. In the remaining 18 of the 54 datasets (33.3 %; 15 RCTs), participants received other medications or placebo. As shown in Table 2, other medications and placebo likewise reduced %HDD to approximately one third.

3.6.1.5. Other medications: E effect. The results of the meta-analysis revealed no differences between other medications and placebo (e effect: −0.47); see Supplement content: S Fig. 4). Visual inspection of the funnel plot (see Supplement content: S Fig. 5) suggested potential publication bias related to the lack of studies with large placebo effects.

3.6.2. %DD

3.6.2.1. All medications: baseline and end of treatment values. A total of 77 datasets (63 RCTs) that met our inclusion criteria were identified. At baseline (see Table 2), participants who received any medication and placebo reported drinking on approximately 70 % of days; at the end of treatment, participants who received both AUD medications and placebo had approximately halved these values.

3.6.2.2. AUD medications: baseline and end of treatment values. In 47 of the 77 datasets (61.0 %; 37 RCTs) participants received AUD medications or placebo. At baseline (see Table 2), the %DD were very high; however, at the end of treatment, both AUD medications and placebo had halved these values.

3.6.2.3. AUD medications: E effect. AUD medications were found to further reduce %DD by 1.85 % (high-certainty evidence), compared to placebo; see Table 3, Fig. 3. Visual inspection of the funnel plot (see Supplement content: S Fig. 6) did not show potential publication bias.

3.6.2.4. Other medications: baseline and end of treatment values. In the remaining 30 of the 77 datasets (39.0 %; 27 RCTs) participants received other medications. As shown in Table 2, at baseline, the mean %DD was

Table 2
Baseline and final values of alcohol outcomes.

	Baseline				End of treatment			
	Medications		Placebo		Medications		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
%HDD								
Any meds	3758	60.5 (16.3)	3107	61.4 (15.9)	3332	18.3 (13.6)	2841	21.8 (15.3)
AUD meds	2766	61.0 (16.9)	2438	62.7 (15.9)	2367	20.6 (14.0)	2914	24.3 (16.4)
Other meds	992	59.5 (15.3)	669	58.9 (16.1)	965	13.8 (11.9)	647	16.7 (11.8)
%DD								
Any meds	4629	69.9 (15.7)	3874	70.9 (14.6)	4276	27.0 (17.1)	3595	30.2 (19.9)
AUD meds	3335	67.9 (15.5)	2658	69.6 (14.3)	3091	25.7 (16.9)	2446	29.5 (19.0)
Other meds	1294	73.0 (15.8)	1216	72.4 (15.2)	1185	29.2 (17.5)	1149	31.2 (21.6)
DDD								
Any meds	3313	12.3 (3.5)	2861	12.0 (3.6)	3100	4.8 (2.8)	2695	5.5 (3.6)
AUD meds	2121	12.7 (3.8)	1748	12.6 (4.0)	2018	4.9 (2.7)	1651	5.5 (3.7)
Other meds	1192	11.7 (3.1)	1113	11.2 (2.7)	1082	4.7 (3.0)	1044	5.4 (3.7)

Legends: Abbreviations: AUD: alcohol use disorder; AUD meds: medication approved or recommended for the treatment of AUD; DDD: number of drinks per drinking days; Other meds: medications not approved neither recommended for the treatment of AUD; SD: standard deviation; %HDD: rate of heavy drinking days; %DD: rate of drinking days.

Table 3
Summary of findings.

AUD medications compared to placebo in people with AUD
Patient or population: People with AUD
Setting: Outpatients
Intervention: AUD medications (approved: acamprosate, disulfiram, nalmefene, and naltrexone; recommended: baclofen, gabapentin, topiramate, and varenicline)
Comparison: Using the generic inverse-variance, AUD medications are compared to both placebo at the end of treatment and AUD medications at baseline

