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Pharmacological management of gambling disorder: A systematic review and network meta-analysis

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ABSTRACT

Background: Clinical guidelines remain unclear on which medications for gambling disorder are to be preferred in terms of efficacy and tolerability. We aimed to compare pharmacological treatments for gambling disorder in terms of efficacy and tolerability, using network meta-analysis (NMA).

Methods: Based on our pre-registered protocol [CRD42022329520], a structured search was conducted across broad range of databases, for double-blind randomized controlled trials (RCTs) of medications for gambling disorder. Data were independently extracted by two researchers. We used standardized mean differences (SMD) using Hedges' g to measure the efficacy outcomes, and for the effect for tolerability we used dropout rate due to medication side effects, expressed as odds ratio (OR). Confidence in the network estimates was assessed using the CINeMA framework. We followed the PRISMA-NMA guidelines for this work. Outcomes were gambling symptom severity and quality of life (for efficacy), and tolerability.

Findings: We included 22 RCTs in the systematic review and 16 RCTs (n = 977 participants) in the NMA. Compared with placebo, moderate confidence evidence indicated that nalmefene [Standardized Mean Difference (SMD): −0.86; 95 % confidence interval (CI: −1.32,-0.41)] reduced gambling severity, followed by naltrexone (SMD: -0.42; 95 %CI: (−0.85,0.01)). Naltrexone (SMD: -0.50; 95 %CI: (−0.85,-0.14)) and nalmefene (SMD: -0.36; 95 %CI: (−0.72,-0.01) were also more beneficial than placebo in terms of quality of life. Olanzapine and topiramate were not more efficacious than placebo. Nalmefene [Odds Ratio (OR): 7.55; 95 %CI: (2.24–25.41)] and naltrexone (OR: 7.82; 95 %CI: (1.26–48.70)) had significantly higher dropout due to side effects (lower tolerability) compared with placebo.

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Interpretation: Based on NMA, nalmefene and naltrexone currently have the most supportive evidence for the pharmacological treatment of gambling disorder. Further clinical trials of novel compounds, and analysis of individual participant data are needed, to strengthen the evidence base, and help tailor treatments at the individual patient level.

1. Introduction

Gambling disorder is a complex behavioural addiction, which affects individuals and those around them and has substantial public health implications worldwide [1]. It is characterized by persistent and recurrent gambling leading to negative consequences, including e.g. interpersonal conflict, serious financial problems, homelessness, mortgage foreclosure, and elevated risk of suicide [2,3]. Gambling disorder is currently classified as a behavioural addiction in the International classification of Disease 11th Edition (ICD-11) [4] and as a Substance-Related and Addictive Disorder in the Diagnostic and Statistical Manual 5th Edition (DSM-5-TR) [5].

Psychological interventions (i.e., gambling focused cognitive-behavioural therapy –CBT–, in its many variants) are widely used to treat gambling disorder [3]. However, there is no clear consensus about the most effective treatment strategies and the optimal sequencing of psychological and pharmacological options. Some international guidelines suggest pharmacological options (specifically, naltrexone), further to CBT, for treatment-resistant gambling disorder [6] or as an adjunct pharmacology to talking therapies or naltrexone as monotherapy [7]. Also, those guidelines recommend against the use of antidepressants (such as selective serotonin reuptake inhibitors, SSRIs) as monotherapy for gambling disorder, unless there is comorbid depression or anxiety.

A growing body of studies of pharmacological treatments for gambling is emerging. There have been previous attempts to pool evidence from these studies. A pairwise meta-analysis including 34 studies (open label, non-randomized and randomized control trials [RCTs], with or without concomitant psychological interventions), showed large effects for pharmacological treatments overall (Hedge's g = 1.35 in terms of global severity of gambling; medium effect size, g = 0.41 when including RCTs only) [8]. However, this analysis was not designed to compare different compounds, and additionally, did not find differences in effects between classes of medication [8].

A recent Cochrane systematic review and pairwise meta-analysis of the pharmacological interventions of disordered and problem gambling [9] used a major-category examination approach (e.g. "antidepressants", "opioid-antagonists") across 17 RCTs (n = 1193). The meta-analysis found evidence that antidepressants and mood stabilizers were not significantly better than placebo in treating gambling symptoms. Opioid antagonists (SMD: −0.46, 95 %CI (−0.74 to −0.19)) and atypical antipsychotics (SMD: −0.59, 95 %CI (−1.10 to −0.08)) were found to be beneficial in treating gambling symptoms versus placebo. However, the Cochrane meta-analysis only considered direct (head-to-head) comparisons, and this limited the number of comparisons included due to the paucity of head-to-head studies for gambling disorder [9]. Moreover, the Cochrane review and previous meta-analyses did not consider any quality of life outcomes, which are highly relevant outcomes in addition to gambling symptoms severity.

Thus, many important questions on the pharmacological treatment of gambling remain unanswered, including: 1) which individual compounds (even from those within the same class, e.g. opioid receptor antagonists) are the most efficacious for gambling disorder? 2) which are best tolerated medications when compared to each other? and 3) which medications have the strongest impact on quality of life?

Network meta-analysis (NMA) can address these crucial gaps in the field, by providing, under certain assumptions, comparative evidence on the efficacy and tolerability of two or more treatments, even when they have not been directly compared in the individual trials included in the NMA [10]. This evidence can then be used to rank or compare the effects of several interventions simultaneously [11], using an a priori stated research question and appropriate ranking metrics, which can help avoid common controversies which arise in comparative effectiveness research [12]. One of the advantages of NMAs is that combining direct and all possible indirect evidence from a network of interventions may increase the precision of the effect size estimate, even when there is direct evidence for that specific comparison [13]. Notably, while the useful insights produced by NMAs are well established, many NMAs are commissioned by industry, are not pre-registered, and never get published to allow for an equitable dissemination of knowledge and public health benefits [14]. At a time when the UK National Institute for Health and Care Excellence (NICE) is developing initial clinical guidelines for gambling disorder [15], an NMA is urgently needed to allow for a thorough and up-to-date examination of evidence supporting pharmacological treatment(s) for gambling disorder. Such work is also likely to directly inform other international guidelines (whether new or updated) in the future. Therefore, we conducted the first NMA to compare the effects of pharmacological treatments on symptoms and quality of life, in the management of gambling disorder, as well as the relative tolerability of such treatments.

2. Methods

The study protocol was pre-registered on the PROSPERO International prospective register of systematic reviews [Registration number: CRD42022329520, available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=329520]. This study reporting followed the PRISMA-NMA guidelines [16] (eAppendix 1 in Supplement 1). The PRISMA-NMA checklist is shown in the supplementary material (eAppendix 2 in Supplement 1).

2.1. Search strategy

We searched for published and unpublished data. The search strategy and syntax were determined by consensus among the co-authors, with further expert refinement from Systematic Review Solutions Ltd. (SRS), an independent professional company specialising in meta-research. The search strings used and full list of electronic databases and clinical trial registries in which the search was conducted are available in the supplementary material (eAppendix 3 in Supplement 1). The initial search was conducted on the 13th of July 2022 and then updated on the 19th of February 2024.

