National Institute for Health and Care Excellence

Draft for consultation

Harmful gambling: identification, assessment and management

[E] Pharmacological treatment of harmful gambling

NICE guideline number tbc

Evidence review underpinning recommendations 1.5.16 to 1.5.19 and research recommendations in the NICE guideline

October 2023

Draft for consultation

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ISBN:

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Pharmacological treatment for harmful gambling

Review question

What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

Introduction

Treatment for harmful gambling aims to help people reduce their gambling activity or abstain from gambling completely. Psychological treatments such as cognitive behavioural therapy are commonly used but there may also be potential to use pharmacological approaches to reduce impulsivity and break the cycle of reward-seeking behaviour. A range of different therapeutic agents have been tried in this context but there are no medications licensed in the UK for the treatment harmful gambling.

The aim of this review was to determine the effectiveness of pharmacological treatments for people experiencing harmful gambling.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	**Inclusion:** People meeting criteria for gambling disorder, pathological gambling or problem gambling using standardised diagnostic or assessment instruments (including validated self-report measures). •
Intervention	• Antidepressants (including serotonin reuptake inhibitors) • Opioid antagonists (for example, naltrexone) • Mood stabilisers and anticonvulsants • Atypical antipsychotics
Comparison	• Placebo (including active and inert placebo conditions) • Interventions in other drug categories within the review
Outcome	**Critical** • Severity of gambling symptoms **Important** • Gambling expenditure • Gambling frequency • Time spent gambling • Depressive symptoms • Anxiety symptoms • Functional impairment • Responder status

For further details see appendix A for a link to the full Cochrane review protocol.

Methods and process

During the development of this guideline, one registered Cochrane protocol was identified which matched the committee's intended objectives for this review question. The Cochrane protocol did differ from the committee's intended population and outcomes. The Cochrane review included people of all ages, compared with the population in the guideline scope, being 18 years and over. Additionally, the Cochrane review specified that included participants had to meet criteria for gambling disorder/pathological gambling/problem gambling using standardised diagnostic or assessment instruments. This slightly differs from the committee's proposed population of people currently experiencing harmful gambling. In terms of outcomes, the Cochrane review did not include 4 of the committee's proposed outcomes: recovery capital, personal, social and life functions, adverse events, and physical and mental health-related quality of life. Conversely, the Cochrane review considered 3 additional outcomes that the committee had not considered: occurrence of clinical diagnoses of pathological gambling, functional impairment, and responder status. However, the committee discussed the Cochrane protocol and agreed the deviations did not represent grounds to discount the review. They agreed that on the whole the interventions being examined, and the outcomes being extracted would provide them with a sound basis on which to make recommendations about pharmacological treatment for people experiencing harmful gambling. Furthermore, no studies were excluded from the Cochrane review that would have been included if the committee's intended PICO had been applied.

The Cochrane review team completed the review investigating the effectiveness of pharmacological interventions for the treatment of disordered and problem gambling (Dowling 2022) during guideline development. The Cochrane review team presented their results to the committee and the committee used the results to make recommendations. Cochrane's methods are closely aligned to standard NICE methods but minor deviations relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence - these include the presentation of summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, and consideration of pharmaceutical industry funding but not gambling industry funding. The Cochrane review team made small changes to their original review protocol included adding responder status and functional impairment as secondary outcomes and removing 'reduced occurrence of clinical diagnoses of pathological gambling'.

Effectiveness evidence

Included studies

One Cochrane review (Dowling 2022) including 17 randomised controlled trials was considered in this report.

The Cochrane review is summarised in Table 2, however full details of the Cochrane review including methods are available in the full publication which can be accessed at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

See the Cochrane review for the literature search strategies, study selection flow charts, forest plots and summary of findings tables at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Excluded studies