Outcomes	**Anticipated absolute effects*** (95 % CI)		Relative effect (95 % CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with AUD medications**				
Rate of heavy drinking days (% HDD)	The mean % HDD was: 24.3	MD **3.57 lower** (6.37 lower to 0.77 lower)	-	5204 (36 datasets; 30 RCTs)	⨁⨁⨁◯ Moderate[a]	Compared to both placebo at end of treatment and AUD medications at baseline, AUD medications reduce the %HDD of 3.57
Rate of drinking days (%DD)	The mean % DD was 29.5	MD **1.85 lower** (3.65 lower to 0.04 lower)	-	6098 (47 datasets; 37 RCTs)	⨁⨁⨁⨁ High	Compared to both placebo at end of treatment and AUD medications at baseline, AUD medications reduce the %DD of 1.85
Drinks per drinking days (DDD)	The mean DDD was 5.5	MD **0.55 lower** (1.02 lower to 0.08 lower)	-	3869 (36 datasets; 29 RCTs)	⨁⨁⨁⨁ High	Compared to both placebo at end of treatment and AUD medications at baseline, AUD medications reduce the DDD of 0.55
Dropouts	285 per 1.000	299 per 1.000 (271−331)	RR 1.05 (0.95–1.16)	8337 (59 datasets; 45 RCTs)	⨁⨁⨁◯ Moderate[b]	Compared to placebo, AUD medications do not increase the number of dropouts
Adverse events	657 per 1.000	736 per 1.000 (703−768)	**RR 1.12** (1.07–1.17)	2961 (17 datasets; 13 RCTs)	⨁⨁⨁⨁ High	Compared to placebo, AUD medications increase the number of participants who report adverse events (absolute effect: 79 per 1000; from 46 more to 112 more)
Serious adverse events	34 per 1.000	33 per 1.000 (25−44)	RR 0.97 (0.73–1.30)	6095 (41 datasets; 29 RCTs)	⨁⨁⨁⨁ High	Compared to placebo, AUD medications do not increase the number of participants who report serious adverse events

AUD: Alcohol use disorder**; CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio. **Bold font:** statistical significance.
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations
a. Downloaded one level ($I^2 = 42$ %)
b. Downloaded one level ($I^2 = 46$ %)
* **The risk in the intervention group** (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI).

high, and, at the end of treatment, both treatments had reduced this value by approximately half.

3.6.2.5. Other medications: E effect. The results of the meta-analysis, including baseline values of alcohol use showed no difference between other medications and placebo (e effect: −0.92; see Supplement content: S Fig. 7). Visual inspection of the funnel plot (see Supplement content: S Fig. 8) suggested potential publication bias probably due to the lack of studies with large placebo effects.

3.6.3. DDD

3.6.3.1. All medications: baseline and end of treatment values. A total 62 datasets (52 RCTs) that met our inclusion criteria were identified. At baseline, participants reported drinking approximately 12 standard drinks per drinking day. At the end of treatment, participants who received both any medication and placebo halved their alcohol consumption as shown in Table 2.