2.2. Eligibility criteria

We included RCTs comparing an active medication vs. placebo, or active medications with each other, for the treatment of Gambling Disorder/Pathological Gambling. Trials with a cross-over design were included if data from the pre cross-over phase were available, to avoid carry-over effects [17]. We included only studies of adults (>18 yrs) with a primary DSM (III onwards) or ICD (9 onwards) diagnosis of Gambling Disorder/Pathological Gambling. For the NMA, we excluded studies which had insufficient data, or those that specifically included a primary psychiatric condition in the whole sample, other than gambling as part of inclusion criteria.

2.3. Data extraction and outcomes

Details on data extraction can be found in the supplementary

material (eAppendix 1 in Supplement 1).

2.4. Data synthesis

We calculated the standardized mean differences (SMD) using Hedges' g to measure the efficacy outcomes, because different scales were used to assess the same outcome. The measure of effect for tolerability was the dropout rate due to medication side effects, expressed as odds ratio (OR). Study arms randomizing the same compound at different dose were merged into a single arm. First, we conducted conventional pairwise meta-analyses with a random-effects model for all outcomes and treatment comparisons with at least two studies, [18] followed by frequentist NMA for all outcomes using random-effects models [19]. We also performed a sensitivity analysis by conducting NMA for gambling severity, by analysing each scale of gambling severity separately, and restricting the analysis to mean difference (MD) only. We used STATA®/IC 18.1 (StataCorp LLC, College Station, TX, USA, the *network* command [20] and the *network graph* package [21]) to perform all analyses and plotting.

2.5. Study risk of bias assessment and confidence in Network Meta-Analysis estimates (CINeMA)

We used the Confidence in Network Meta-Analysis (CINeMA) framework to assess the confidence in the estimates obtained from the NMA. More information about how CINeMA was implemented is presented in the supplementary material (eAppendix 4 in Supplement 1).

Table 1
Overview of literature included in the NMA.

#	First Author (Year)	Study Type and Design	Arms	N randomized Active/ placebo	Duration	Statistical analysis	Was active treatment superior to placebo in the original publication?
1	Alho et al. [23] (2022)	Double Blind RCT Parallel design, 2 arms	naloxone vs. placebo	62/64	12-weeks	ITT, Linear mixed-effects model	No
2	De Brito et al. [24] (2017)	Double Blind RCT Parallel design, 2 arms	topiramate vs. placebo	18/20	12-weeks	No ITT, imputation method not clearly stated	Yes
3	Kovanen et al. [31] (2016)	Double Blind RCT Parallel design, 2 arms	naltrexone vs. placebo	50/51	20-weeks	Linear Random Effects model (outcome-time)	No
4	McElroy et al. [32] (2008)	Double Blind RCT Parallel design, 2 arms	olanzapine vs. placebo	21/21	12-weeks	ITT Random-effects regression (treatment, time and treatment × time interaction)	No
5	Berlin et al. [33] (2013)	Double Blind RCT Parallel design, 2 arms	topiramate vs. placebo	20/22	14-weeks	Completers only (ITT with regression used for CGI-I only, not included in NMA due to data format limitations)	No
6	Grant et al. [37] (2010)	Double Blind RCT Parallel design, 3 arms	nalmefene vs. placebo	159/74	16-weeks	Completers only (ITT with MLM used in the paper but not available for NMA due to data format limitations)	Yes (only for those who received full titration for at least 1 week)
7	Grant et al. [36] (2008)	Double Blind RCT Parallel design, 2 arms	naltrexone vs. placebo	58/19	17-weeks	ITT linear mixed model, the covariance structure of repeated visit data was modelled as autoregressive	Yes
8	Fong et al. [25] (2008)	Double Blind RCT Parallel design, 2 arms	olanzapine vs. placebo	11/12	6-weeks	ITT, mixed model repeated measures approach	No
9	Black et al. [26] (2008)	Double Blind RCT Parallel design, 2 arms	bupropion vs. placebo	18/21	12-weeks	ITT, linear mixed-effects model (treatment, time and treatment × time interaction)	No
10	Grant et al. [35] (2006)	Double Blind RCT Parallel design, 4 arms	nalmefene vs. placebo	156/51	16-weeks	Linear mixed-effects model treatment, time, site, treatment × time, treatment × site for all participants with two data points	Yes
11	Dannon et al. [27] (2005)	Single-blinded (rater) RCT Parallel design, 2 arms	naltrexone vs. bupropion	17/19	12-weeks	ITT method not clearly stated	N/A
12	Kim et al. [30] (2002)	Double Blind RCT Parallel design, 2 arms	paroxetine vs. placebo	23/22	8-weeks	ITT with LOCF for all participants with two data points	Yes
13	Grant et al. [34] (2003)	Double Blind RCT Parallel design, 2 arms	paroxetine vs. placebo	36/40	16-weeks	ITT with LOCF for all participants with two data points	No
14	Kim et al. [28] (2001)	Double Blind RCT Parallel design, 2 arms	naltrexone vs. placebo	20/25	11-weeks	LOCF for all participants who reached week 6, according to a priori hypothesis	Yes
15	Hollander et al. [29] (2000)	Double Blind RCT Cross-over design, 2 arms	fluvoxamine vs. placebo	6/7	8-weeks	Completers only	Yes
16	Grant et al. [38] (2024)	Double Blind RCT Parallel design, 2 arms	silymarin vs placebo	17/26	8-weeks	ITT, Linear mixed-effect model treatment, time, treatment × time	No

Legend: RCT = Randomized Control Trial; ITT = Intend-to-Treat; LOCF = Last Observation Carried Forward; MLM = Mixed Linear Models; CGI-I = Clinical Global Impression-Improvement; NMA = Network Meta-Analysis.

3. Results

The search yielded 4261 references from electronic databases and 71 hits from clinical trial registries. A final set of 22 eligible RCTs were selected for inclusion in the systematic review. Inter-rater reliability, determined using the Finn coefficient, was 0.863 (good) for the initial search and 0.991 (excellent) for the updated search, calculated using R [package "irr"]([22])). All disagreements were resolved by consensus. Six of these RCTs were excluded from the NMA either due to insufficient data ($n = 4$), or the inclusion of a primary psychiatric co-concurrent condition in the whole sample ($n = 2$), which we deemed violated the NMA transitivity assumption. Randomized participants were ~ 49 % males (674/1371), and their ages ranged from 29.7 to 51.5 years (Mean = 43.56; SD = 5.81). Each of the 16 RCTs included in the NMA (total participants: 977) contributed to one pairwise comparison, totalling 16 comparisons across studies (16 for gambling severity, 12 for tolerability, nine for quality of life). The main characteristics of those studies included in the NMA ([22–37]) are presented in Table 1.

Full details about the search results are presented in the PRISMA flowchart (Fig. 1). Full characteristics of the studies, RoB 2 assessment and ORBIT classifications are presented in the supplementary material (eAppendix 5 in Supplement 1).