See the list of excluded studies with reasons for their exclusion at:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Comparison	Outcomes
Dowling 2022 Systematic review	Number of studies: 17 Number of participants: 1193 randomised	**Anti-depressants compared to placebo** 6 RCTs, N=268 adults experiencing disordered and problem gambling (Black 2007, Blanco 2002, Grant 2003, Hollander 2000, Kim 2002, Saiz-Ruiz 2005) **Opioid antagonists compared to placebo** 4 RCTs, N=562 adults experiencing disordered and problem gambling (Grant 2006a, Grant 2008, Grant 2010, Kim 2001a) **Mood stabilisers compared to placebo** 2 RCTs, N=71 adults experiencing disordered and problem gambling (Berlin 2003, Hollander 2005) **Atypical antipsychotics compared to placebo** 2 RCTs, N=63 adults experiencing disordered and problem gambling (Fong 2008, McElroy 2008 2009) **Antidepressants compared to opioid antagonists** 2 RCTs, N=62 adults experiencing disordered and problem gambling (Dannon	Primary outcomes: • Reduction in severity of gambling symptoms Secondary outcomes: • Reduction in gambling expenditure • Reduction in gambling frequency • Reduction in time spent gambling • Reduction in depressive symptoms • Reduction in anxiety symptoms • Reduction in functional impairment • Responder status

Study	Population	Comparison	Outcomes
		2005a, Rosenburg 2013) **Antidepressants compared to mood stabilisers** 2 RCTs, N=58 adults experiencing disordered and problem gambling (Dannon 2005a, Rosenburg 2013) **Opioid antagonists compared to mood stabilisers** 1 RCT, N=24 adults experiencing disordered and problem gambling (Rosenburg 2013)	

N: Number; RCT: Randomised controlled trial

Summary of the evidence

The Cochrane review of pharmacological interventions for the treatment of disordered and problem gambling investigated the following comparisons (certainty of the evidence is described according to GRADE criteria):

Comparison 1: Antidepressants versus placebo

There was very low to low certainty evidence that anti-depressants were no more effective than placebo, post-treatment, for all outcomes.

Comparison 2: Opioid antagonists versus placebo

There was low certainty evidence that opioid antagonists (naltrexone and nalmefene) were more effective than placebo at reducing gambling symptom severity, post-treatment but the intervention was no more effective than placebo at improving responder status post-treatment (very low certainty evidence). One study of naltrexone showed beneficial effects at 18 week follow up on depressive symptoms, anxiety symptoms and functional impairment (low certainty evidence).

None of the primary studies evaluated gambling expenditure, gambling frequency, nor time spent gambling so no analyses could be conducted for these outcomes.

Comparison 3: Mood stabilisers versus placebo

In one study, a mood stabiliser (sustained-release lithium) was more effective than placebo at the end of the 10-week treatment for responder status (very low certainty evidence), in a population with comorbid bipolar disorder.

There was no evidence of an effect post-treatment for mood stabilisers compared with placebo for any other outcomes (very low certainty evidence).

Comparison 4: Atypical antipsychotics versus placebo

An atypical antipsychotic (olanzapine) was more effective than placebo post-treatment for gambling severity (very low certainty evidence).

There was very low to low certainty evidence that olanzapine was no more effective than placebo at the end of 7- or 12-week treatment, for gambling expenditure, gambling frequency, time spent gambling, depressive symptoms, anxiety symptoms or responder status (very low to low certainty evidence).

None of the primary studies evaluated functional impairment so no analyses could be conducted for this outcome.

Comparison 5: Antidepressants versus opioid antagonists

There was no difference in post-treatment effectiveness between antidepressants (either antidepressants in general or sustained release bupropion specifically) and opioid antagonists (either general opioid antagonists or naltrexone specifically) for gambling symptom severity, depressive symptoms, anxiety symptoms or responder status (very low certainty evidence).

None of the primary studies evaluated gambling expenditure, gambling frequency, time spent gambling or functional impairment so no analyses could be conducted for these outcomes.

Comparison 6: Antidepressants versus mood stabilisers

There was no difference in post-treatment effectiveness between antidepressants in general or selective serotonin reuptake inhibitors specifically and mood stabilisers (either general mood stabilisers or topiramate specifically) for gambling symptom severity, depressive symptoms, anxiety symptoms or responder status (very low certainty evidence).

None of the primary studies evaluated gambling expenditure, gambling frequency, time spent gambling or functional impairment so no analyses could be conducted for these outcomes.

Comparison 7: Antidepressants versus atypical antipsychotics

None of the primary studies compared antidepressants with atypical antipsychotics, and no analyses could be conducted for this comparison.