3.6.3.2. AUD medications: baseline and end of treatment values. In 36 of

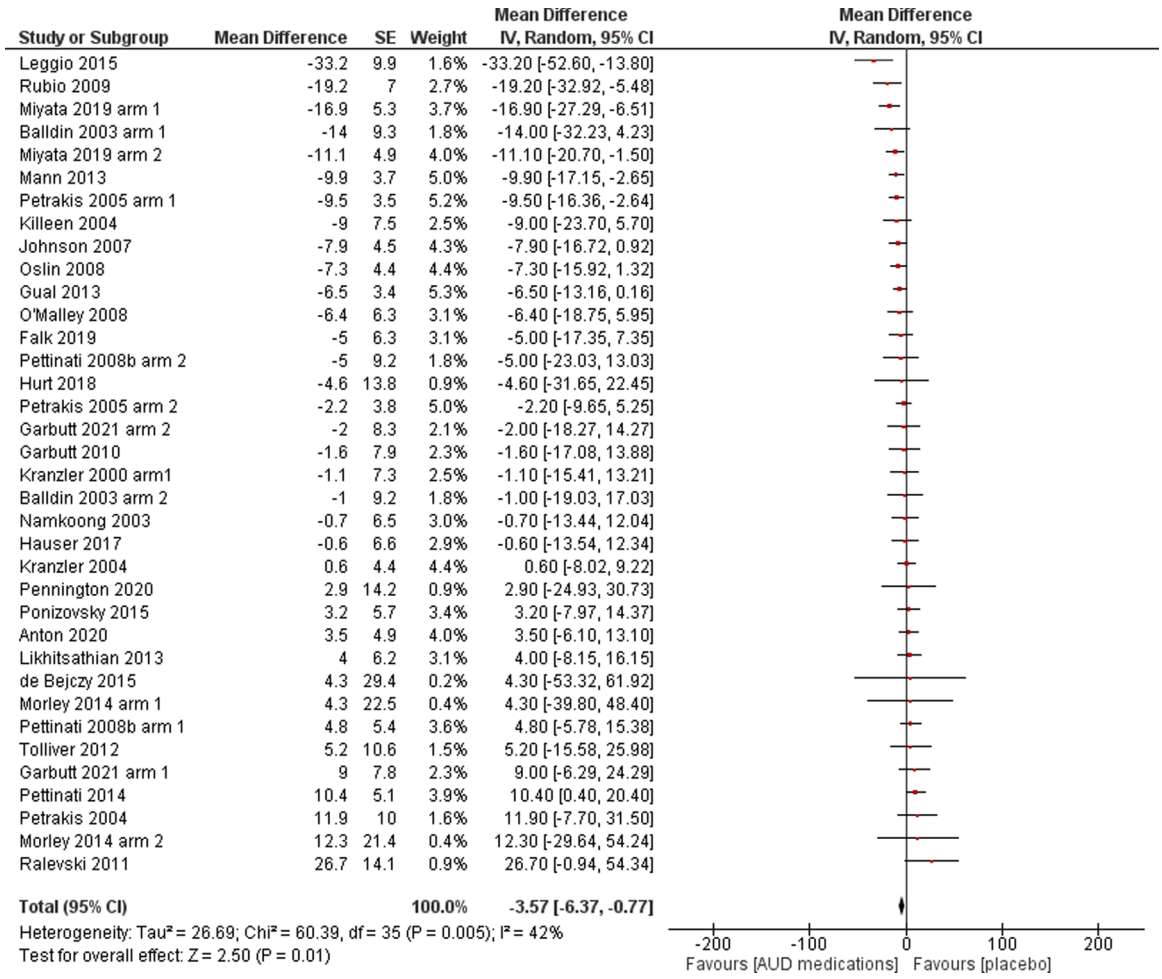

Fig. 2. Forest plot %HDD for AUD medications. Legend: Forest plot of the outcome % of heavy drinking days (%HDD) using the generic inverse-variance "e" effect, expressed as a mean difference (MD) between baseline and end of treatment values of both medication and placebo values. In this analysis, medications include those approved and recommended for the treatment of alcohol use disorder (AUD).

these 62 datasets (58.1 %; 29 RCTs), participants received AUD medications or placebo (see Table 3). At baseline, the mean number of DDD was higher than 12.5 standard drinks, and, at the end of treatment, this value had been halved by both treatments (see Table 2).

3.6.3.3. AUD medications: E effect. AUD medications further reduced the number of DDD by 0.55 drink (high-certainty evidence), compared to placebo (see Table 3, Fig. 4). Visual inspection of the funnel plot (see Supplement content: S Fig. 9) showed no potential publication bias.

3.6.3.4. Other medications: baseline and end of treatment values. In the remaining 26 of the 62 datasets (41.9 %; 24 RCTs) participants received other medications or placebo. At baseline, the mean number of DDD was approximately 11 standard drinks; at the end of treatment, both treatments had approximately halved this value (see Table 2).

3.6.3.5. Other medications: E effect. Other medications further reduced the number of DDD by 1.18 (e effect: −1.18; see Supplement content: S Fig. 10). Visual inspection of the funnel plot (see Supplement content: S Fig. 11) showed no potential publication bias.