Comparisons included in the NMA comprised nine different medications: three opioid receptor antagonists, (naltrexone, nalmefene, naloxone); two selective serotonin reuptake inhibitors (SSRIs - paroxetine and fluvoxamine); one mood stabilizer/antiepileptic (topiramate); one norepinephrine–dopamine reuptake inhibitor (NDRI, bupropion); one antipsychotic (olanzapine); and one plant-based antioxidant (silymarin). Six more medications were included in the studies retained in the systematic review only: lithium, sertraline, clomipramine, baclofen, acamprosate and *n*-acetyl-cysteine (NAC). We did not identify any clear evidence that the transitivity assumption did not hold.

Results from the conventional pairwise meta-analysis for each outcome and within each treatment comparison are showed in the forest plots in the supplementary material (eAppendix 6 in Supplement 1). Fig. 2 shows the network plots for efficacy on gambling severity, tolerability and efficacy on quality of life.

Forest plots of NMA results for gambling severity, tolerability, and quality of life showing the network estimates for each treatment versus placebo are presented in Fig. 3. The results of the NMA for efficacy on gambling severity and tolerability for all possible comparisons are shown in Table 2. The results of the NMA for quality of life are presented in Table 3. The NMA showed that, in terms of gambling severity, among nine active drugs and placebo, nalmefene [SMD: −0.86; 95 % confidence interval (CI: −1.32, −0.41)] was associated with higher efficacy compared with placebo, followed by naltrexone (SMD: -0.42; 95 %CI: (−0.85, 0.01)). Across medications, we identified a superiority of nalmefene over naloxone (SMD: 1.01; 95 %CI: (0.20, 1.82)). In terms of tolerability, nalmefene (OR: 0.13; 95 %CI: (0.04, 0.45)) and naltrexone (OR: 0.13; 95 %CI: (0.02, 0.80)) were found to be the least tolerated (i.e., having the highest dropout risk due to side effects) as compared with placebo. We did not find any significant difference between active treatments on tolerability. Naltrexone (SMD: -0.50; 95 %CI: (−0.85, −0.14)) and nalmefene (SMD: -0.36; 95 %CI: (−0.01, −0.72)) were associated with higher quality of life outcomes compared with placebo. Across medication treatments, we identified a superiority of nalmefene over naloxone (SMD: -1.01; 95 %CI: (−1.82, −0.20)) on gambling severity and naltrexone over naloxone (SMD: -0.61; 95 %CI: (−1.13, −0.09)) on quality of life. Sensitivity analyses did not indicate any material changes the main NMA results. Main NMA results from sensitivity analyses of gambling severity are presented in the supplementary material (eAppendix 7 in Supplement 1).

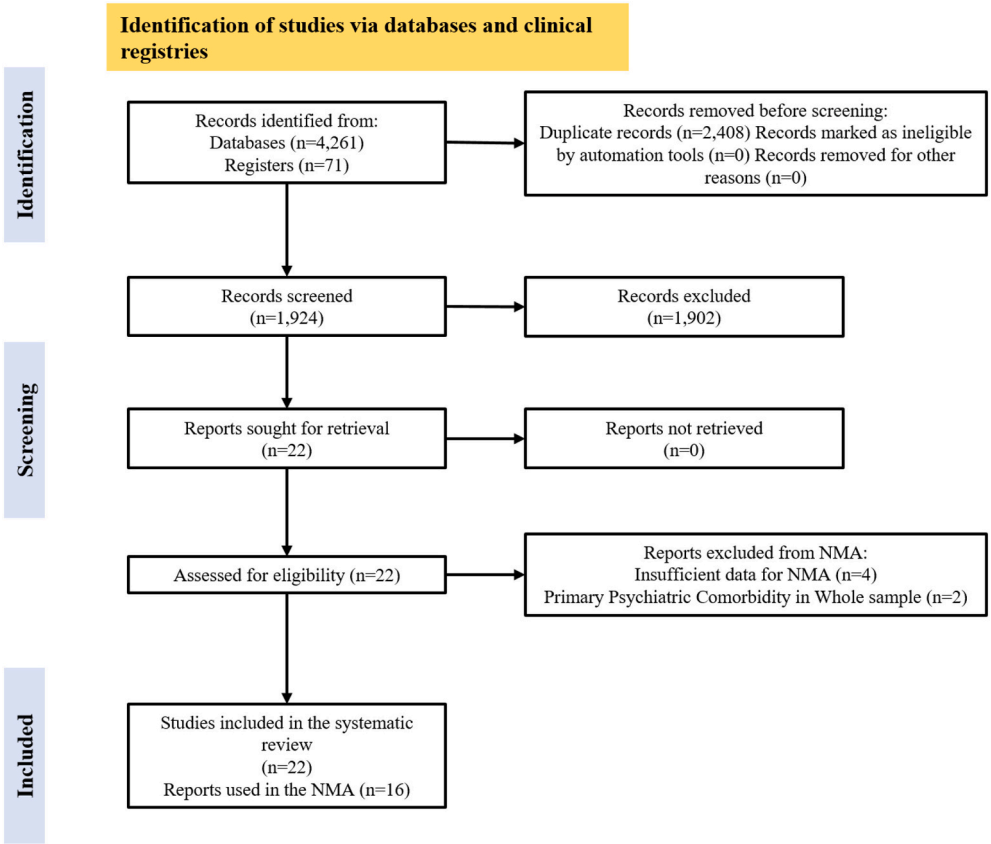

Fig. 1. PRISMA Flowchart.
Legend: PRISMA flowchart.