Comparison 8: Opioid antagonists versus mood stabilisers

There was no difference in post-treatment effectiveness between the opioid antagonist, naltrexone and topiramate for depressive symptoms or, anxiety symptoms (very low certainty evidence).

None of the primary studies evaluated gambling symptom severity, gambling expenditure, gambling frequency, time spent gambling, functional impairment, or responder status so no analyses could be conducted for these outcomes.

Comparison 9: Opioid antagonists versus atypical antipsychotics

None of the primary studies compared opioid antagonists with atypical antipsychotics, and no analyses could be conducted for this comparison.

Comparison 10: Mood stabilisers versus atypical antipsychotics

None of the primary studies compared mood stabilisers with atypical antipsychotics, and no analyses could be conducted for this comparison.

See the Cochrane review for summary of findings tables and full results, including all primary and secondary outcomes and sub-group analyses at:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G. No economic evidence was identified for this review.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Cost analysis

This topic was prioritised for de novo economic modelling. However, the size of the available clinical evidence was small and characterised by limitations, and therefore it did not allow the development of a robust model that could inform recommendations. Based on this evidence and their experience, the committee agreed to make a weak ('consider') recommendation for naltrexone and were interested in estimating the intervention costs of naltrexone treatment, to consider qualitatively whether the benefits of providing naltrexone were worth the extra costs associated with its provision. The intervention cost of treatment with naltrexone includes drug acquisition, laboratory testing and healthcare professionals' time. The committee advised on the appropriate resource use on all cost elements. These were subsequently combined with respective, national unit costs to estimate the total cost of treatment with naltrexone. The cost elements, estimated resource use, and respective unit costs are reported in Table 3. By combining these data, the estimated total cost of treatment with naltrexone was £1134. It needs to be noted that this cost captures only provision of naltrexone. Naltrexone may be offered as an adjunct to psychological treatment, but the cost of the latter has not been estimated as part of this costing exercise.

Table 3:Intervention costs of treatment with naltrexone over six months (24 weeks)

Cost element	Resource use	Unit costs [2022 price]	Source	Cost [2022 price]
Drug acquisition	25mg daily for 3 days + 50mg daily for 24 weeks	28 x 50mg tablets = £77.77	NHS Business Services Authority, NHS Prescription Services. NHS England and Wales. Electronic Drug Tariff. Issue: May 2023. Compiled on the behalf of the Department of Health and Social Care. NHS Business Services Authority, 2023. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff	£472.18
Laboratory testing	At baseline: FBC, LFT, U&E At 4 weeks: LFT At 6 months: LFT At each point: 10 min of HCA time (30 min in total)	FBC £3.03; LFT: £3.18; U&E: £2.43 HCA: £25/hour (NHS AfC band 2)	Akhtar W, Chung Y. Saving the NHS one blood test at a time. BMJ Qual Improv Rep 2014; 2:u204012.w1749 Jones KC, Weatherly H, Birch S, et al. (2023) Unit Costs of Health & Social Care 2022 Manual. Technical report. Canterbury: Personal Social Services Research Unit, University of Kent & Centre for Health Economics, University of York	£27.50
Healthcare professional time	Initial contact - 30 min Consultant contact - 30 min Care-plan meeting and 6-weeks prescription - 30 min Follow up check 3-4 days after start of meds - 10 min Follow up with consultant - 30 min Review and 2nd 6-week repeat prescription - 30 min Review and 3rd 6-week repeat prescription - 30 min Review and 4th 6-week repeat prescription - 30 min Final contact - 30 min	MH nurse Band 6: • per working hour: £57 • per hour of patient contact: £84 Consultant psychiatrist: • per working hour: £143 • per hour of patient contact £369	Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, Forder JE, Gao J, Hinde S, Markham S et al. (2023) Unit Costs of Health & Social Care 2022 Manual. Technical report. Canterbury: Personal Social Services Research Unit, University of Kent & Centre for Health Economics, University of York Ratio of direct (face-to-face contacts) to indirect time: Consultant psychiatrist: 1 to 1.58; Nurse: 1 to 0.47 (taken from Unit Costs of Health & Social Care 2012)	£634.28
Total cost				**£1,134**

AfC: Agenda for change; FBC: Full blood count; HCA: Healthcare assistant; LFT: Liver function tests; NHS: National Health Service; U&E: Urea and electrolytes