3.7. Safety outcomes

3.7.1. Dropout

3.7.1.1. All medications. A total of 96 datasets (75 RCTs) that met our inclusion criteria were identified. At the end of treatment, approximately 30 % dropouts from the groups receiving any medication and placebo were determined (see Table 4).

3.7.1.2. AUD medications. In 59 datasets (45 RCTs; 8354 participants), participants received AUD medications or placebo (see Table 3). At the end of treatment, there were approximately 28 % dropouts among participants of both groups (see Table 4). The results of the meta-analysis revealed no differences in dropout rate between AUD medications and placebo (moderate-certainty evidence) (see Supplement content: S Fig. 12). Visual inspection of the funnel plot (see Supplement content: S Fig. 13) did not show potential publication bias.

3.7.1.3. Other medications. In the remaining 37 datasets (32 RCTs), participants received other medications or placebo. At the end of treatment, a total of approximately 30 % dropouts were reported among participants of both groups (see Table 4). No differences were detected between these two treatments (see Supplement content: S Fig. 14]. Visual inspection of the funnel plot (see Supplement content: S Fig. 15) suggested potential publication bias.

3.7.2. Adverse events

3.7.2.1. All medications. We found 30 datasets (21 RCTs) in which, at the end of treatment, more than 70 % and 60 % of participants who received any medication and placebo, respectively, reported at least one