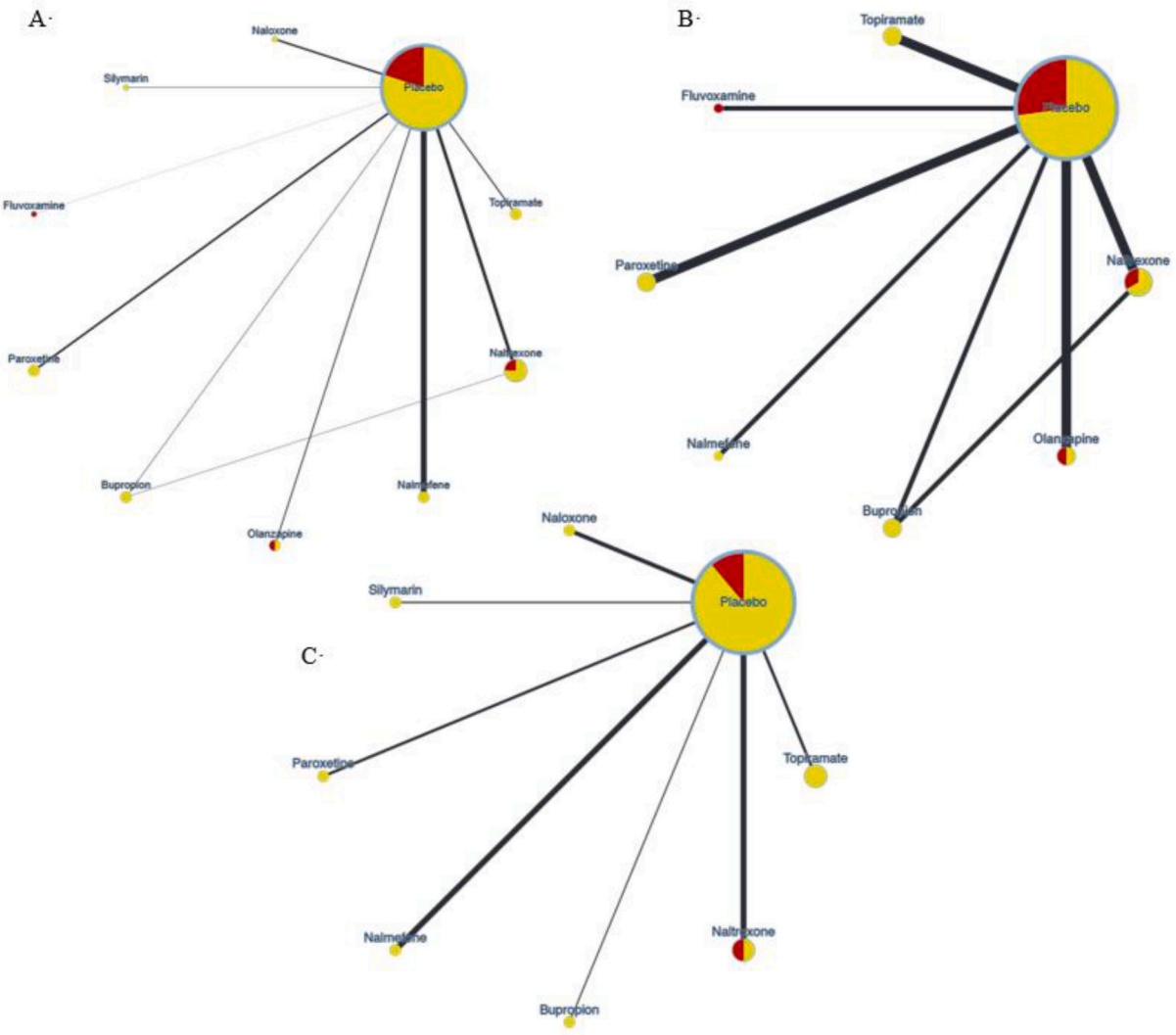

Fig. 2. Network plots.
Legend: Network plots for: (A) – Efficacy on gambling severity (16 studies); (B) tolerability (12 studies); (C) Efficacy on quality of life (9 studies). Size of nodes represents the number of studies in each comparison. Width of the edges represents the number of participants in each comparison. Colour of nodes is according to Rob 2 i.e. green = low, yellow = some concerns, red = high. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Heterogeneity measures (i.e., common standard deviation heterogeneity estimates) and results from incoherence assessment for all outcomes are presented in the supplementary material (eAppendix 8 in Supplement 1). We found low heterogeneity within each network and we did not find evidence of incoherence. In ROB-MEN, since all comparisons had fewer than 10 studies, the construction of funnel plots and testing for small-study effects was not possible.

Treatment ranking measures based on NMA results are presented in detail in the supplementary material (eAppendix 9 in Supplement 1) for primary outcomes. Sensitivity analysis for low risk of bias studies was not possible due to all available studies having scored "some concerns" or above.

3.1. Confidence in network meta-analysis estimates based on CINeMA

The confidence in the NMA estimates ranged between very low to high. Moderate confidence was assigned to most of the comparisons versus placebo. In particular, we were moderately confident that nalmefene and naltrexone were the most effective when compared to placebo. We were highly confident that nalmefene was the least tolerated treatment when compared to placebo. The main reasons for downgrading confidence were within-study-bias, imprecision and heterogeneity. Full CINeMA assessment for gambling severity, tolerability, quality of life and sensitivity analyses are presented in the supplementary material (eAppendix 10 in Supplement 1).

4. Discussion

This is the first NMA of RCTs for the pharmacological management of gambling disorder. Based on NMA, we found moderate confidence evidence indicating that the opioid antagonist nalmefene was the most efficacious treatment in reducing gambling symptom severity. The other opioid antagonist often used in clinical practice, naltrexone, had moderate confidence evidence of being the second most efficacious treatment and the highest probability of improving quality of life, but with very low confidence in the evidence for the latter. However, both these treatments were associated with significantly higher dropout, due to side effects, than placebo, with confidence of the evidence from moderate (naltrexone) to high (nalmefene). Both nalmefene (in gambling severity, low confidence) and naltrexone (in quality of life, low

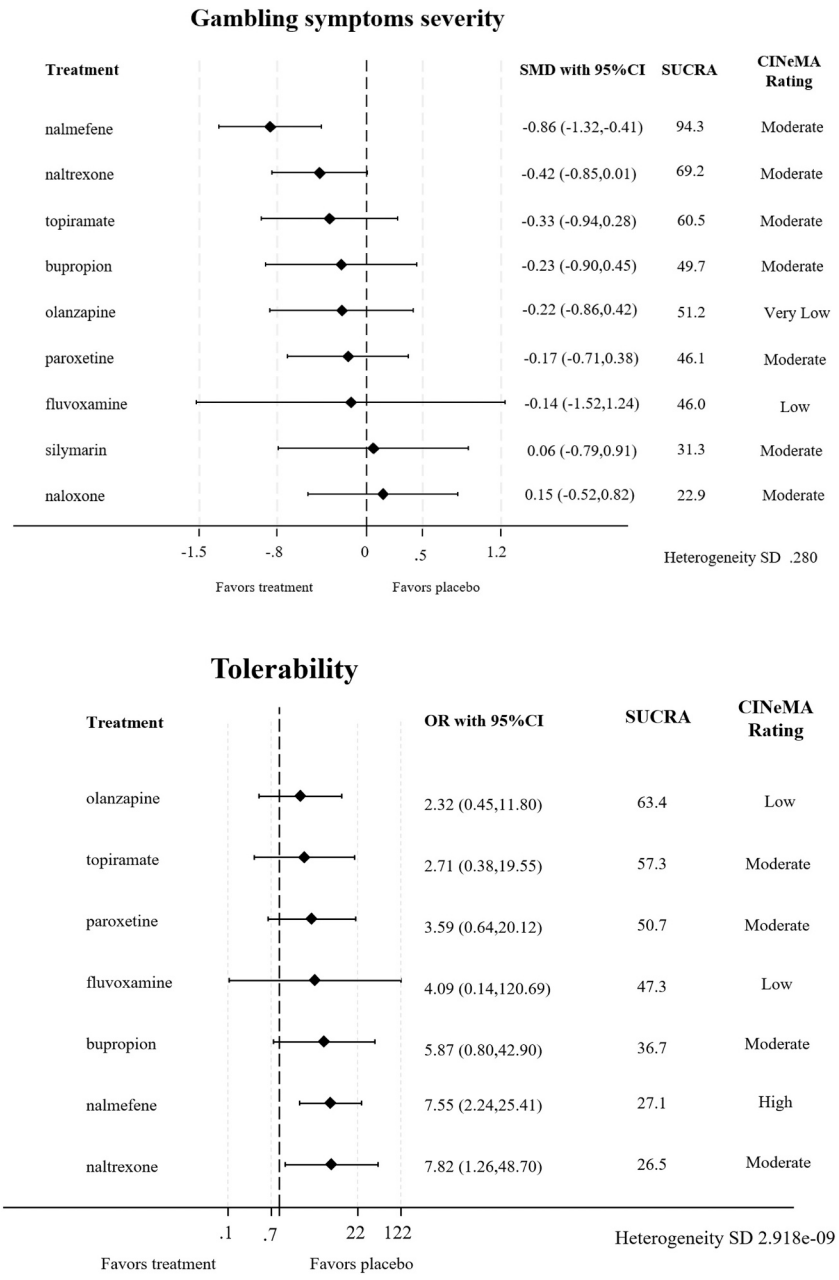

Fig. 3. Forest plots of Network Meta-Analysis results for gambling severity, tolerability and quality of life.
Legend – Forest plots of NMA results; SUCRA = surface under the cumulative ranking curve, expressed in percentages; CINeMA = Confidence in network meta-analysis; SD = standard deviation.