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The Cochrane review's primary outcome was reduction in the severity of gambling symptoms, which the committee agreed is a critical outcome as the main aim of gambling treatment is to reduce gambling or lead to total abstention from gambling. The Cochrane review included a number of other measures to assess the amount of gambling activity and these included gambling expenditure, gambling frequency and time spent gambling and the committee agreed these were also critical outcomes as they also indicated the effectiveness of treatments at reducing gambling. The Cochrane review also included depressive symptoms, anxiety symptoms and functional impairment which the committee agreed were important outcomes as harmful gambling may lead to depression, anxiety and functional impairment and so medication having a beneficial effect on these symptoms may reduce the overall harm associated with gambling. Finally, responder status was an outcome included by Cochrane which assessed improvement based on the Clinical Global Impression improvement scale, other similar scales, or by classifying people who had abstained from gambling for a prespecified period as responders. The committee agreed that this was an alternative way of assessing the effectiveness of treatments and considered it as an important outcome.

The quality of the evidence

The Cochrane review assessed the evidence using GRADE methodology and found that it ranged from very low to low quality, with most of the evidence being very low quality. Evidence was mainly downgraded due to imprecision of the effect size (for example, where the 95% confidence intervals for the pooled effect included the null value), risk of bias as determined by the Cochrane Risk of Bias tool 2.0 (for example, due to lack of information on the randomisation processes, allocation concealment or blinding of participants). Studies were also downgraded for inconsistency (for example, where there was significant heterogeneity between studies as indicated by a large I^2 value) and indirectness (for example, where studies had included comorbidities as an inclusion criterion).

The methodological limitations of the Cochrane review were assessed using the ROBIS tool to assess risk of bias in systematic reviews. The overall quality of the Cochrane review was considered to be high (see appendix L for further details).

Benefits and harms

Recommendations based on this review are for commissioners and providers of gambling treatment services.

The committee agreed that only 2 comparisons showed any evidence of benefit in terms of reducing gambling severity: these were the comparisons of opioid antagonists versus placebo, and atypical antipsychotics versus placebo. There was also some evidence that mood stabilisers improved responder status compared to placebo. The committee were aware that none of these medications were approved to treat harmful gambling and so any recommendations they made would be 'off label'.

The committee discussed that the inclusion criteria into the studies allowed people who were defined as having gambling disorder or pathological gambling using any clinical diagnostic tool or self-report measure and therefore may be people with 'more severe' harmful gambling, but that the use of self-report measures meant there was likely to be some variations. The committee also noted that people in the opioid antagonist studies could not be on any other current treatment and were excluded from some of the studies if they had

had any treatment in the last 3 or 6 months. The committee discussed that the evidence had mainly been obtained from people without comorbidities (such as depression and anxiety) as the primary studies had excluded these populations. The committee therefore questioned the applicability of the studies to real-world practice as they were aware that many people entering treatment for harmful gambling were likely to have comorbid depression and anxiety, and that often treatment of the conditions were interlinked: treating harmful gambling could reduce depression and anxiety, and treating depression and anxiety could also help the person or enable their engagement in psychological treatments.

The committee considered the evidence for opioid antagonists in more detail and noted that the evidence for benefit on gambling severity was low quality evidence from 3 studies (n=259) and included evidence for both naltrexone and nalmefene. There was also evidence from 1 study of naltrexone (n=77) that it improved depression and anxiety symptoms and reduced functional impairment. Based on this evidence the committee agreed that there was a place in treatment of harmful gambling for opioid antagonists but because this evidence was low quality and based on a small number of studies and participants they were only able to make a weak 'consider' recommendation. The committee discussed that the studies did not analyse the results by dose and had not compared different doses of opioid antagonists so could not be used to provide guidance on the recommended dose. However, the committee considered the doses used in the included studies and noted that the naltrexone studies used doses that were similar to the approved doses used in the UK for the indication of prevention of relapse in formerly opioid- and alcohol-dependent people. There was also clinical experience amongst the committee members using naltrexone in the treatment of harmful gambling. In contrast, the nalmefene doses used in the studies were much greater than those approved in the UK for the treatment of alcohol dependence and there was no clinical experience of its use for harmful gambling. Based on this the committee opted to recommend naltrexone at its approved dosage, although they agreed the evidence was not strong enough to recommend its use as first-line therapy and that it should therefore be used for people in whom psychological therapy (for which the evidence of benefit was greater) had either been unsuccessful or the person had had multiple relapses.