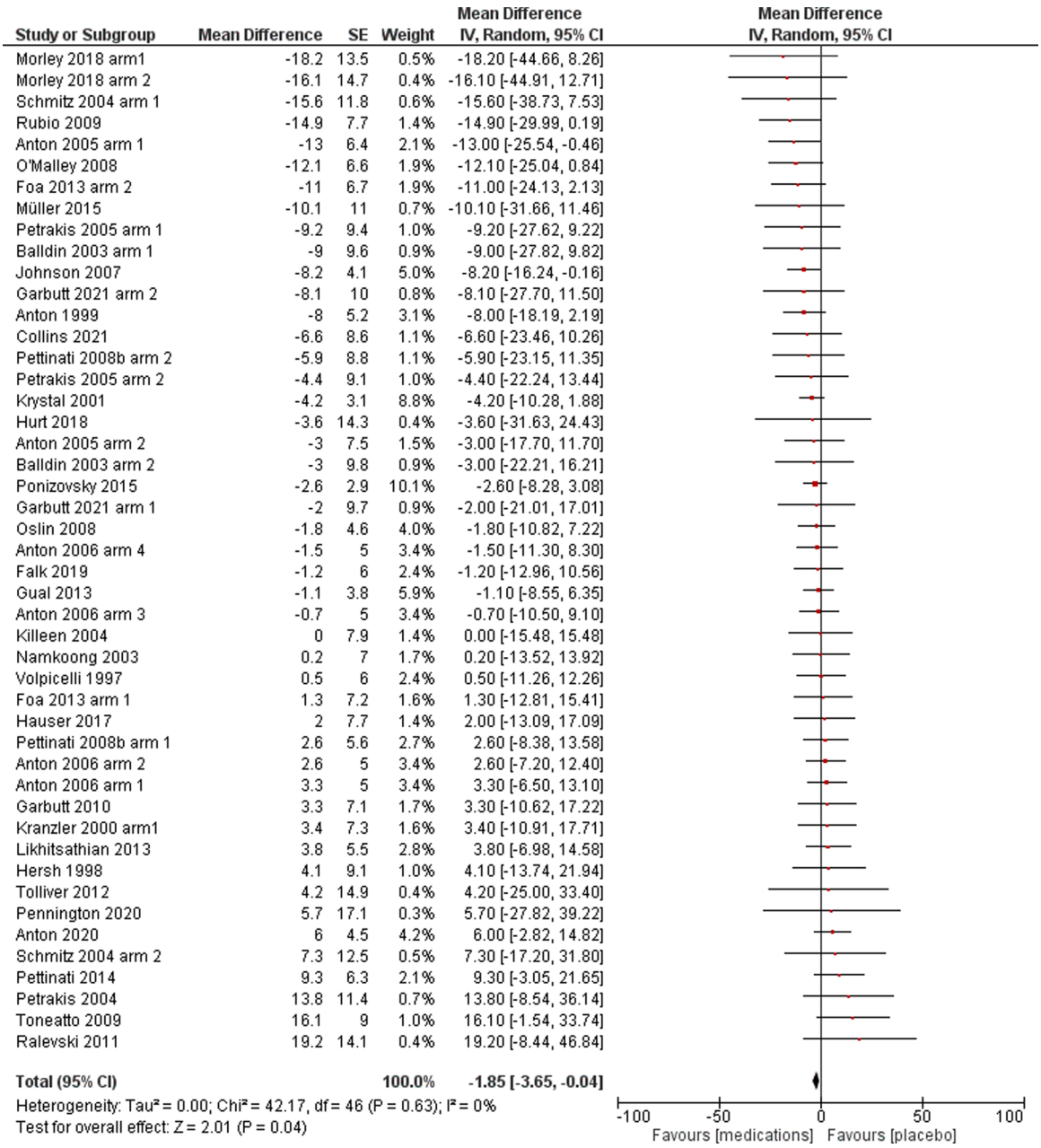

Fig. 3. Forest plot %DD for AUD medications. Legend: Forest plot of the outcome % of drinking days (%DD) using the generic inverse-variance "e" effect, expressed as a mean difference (MD) between baseline and end of treatment values of both medication and placebo values. In this analysis, medications include those approved and recommended for the treatment of alcohol use disorder (AUD).

adverse event (see Table 4).

3.7.2.2. AUD medications. In 17 datasets (13 RCTs), participants received AUD medications or placebo. Compared to placebo, AUD medications were found to increase the risk for adverse events (RR: 1.12; high-certainty evidence; see Tables 3 and 4; Supplement content: S Fig. 16).

Visual inspection of the funnel plot (see Supplement content: S Fig. 13) showed no potential publication bias.

3.7.2.3. Other medications. In the other 13 datasets (9 RCTs), participants received other medications or placebo. The meta-analysis found that other medications increased the risk for adverse events (RR: 1.17; see Table 4; Supplement content: S Fig. 18). Visual inspection of the funnel plot (see Supplement content: S Fig. 19) did not show potential publication bias.

3.7.3. Serious adverse events

3.7.3.1. All medications. A total of 58 datasets (43 RCTs; see Table 4) were identified in which, at the end of treatment, more than 3 % of participants reported at least one serious adverse event.

3.7.3.2. AUD medications. In 41 datasets (29 RCTs), participants received AUD medications or placebo. No differences were found between AUD medications and placebo in risk of developing serious adverse events (see Tables 3 and 4; see Supplement content: S Fig. 20). Visual inspection of the funnel plot (see Supplement content: S Fig. 21) did not show potential publication bias.