confidence) showed superiority against naloxone in indirect comparisons. We did not find any other significant differences among medications. Naloxone did not differentiate from placebo in the one available study [23]. Notably, naloxone is an opioid antagonist but has a very short duration of effect (short half-life) [39], so lack of efficacy is perhaps unsurprising. Overall, these results provide useful insights that can support clinical decision-making around the pharmacological management of gambling. There are differences between opioid receptor antagonists in how they bind to brain receptors. For example, naltrexone has a preference for mu opioid receptors (MOR) and binds to a lesser extend to kappa opioid receptors (KOR), while nalmefene binds with similar strength to MOR and KOR [39]. Such differences could theoretically influence treatment effects and tolerability profiles, but ultimately, both medications are thought to dampen dopamine neurotransmission in the nucleus accumbens and associated motivational neurocircuitry, reducing gambling excitement and craving [40]. In the context of other disorders, it has been argued that nalmefene may have advantages over naltrexone in terms of its bioavailability, ability to bind differentially to particular brain opioid receptors (stronger affinity to kappa opioid receptors, mechanistically relevant in exerting antidepressant effects, but can also alter the side effect profile), [41,42] and its apparent absence of dose-dependent liver toxicity (for discussion see Soyka) [43]. However, given that the side-effect profiles and overall tolerability can impact on the treatment's effectiveness in clinical practice, it is important to cautiously interpret the efficacy results and pursue further ascertainment of naltrexone's and nalmefene's effectiveness. Further to that, it is important to acknowledge that there is currently no licensed pharmacological option for the treatment of

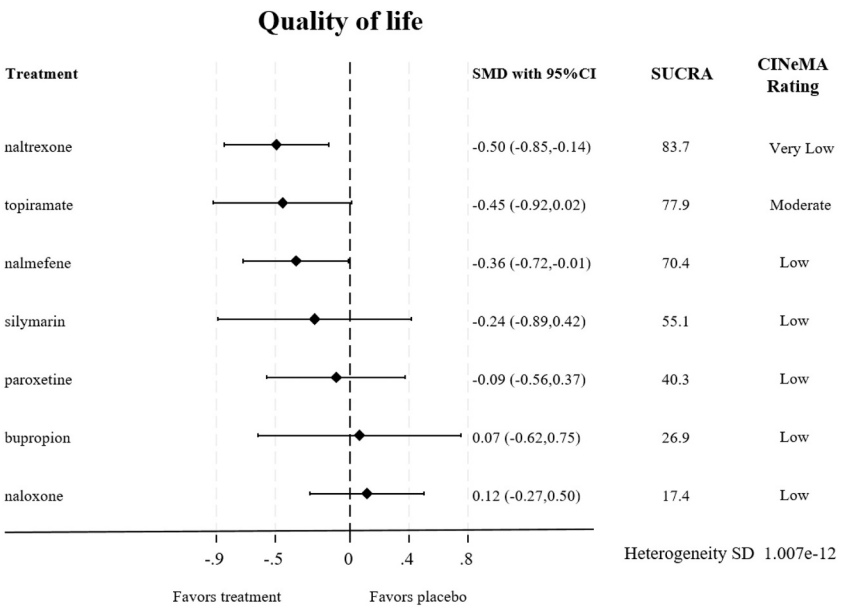

Fig. 3. (*continued*).

gambling disorder, so that any such prescriptions would be off-label. It is, however, important to highlight the distinction between "off-label" and lacking supportive evidence for efficacy, as often prescribing off-label is a common feature of prescribing in general psychiatry and having a license does not constitute proof of efficacy or safety [44]. The pros and cons of such prescriptions need to be considered on a case-by-case basis and a balance has to be struck between undue therapeutic conservatism that limits patient choice and reduces chances of optimising treatment approaches (i.e. in this case by restricting access to valid medication options) and overenthusiastic approaches which may steer away from best-treatment approaches [44] (e.g. in this case by over-relying on pharmacotherapies for GD while withholding other evidence-based options).

Contrary to a previous Cochrane review [9], this NMA showed that olanzapine was not statistically better than placebo in terms of primary or secondary efficacy outcomes. Due to combining direct and indirect evidence, as well as head-to-head comparisons, an NMA analysis may provide more accurate and complete results as compared to a conventional pairwise meta-analysis. Our NMA indicated that olanzapine is a less suitable treatment option for gambling disorder than previously considered, due to lack of efficacy. We found low confidence evidence indicating that olanzapine was the most well-tolerated among treatments. This is in contrast with the side effect profile reported more widely in the psychiatric literature [45]. However, considering the lack of evidence of its efficacy, a preferable tolerability profile becomes less relevant.

Furthermore, we observed moderate confidence evidence that topiramate was not different from placebo in NMA on any of the primary or secondary outcomes, however it achieved relatively good rankings in all outcomes. It is also important to consider that in general terms the placebo effects in the pharmacological trials of GD are of large magnitude, making it challenging to detect a true active effect of medication [46]. Topiramate has a complex pharmacology and has been used in other areas of addiction psychiatry. Therefore, given the relatively good rankings, topiramate might merit further evaluation in clinical trials before being dismissed as a treatment option for gambling disorder.

4.1. Limitations

Several limitations should be considered, reflecting both limitations of the included RCTs and of our NMA. In terms of limitations of the included RCTs, 81.25 % [13/16] of them were judged of moderate quality and 18.75 % [3/16] of low quality at the RoB2, mainly due to concerns over bias in the selection of reported result, but also missing outcome data. This reflects the state of the field and the fact that gambling disorder has been relatively neglected as compared to other mental health conditions, with most studies having been completed more than a decade ago. High quality RCTs are scarce and, in our view, this highlights further the importance of this NMA analysis in guiding the design of future RCTs. Moreover, the vast majority of the samples included both genders of middle aged participants. Differential gender effects could not be examined and the results cannot be extrapolated to other age groups e.g. older people or children and adolescents. Furthermore, while we did not detect significant heterogeneity across studies overall, there were some methodological differences among studies that need to be considered. Different dosing schemes could have accounted for some heterogeneity – for example, Kovanen et al. [31] used as required (PRN) dosing of naltrexone, as opposed to previous studies which used daily schemes with titration to a maximum tolerated dose using clinical judgement [28,36]. Similarly, the two nalmefene studies used different dosing schemes (20 mg/40 mg vs. 25 mg/50 mg/100 mg) [35,37], and dose can potentially influence efficiency and tolerability outcomes, including dropout rates. In terms of limitations of our NMA, due to the presence of few closed loops in our network, we were not able to assess incoherence in all areas of our network. In the loops assessed we did not find evidence of incoherence. Moreover, due to the limited number of available studies, we were not able to meaningfully perform meta-regression to assess whether duration of treatment or mode of administration or dosing moderated effects in our network. However, most of the included studies had a similar duration of treatment between 12 and 20 weeks and used oral treatments. Furthermore, we did not have enough data to test effect modifiers like study sponsorship, comorbid psychiatric conditions, and mean baseline severity. Similarly, due to the small overall number of studies, we were not able to produce funnel plots to graphically identify reporting bias in ROB-MEN; while we could not detect such biases, this does not mean that those do not exist. Furthermore, some of the early studies in the field used Last-Observation-carried-Forward (LOCF) approach which can bias results when there is an interaction of time × outcome. We opted to use completers only data when these were available (e.g. in Kim et al. 2001). Adherence to intention-to-treat (ITT) principles as well as fostering wider collaborations to support data synthesis using individual

Table 2
NMA results for all possible comparisons for gambling severity (lower triangle) and tolerability (upper triangle).

placebo	3.59 (0.64,20.12)	7.82 (1.26,48.70)	NA	2.71 (0.38,19.55)	NA	3.59 (0.64,20.12)	7.55 (2.24,25.41)	4.09 (0.14,120.69)	5.87 (0.80,42.90)
0.22 (−0.42,0.86)	olanzapine	3.38 (0.29,39.08)	NA	1.17 (0.09,15.14)	NA	1.55 (0.14,16.60)	3.26 (0.43,24.84)	1.77 (0.04,75.55)	2.54 (0.19,33.14)
0.42 (−0.01,0.85)	0.20 (−0.57,0.97)	naltrexone	NA	0.35 (0.02,5.12)	NA	0.46 (0.04,5.67)	1.04 (0.12,9.31)	0.52 (0.01,24.52)	0.75 (0.19,2.98)
−0.15 (−0.82,0.52)	−0.37 (−1.30,0.56)	−0.57 (−1.36,0.23)	naloxone	NA	NA	NA	NA	NA	NA
0.33 (−0.28,0.94)	0.11 (−0.78,0.99)	−0.09 (−0.83,0.65)	0.48 (−0.43,1.38)	topiramate	NA	1.32 (0.10,18.22)	2.78 (0.27,28.29)	1.51 (0.03,75.96)	2.17 (0.13,35.73)
−0.06 (−0.91,0.79)	−0.28 (−1.35,0.78)	−0.48 (−1.43,0.47)	0.09 (−1.00,1.17)	−0.39 (−1.44,0.65)	silymarin	NA	NA	NA	NA
0.17 (−0.38,0.71)	−0.06 (−0.89,0.78)	−0.25 (−0.94,0.43)	0.31 (−0.55,1.17)	−0.17 (−0.98,0.65)	0.23 (−0.78,1.23)	paroxetine	2.10 (0.26,17.30)	1.14 (0.03,50.82)	1.64 (0.12,22.72)
0.86 (0.41,1.32)	0.64 (−0.15,1.43)	0.44 (−0.18,1.07)	1.01 (0.20,1.82)	0.53 (−0.23,1.29)	0.92 (−0.04,1.89)	0.70 (−0.01,1.41)	nalmefene	0.54 (0.01,19.75)	0.78 (0.08,8.00)
0.14 (−1.24,1.52)	−0.08 (−1.61,1.44)	−0.28 (−1.73,1.17)	0.29 (−1.25,1.82)	−0.19 (−1.70,1.32)	0.20 (−1.42,1.82)	−0.03 (−1.51,1.46)	−0.72 (−2.18,0.73)	fluvoxamine	1.44 (0.03,72.75)
0.23 (−0.45,0.90)	0.00 (−0.93,0.94)	−0.19 (−0.88,0.49)	0.37 (−0.58,1.32)	−0.10 (−1.01,0.81)	0.29 (−0.80,1.37)	0.06 (−0.80,0.93)	−0.64 (−1.45,0.18)	0.09 (−1.45,1.62)	bupropion

Legend: Lower triangle: SMD and 95 %CI in brackets for efficacy on gambling severity; read from left to right, positive scores favour treatment on the right (better treatment effect). Upper triangle: tolerability assessed with ORs from drop outs due to side effects and relative 95 %CI; read from right to left; ORs below 1 favour treatment on the left (better tolerated). Note: Alho et al. 2022 (naloxone vs. placebo) and Grant et al. 2024 (silymarin vs. placebo) were excluded from tolerability analysis due to non-events in both treatment arms.

participant data (IPD) is critical for the future. Finally, while NMAs, in general, do not generate randomized evidence, they do provide observational evidence and helpful insights into the clinical dilemma of choosing between pharmacological options. Therefore, while NMA allows for indirect head-to-head comparisons, those could theoretically be better estimated from real-life RCTs. In practice, though, this can be prohibitively expensive and time consuming.

4.2. Implications of the results for practice, policy, and future research

The current NMA provides the highest level of evidence synthesis to inform clinical practice as well as national and international treatment guidelines in terms of pharmacological options that should be considered for gambling disorder. Based on the NMA findings, nalmefene and naltrexone should currently be regarded as having the best available evidence for efficacy in the treatment of gambling disorder. However, there are limitations applicable in this data synthesis mainly stemming from the relatively small number and variable quality of reporting of available RCTs. In the absence of direct head-to-head comparisons of these two medications in gambling disorder, and rigorous health-economic evaluations, we would suggest that both are retained equally as first-line pharmacological treatment options. Retaining several options may also reduce the likelihood of patients having no feasible pharmacological treatment option – such as if one medication is not available in a particular geographical area/country, or in the case of supply disruptions.

Given the limited number of treatment options identified in the current NMA, and the high public health priority of gambling disorder [3,47], further large-scale clinical trials are urgently needed in relation to these and other medications for gambling disorder. A major reason for the low yearly rate (<1/year) of pharmacological RCTs for gambling disorder over the past decade, and relatively small number of studies accrued over time, is the lack of independent research funding being made available. Therefore, we encourage funding bodies to support independent clinical trials into gambling disorder. A summary of recommendations for future clinical trials for gambling disorder are made in Box 1, based on the findings of this review.

Analytic code availability

Example STATA code and package information for NMA can be found in the supplementary material (eAppendix 11 in Supplement 1).

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Author contribution

KI, CT, JES, SC, SRC contributed to the design of the study; CT led the initial pre-registration; CT and JES led the search and screening process; KI, JES, CDG, SRC contributed to data collection. KI, JES, CDG and SRC had access to the data. KI and CDG conducted the NMA analysis and take responsibility for the integrity and accuracy of the data analysis itself. SHW and VP led and equally contributed on the RoB2 scoring. All authors have intellectually contributed and reviewed the final submitted manuscript. All authors accept responsibility for the conduct of the study and its integrity.