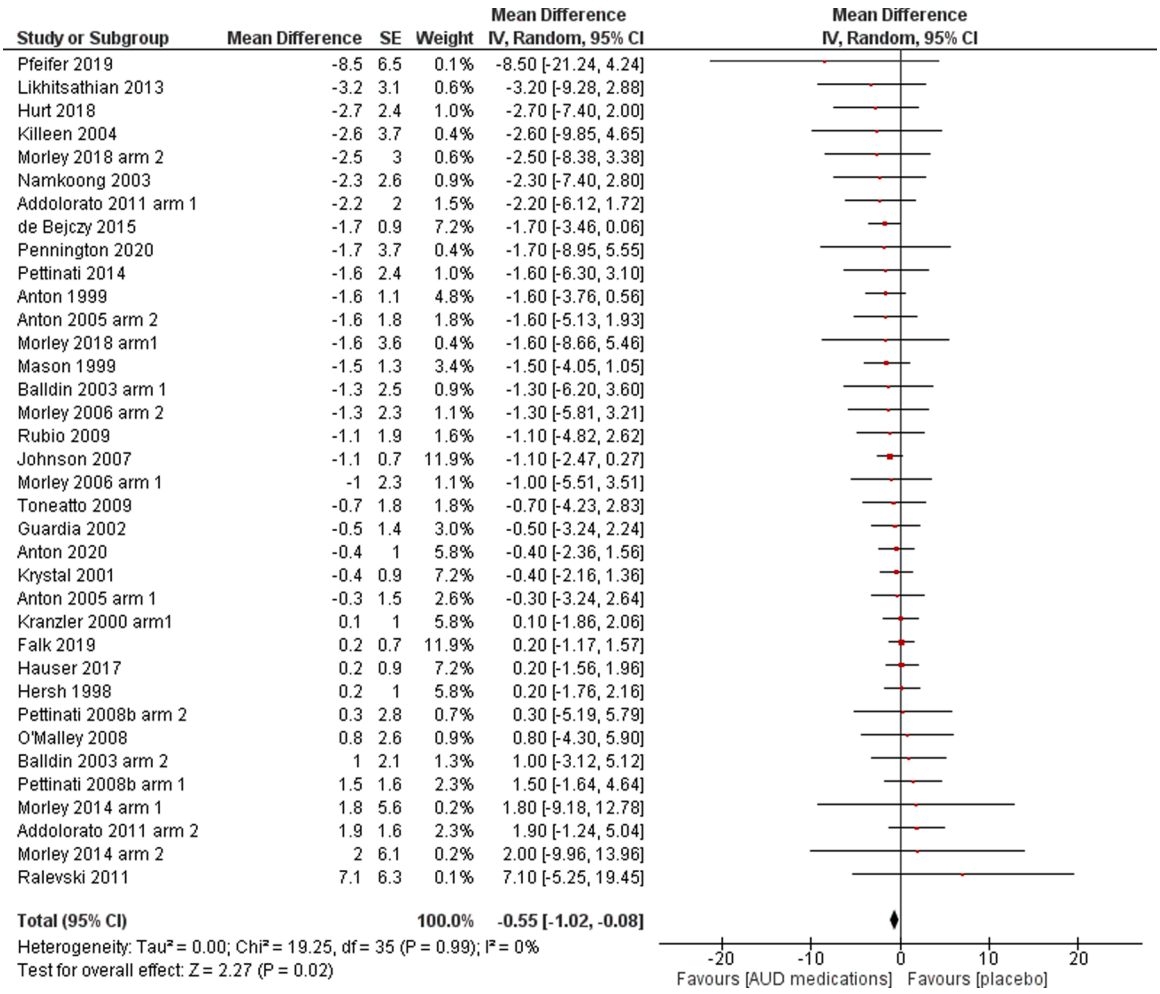

Fig. 4. Forest plot DDD for AUD medications. Legend: Forest plot of the outcome % of drinks per drinking day (%DD) using the generic inverse-variance "e" effect, expressed as a mean difference (MD) between baseline and end of treatment values of both medication and placebo values. In this analysis, medications included those approved and recommended for the treatment of alcohol use disorder (AUD).

Table 4
Final values of dropouts, adverse events, and serious adverse events.

	Medications			Placebo		
	Event	Participants	%	Event	Participants	%
Dropouts						
Any meds	2076	6428	32.3	1442	5061	28.5
AUD meds	1473	4659	28.5	1048	3678	28.5
Other meds	601	1886	31.9	418	1530	27.3
Adverse events						
Any meds	1880	2560	73.4	1144	1843	62.1
AUD meds	1273	1641	75.4	867	1320	65.7
Other meds	643	919	70.0	277	523	53.0
Serious adverse events						
Any meds	148	4532	3.3	127	3499	3.6
AUD meds	107	3412	3.1	91	2683	3.4
Other meds	41	1120	3.7	816	1936	4.4

Legends: Abbreviations: AUD: alcohol use disorder; AUD meds: medication approved or recommended for the treatment of AUD; Other meds: medications not approved neither recommended for the treatment of AUD.