CRediT authorship contribution statement

Konstantinos Ioannidis: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation,

Table 3
NMA results for all possible comparisons for quality of life.

topiramate							
−0.45 (−0.92,0.02)	placebo						
−0.36 (−1.02,0.30)	0.09 (−0.37,0.56)	paroxetine					
0.04 (−0.55,0.63)	0.50 (0.14,0.85)	0.40 (−0.18,0.99)	naltrexone				
−0.57 (−1.18,0.03)	−0.12 (−0.50,0.27)	−0.21 (−0.81,0.39)	−0.61 (−1.13,−0.09)	naloxone			
-0.09 (−0.68,0.50)	0.36 (0.01,0.72)	0.27 (−0.32,0.86)	−0.13 (−0.64,0.37)	0.48 (−0.04,1.00)	nalmefene		
−0.22 (−1.02,0.59)	0.24 (−0.42,0.89)	0.15 (−0.66,0.95)	−0.26 (−1.00,0.48)	0.35 (−0.40,1.11)	−0.12 (−0.87,0.62)	silymarin	
−0.52 (−1.35,0.31)	−0.07 (−0.75,0.62)	−0.16 (−0.99,0.67)	−0.56 (−1.33,0.21)	0.05 (−0.73,0.84)	−0.43 (−1.20,0.34)	−0.30 (−1.25,0.64)	bupropion

Legend: Lower triangle: SMD and 95 %CI in brackets for quality of life; read from left to right, positive scores favour treatment on the right (better treatment effect).

Box 1
Considerations for future clinical trials of pharmacological interventions for gambling

- Full data reporting and adherence to intention to treat principles.
- Fostering wider collaborations and research design and dissemination practices to support data synthesis using individual participant data (IPD) is critical
- Standardization of treatment duration and follow up
- Nalmefene and naltrexone show the best efficacy profile, however they coupled with relatively lower tolerability versus other compounds or placebo. To address tolerability issues, clinicians should initially consider doses found to be effective but not in the high range e.g. 50 mg–100 mg for naltrexone, 50 mg or less for nalmefene. At the same time, it should be appreciated that higher doses may be needed in particular cases, such as in treatment non-response or partial response.
- Topiramate ranked relatively highly in terms of efficacy and tolerability profile, but it was not statistically better than placebo. Further studies are warranted to determine if this is an issue with statistical power.
- Due to its good tolerability profile, future controlled studies should further examine NAC to assess its efficacy.

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Declaration of competing interest

Dr. Ioannidis is clinical lead for the Southern Gambling Service and receives a stipend from Elsevier for journal editorial work. Professor Chamberlain is service director for the NHS Southern Gambling Service. Professor Chamberlain receives a stipend from Elsevier for journal editorial work. Professor Bowden-Jones is National Clinical Advisor on Gambling Harms in the UK, and is Director of the National Problem Gambling Clinic and the National Centre for Gaming Disorders. Professor Bowden-Jones' clinics receive funding from NHS England and CNWL NHS Trust. Professor Bowden-Jones' clinics previously received funding from GambleAware. Cinzia Del Giovane's time on the project was funded partly through the grant funding to SRC. Dr. Grant has received research grants from Janssen and Biohaven Pharmaceuticals. He receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies and has received royalties from Oxford University Press, American Psychiatric Publishing, Inc., Norton Press, and McGraw Hill. None of the authors have conflicts of interest in relation to the gambling or gaming industry. None of the authors accept voluntary donations from the gambling or gaming industry either personally or in terms of institutional funds held in their name.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2024.152566.

Data availability

The data that support the findings of this study are available upon reasonable request from the corresponding author (e.g. for peer review purposes) and will be published upon acceptance of the manuscript.

References

[1] The Lancet Public Health. Gambling: a neglected public health issue. Lancet Public Health 2021;6:e1. https://doi.org/10.1016/S2468-2667(20)30290-5.
[2] Grant JE, Chamberlain SR. Gambling and substance use: Comorbidity and treatment implications. Prog Neuro-Psychopharmacol Biol Psychiatr 2020;99:109852. https://doi.org/10.1016/J.PNPBP.2019.109852.
[3] Bowden-Jones H, Hook RW, Grant JE, Ioannidis K, Corazza O, Fineberg NA, et al. Gambling Disorder in the United Kingdom: key research priorities and the urgent need for independent research funding. Lancet Psychiatry 2022;9:321. https://doi.org/10.1016/S2215-0366(21)00356-4.
[4] ICD-11. ICD-11 for Mortality and Morbidity Statistics. 2021. https://icd.who.int/browse11/l-m/en#/http%3A%2F%2Fid.who.int%2Ficd%2Fentity%2F263852475 (accessed September 19, 2021).
[5] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Diagnostic Stat Man Ment Disord. 2022. doi:10.1176/APPI.BOOKS.9780890425787.
[6] Bowden-Jones H, Drummond C, Thomas S. Rapid evidence review of the evidence-based treratment for Gambling disorder in Britain. RCPsych 2016:1–5. https://www.rcpsych.ac.uk/docs/default-source/members/faculties/addictions-psychiatry/addictions-resources-for-specialists-rapid-evidence-for-gambling.pdf?sfvrsn=736e144a_2.
[7] Thomas SA, Merkouris SS, Radermacher HL, Dowling NA, Misso ML, Anderson CJ, et al. Australian guideline for treatment of problem gambling: an abridged outline. Med J Aust 2011;195:664–5. https://doi.org/10.5694/MJA11.11088.
[8] Goslar M, Leibetseder M, Muench HM, Hofmann SG, Laireiter AR. Pharmacological Treatments for Disordered Gambling: A Meta-analysis. J Gambl Stud 2019;35:415–45. https://doi.org/10.1007/S10899-018-09815-Y.
[9] Dowling N, Merkouris S, Lubman D, Thomas S, Bowden-Jones H, Cowlishaw S. Pharmacological interventions for the treatment of disordered and problem gambling. Cochrane Database Syst Rev 2022;2022. doi:10.1002/14651858.CD008936.PUB2/MEDIA/CDSR/CD008936/IMAGE_N/NCD008936-CMP-014.04.SVG.
[10] Ades AE, Welton NJ, Dias S, Phillippo DM, Caldwell DM. Twenty years of network meta-analysis: Continuing controversies and recent developments. Res Synth Methods 2024. https://doi.org/10.1002/JRSM.1700.
[11] Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–17. https://doi.org/10.1177/0272989X12458724.