3.7.3.3. Other medications. In the remaining 17 datasets (14 RCTs; 1972 participants), participants received other medications or placebo. As shown in Table 4, no differences were detected for severe adverse events between other medications and placebo (see Supplement content: S Fig. 22). Visual inspection of the funnel plot (see Supplement content: S Fig. 23) did not show potential publication bias.

4. Discussion

This systematic review was aimed at evaluating the efficacy of medications used in the treatment of AUD whilst excluding the potential influence of AUD severity at baseline using the generic inverse-variance, which facilitated comparison of medications and placebo both at the end of the study and, concomitantly, to baseline values of the same participants. To achieve this aim, we selected only RCTs providing both baseline and end of treatment values of at least one alcohol outcome comprising %HDD, %DD, and DDD. In total, 79 RCTs, 101 datasets, 11,737 participants that met our inclusion criteria were included. Our sample was made up mainly of men aged approximately 44 years who, at baseline, consumed approximately 12 drinks per drinking days (DDD), for approximately 70 % of days (%DD), consuming heavy amounts of alcohol (%HDD) on approximately 61 % of days. As shown in Table 2, these three alcohol use outcomes were greatly reduced when participants received placebo: the number of DDD reduced from 12 to 5.5; the %DD, from 70.9 % to 30.2 %; and the %HDD, from 61.4 % to 21.8 %. The addition of AUD medications further reduced alcohol consumption, although increasing the rate of participants reporting at least one adverse event, but no serious adverse effects. However, as shown in Table 3, compared to placebo, the effects induced by AUD medications were lower than 4 % HDD, 2 % DD, and one DDD. The limited size of their efficacy contributes, at least in part, to the low utilization of AUD medications. Our findings underscore the significance of placebo effects in treating AUD. This observation is not entirely unexpected considering

the role of opioid [142–146] and dopamine [147,148] mechanisms in the neurobiology of placebo effects. Indeed, mounting evidence suggests that placebo effects take place in response to the release of endogenous opioids [144] and that the mu-opioid antagonists naloxone/naltrexone block placebo effects in both pain [149] and depression [150]. While there is no direct evidence of the role of the endogenous opioid system in AUD patients, this hypothesis remains plausible, potentially explaining reduced placebo effects within the drug arm among AUD patients treated with naltrexone, consequently diminishing drug-placebo differences. Further research is thus needed to elucidate the biological mechanism of placebo effects in patients with AUD and understand the contribution of these mechanisms in the failure of current AUD trials.

Our results should also be discussed whilst taking into account the limited number of people with AUD who receive pharmacological treatment [43–45]. Besides the modest efficacy of AUD medications, the large heterogeneity of people with AUD and inadequate training of physicians contribute to limited clinical use of these medications [16]. Regarding the heterogeneity of people with AUD, patients have been divided into different typologies according to the onset of AUD, familiarity of AUD, comorbid mental disorders, AUD severity, and/or specific endophenotypes to help physicians in the choice of the best pharmacological option for their patients [150–153]. As an example, a recent study found that low doses of ondansetron, a 5-HT3 antagonist, may be more effective for “heavy drinking” individuals than for “very heavy drinkers”, phenotypes related to specific genetic variants of the serotonin transporter and serotonin-3AB receptor [154]. Unfortunately, evidence regarding genetic predictors of medication efficacy is still limited [155]. Further studies should address the possibility of a precision medicine approach focused at identifying specific subgroups of patients with the greatest potential benefit for each medication [155,156]. On the other hand, the results of our present systematic review highlight how people affected by AUD reduce alcohol consumption when they receive both placebo and pharmacological treatment. Accordingly, it is unacceptable that the majority of people with AUD fail to receive any form of treatment. AUD medications should be considered an incentive aimed at increasing the number of AUD sufferers seeking treatments. Further studies should be conducted to investigate the efficacy of AUD medications in people with AUD grouped on the basis of potential influencing factors such as AUD severity at baseline [52,53] and sex and gender differences [48].

The strengths of this review are unique. We conducted a comprehensive review of *all* medications that had been used to better understand their potential effectiveness in treating this disorder. We emphasized the direct effects produced on alcohol consumption in three common and critical measures. The studies included were representative of the highest quality clinical studies performed in the AUD field based on the meticulous study designs, all of which took into account baseline levels. Disease severity both before and after treatments was considered in the meta-analyses for accurate efficacy.

Our review however has several limitations. By including only those studies that provided both baseline and end of treatment alcohol outcomes, we were obliged to exclude several studies that did not allow us to draw precise conclusions focused on single medications. As an example, for certain medications, particularly those approved several years ago such as disulfiram, we included a limited number of studies and were unable to collect sufficient information on the medication. For the same reason, no secondary analyses were conducted to evaluate potential influences of other factors like gender or comorbid mental disorders. We neither estimated the effects of addon treatments nor defined the duration coverage of treatment end measures. In addition, as the majority of RCTs were conducted in the US or Europe, this narrow geographic distribution does not allow us to generalize our findings to other countries.

Previous reviews have failed to include baseline values of alcohol consumptions in their analyses. As an example, a recent review evaluated abstinence and heavy drinking without considering disease severity at baseline [157], other reviews focused on approved and off-label drugs including naltrexone, acamprosate and topiramate [158–160], and gabapentin and pregabalin [161]. Likewise, in 2023, a review focused on nine drugs (the three FDA-approved drugs and 6 off labels) did not include baseline values of alcohol use in their analyses [36]. None of the previous reviews adopted the method we used to consider both placebo and baseline values. These reviews evaluated the efficacy of single medications or classes of medications, while we have provided a broad overview of AUD participants recruited by those RCTs providing both baseline and end of treatment data on alcohol consumption.

In conclusion, the results of our study show that, despite the large placebo effect, AUD medications further reduce the intensity and frequency of alcohol consumption in people with AUD when analysis accounts for the influence of baseline AUD severity. These findings support the benefits of providing AUD medications to people with AUD to help them reduce alcohol consumption and related consequences.

Abbreviations

AUD: alcohol use disorder; CI: confidence interval; CT: clinical trial; %DD: rate of drinking days; DDD: drinks per drinking day; e effect: mean difference for each outcome between baseline and end of treatment values of both medication and placebo values; EMA: European Medicines Agency; FDA: Food and Drug Administration; GHB: gamma hydroxybutyric acid; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; %HDD: rate of heavy drinking days; MD: mean difference; PMC: PubMed Central; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PTSD: post-traumatic stress disorder; RCT: randomized clinical trial; RR: risk ratio; SD: standard deviation; SE: standard error.

CRediT authorship contribution statement

Roberta Agabio: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Hugo Lopez-Pelayo:** Writing – review & editing, Writing – original draft, Investigation. **Pol Bruguera:** Writing – review & editing, Investigation. **San-Yuan Huang:** Writing – review & editing. **Salvatore Sardo:** Methodology, Investigation. **Marta Pecina:** Writing – review & editing. **Evgeny M. Krupitsky:** Writing – review & editing. **Garrett M Fitzmaurice:** Writing – review & editing, Supervision, Methodology. **Zhicheng Lin:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

On behalf of all authors, I state that: (a) each author has contributed significantly to the work and agrees to submission of the manuscript, (b) none of the original material contained in the manuscript has been

submitted for consideration nor will any of it be published elsewhere, and (c) each author has no conflict of interest that is directly relevant to the content of this manuscript.

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Author contributors

ZL conceived the study, formed the research team, carried out data analyses, prepared result presentations, drafted and was responsible for finalizing the manuscript; RA led systematic review and was responsible for generating data extraction book and performing meta-analysis, and manuscript preparation; RA, ZL, HL and PB completed study selection processes; HLP, PB and ZL were responsible for contacting authors for additional information; SS contributed to data analysis; GF was responsible for statistics and streamlining findings; all authors contributed to manuscript finalization.

Reproducible research statement

Study protocol: Available on PROSPERO (CRD42022314927). Statistical code and data set: Not available.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2024.107454.

Data availability

Data will be made available on request.

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