[12] Salanti G, Nikolakopoulou A, Efthimiou O, Mavridis D, Egger M, White IR. Introducing the Treatment Hierarchy Question in Network Meta-Analysis. Am J Epidemiol 2022;191:930–8. https://doi.org/10.1093/AJE/KWAB278.
[13] Cipriani A, Higgins JPT, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013;159:130–7. https://doi.org/10.7326/0003-4819-159-2-201307160-00008.
[14] Schuit E, Ioannidis JPA. Network meta-analyses performed by contracting companies and commissioned by industry. Syst Rev 2016:5. https://doi.org/10.1186/S13643-016-0377-3.
[15] NICE. Project information | Harmful gambling: identification, assessment and management | Guidance | NICE. https://www.nice.org.uk/guidance/indevelopment/gid-ng10210; 2023 (accessed July 21, 2023).
[16] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84. https://doi.org/10.7326/M14-2385.
[17] Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5:727–38. https://doi.org/10.1016/S2215-0366(18)30269-4.
[18] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Editio. Chichester (UK): John Wiley & Sons; 2019.
[19] Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80–97. https://doi.org/10.1002/JRSM.1037.
[20] White I. White, Ian. Network meta-analysis. Stata J 2015;15:951–85.
[21] Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. PloS One 2013;8:e76654. https://doi.org/10.1371/JOURNAL.PONE.0076654.
[22] Gamer M, Lemon J, Fellows I, Singh P. Various Coefficients of Interrater Reliability and Agreement - Package "irr". CRAN Proj 2022. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://cran.r-project.org/web/packages/irr/irr.pdf.
[23] Alho H, Mäkelä N, Isotalo J, Toivonen L, Ollikainen J, Castrén S. Intranasal as needed naloxone in the treatment of gambling disorder: A randomised controlled trial. Addict Behav 2022;125:107127. https://doi.org/10.1016/J.ADDBEH.2021.107127. Epub 2021 Sep 30.
[24] de Brito AMC, de Almeida Pinto MG, Bronstein G, Carneiro E, Faertes D, Fukugawa V, et al. Topiramate Combined with Cognitive Restructuring for the Treatment of Gambling Disorder: A Two-Center, Randomized. Double-Blind Clinical Trial J Gambl Stud 2017;33:249–63. https://doi.org/10.1007/S10899-016-9620-Z/METRICS.
[25] Fong T, Kalechstein A, Bernhard B, Rosenthal R, Rugle L. A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. Pharmacol Biochem Behav 2008;89:298–303. https://doi.org/10.1016/J.PBB.2007.12.025.
[26] Black DW, Arndt S, Coryell WH, Argo T, Forbush KT, Shaw MC, et al. Bupropion in the treatment of pathological gambling: a randomized, double-blind, placebo-controlled, flexible-dose study. J Clin Psychopharmacol 2007;27:143–50. https://doi.org/10.1097/01.JCP.0000264985.25109.25.
[27] Dannon PN, Lowengrub K, Musin E, Gonopolski Y, Kotler M. Sustained-release bupropion versus naltrexone in the treatment of pathological gambling: a preliminary blind-rater study. J Clin Psychopharmacol 2005;25:593–6. https://doi.org/10.1097/01.JCP.0000186867.90289.ED.
[28] Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry 2001;49:914–21. https://doi.org/10.1016/S0006-3223(01)01079-4.
[29] Hollander E, Decaria CM, Finkell JN, Begaz T, Wong CM, Cartwright C. A randomized double-blind fluvoxamine/placebo crossover trial in pathologic gambling. Biol Psychiatry 2000;47:813–7. https://doi.org/10.1016/S0006-3223(00)00241-9.
[30] Kim SW, Grant JE, Adson DE, Zaninelli R. A Double-Blind Placebo-Controlled Study of the Efficacy and Safety of Paroxetine in the Treatment of Pathological Gambling. J Clin Psychiatry 2002;63:4776.
[31] Kovanen L, Basnet S, Castrén S, Pankakoski M, Saarikoski ST, Partonen T, et al. A Randomised, Double-Blind, Placebo-Controlled Trial of As-Needed Naltrexone in the Treatment of Pathological Gambling. Eur Addict Res 2016;22:70–9. https://doi.org/10.1159/000435876.
[32] McElroy SL, Nelson EB, Welge JA, Kaehler L, Keck PE. Olanzapine in the treatment of pathological gambling: a negative randomized placebo-controlled trial. J Clin Psychiatry 2008;69:433–40. https://doi.org/10.4088/JCP.V69N0314.
[33] Berlin HA, Braun A, Simeon D, Koran LM, Potenza MN, McElroy SL, et al. A double-blind, placebo-controlled trial of topiramate for pathological gambling. World J Biol Psychiatry 2013;14:121–8. https://doi.org/10.3109/15622975.2011.560964.
[34] Grant JE, Kim SW, Potenza MN, Blanco C, Ibanez A, Stevens L, et al. Paroxetine treatment of pathological gambling: a multi-centre randomized controlled trial. Int Clin Psychopharmacol 2003;18:243–9. https://doi.org/10.1097/00004850-200307000-00007.
[35] Grant JE, Potenza MN, Hollander E, Cynningham-Williams R, Nurminen T, Smits G, et al. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am J Psychiatry 2006;163:303–12. https://doi.org/10.1176/APPI.AJP.163.2.303.
[36] Grant JE, Suck WK, Hartman BK. A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. J Clin Psychiatry 2008;69:783–9. https://doi.org/10.4088/JCP.v69n0511.
[37] Grant JE, Odlaug BL, Potenza MN, Hollander E, Kim SW. Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. Br J Psychiatry 2010;197:330–1. https://doi.org/10.1192/BJP.BP.110.078105.
[38] Grant JE, Driessens C, Chamberlain SR. Milk Thistle (Silymarin) Treatment of Adults with Gambling Disorder: A Double-Blind, Placebo-Controlled Trial. Clin Neuropharmacol 2024;47(2):54–8. https://doi.org/10.1097/WNF.0000000000000585.
[39] Clark SD, Abi-Dargham A. The Role of Dynorphin and the Kappa Opioid Receptor in the Symptomatology of Schizophrenia: A Review of the Evidence. Biol Psychiatry 2019;86:502–11. https://doi.org/10.1016/J.BIOPSYCH.2019.05.012.
[40] Victorri-Vigneau C, Spiers A, Caillet P, Bruneau M, IGNACE-consortium, Challet-Bouju G, et al. Opioid Antagonists for Pharmacological Treatment of Gambling Disorder: Are they Relevant? Curr Neuropharmacol 2018;16:1418. https://doi.org/10.2174/1570159X15666170718144058.
[41] Browne CA, Smith T, Lucki I. Behavioral effects of the kappa opioid receptor partial agonist nalmefene in tests relevant to depression. Eur J Pharmacol 2020:872. https://doi.org/10.1016/J.EJPHAR.2020.172948.
[42] Nalmefene. Meyler's Side Eff Drugs. 2016. p. 12–3. https://doi.org/10.1016/B978-0-444-53717-1.01127-6.
[43] Soyka M. Nalmefene for the treatment of alcohol dependence: a current update. Int J Neuropsychopharmacol 2014;17:675–84. https://doi.org/10.1017/S1461145713001284.
[44] Baldwin DS, Kosky N. Off-label prescribing in psychiatric practice. Adv Psychiatr Treat 2007;13:414–22. https://doi.org/10.1192/APT.BP.107.004184.
[45] Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019;394:939–51. https://doi.org/10.1016/S0140-6736(19)31135-3.
[46] Ioannidis K, Huneke NTM, Solly JE, Fusetto Veronesi G, Tzagarakis C, Parlatini V, et al. Placebo and nocebo effects in gambling disorder pharmacological trials: a meta-analysis. Acta Neuropsychiatr 2024:1–11. https://doi.org/10.1017/neu.2024.52. Online ahead of print.
[47] Chamberlain SR, Ioannidis K, Bowden-Jones H. The UK Gambling White Paper: comments on implementation and timing. Compr Psychiatry 2023;126:152410. https://doi.org/10.1016/j.comppsych.2023.152410. Epub 2023 Aug 6.