The studies did not provide any information about whether opioid antagonists were effective when psychological therapies had failed, but committee members had experience of using opioid antagonists when psychological interventions had not been effective, and other members suggested that they may be of benefit in people who relapsed despite psychological therapy, or in combination with psychological therapy. The committee also agreed that as the evidence for psychological therapies was greater, it would be logical to use the naltrexone as an adjunct to psychological treatment. The committee knew from their knowledge and experience that some psychological conditions may require combination therapy to achieve successful outcomes, and that this may be the case with gambling but that there was no evidence on which to determine whether this was the case, as none of the included studies had looked at combination treatments.

The committee agreed that due to the limited evidence for naltrexone, the weak recommendation and the need for monitoring it should only be initiated by or under the supervision of a specialist. The committee noted that this is recommended by the BNF for the use of naltrexone for its licensed indications, and therefore they agreed this was even more important for its unlicensed use to treat harmful gambling. However, the committee recognised that as experience with its use increases it would be possible for ongoing prescriptions to be issued in primary care if the appropriate shared care agreement was in place.

Based on their knowledge and experience, and the recommendations in the BNF and the summary of product characteristics for naltrexone, the committee discussed the safety and monitoring requirements associated with naltrexone usage, specifically the need to check kidney and liver function prior to and during treatment and the need to avoid opioids. They

therefore recommended that people starting naltrexone have baseline kidney and liver function tests and be advised to avoid opioids for the duration of treatment. Regular follow-ups should be scheduled to appropriately monitor how well an individual is responding to the medication, how they are tolerating it, and to identify any side effects they may be experiencing.

The committee discussed the evidence for atypical antipsychotics: both studies had included olanzapine, and all the evidence was very low quality and based on only 63 participants. The committee discussed, based on their knowledge and experience, that olanzapine may lead to a range of side-effects and so concluded that the evidence of benefit was not strong enough to outweigh the possible harms and so they chose not to recommend olanzapine.

Finally, the committee considered the evidence for mood stabilisers compared to placebo but noted that the only evidence of benefit was for responder status, was based on the results of 1 study of topiramate with 40 participants and was of very low quality so they also chose not to recommend mood stabilisers.

In addition to practice recommendations, the committee made recommendations for future research to address evidence gaps. The gaps stemmed from a paucity of good quality evidence for the effectiveness of pharmacological therapy for the treatment of harmful gambling; a lack of evidence relating to certain patient sub-groups; and a lack of data about the effectiveness of combination therapies compared with single therapies. The research recommendations and their rationale are described in appendix K.

Cost effectiveness and resource use

No economic evidence was identified for this review question. The committee noted that provision of naltrexone entails additional costs relating to the treatment of adults experiencing harmful gambling. However, they anticipated that recommendations would have a moderate resource impact, as they agreed that, due to the limited evidence base, naltrexone should be considered as a treatment option for people for whom psychological treatments have not been effective or where the person has repeated relapses with psychological treatments; therefore, the number of people who receive naltrexone as a treatment for gambling-related harms is expected to be small. The committee agreed that, for this subgroup of people, the costs of treatment with naltrexone are likely to be offset by the treatment benefits.

Other factors the committee took into account

The funding sources for the studies included in this evidence review were:

- Any industry funding: Berlin 2013, Kim 2001
- No industry funding: Black 2007, Blanco 2002, Fong 2008, Grant 2003, Grant 2006, Grant 2008, Grant 2010, Kim 2002, Rosenberg 2013, Saiz-Ruiz 2005
- Unclear funding source: Hollander 2000, Hollander 2005, McElroy 2008, Dannon 2005a, Dannon 2005b

The committee discussed the funding for the included studies. They agreed that the majority of the studies had not received funding from the gambling industry, although many had received funding from the pharmaceutical industry. This is not uncommon in trials of medication and had already been taken into account in Cochrane's assessment of bias.

The 4 studies that did have gambling industry funding or were unclear (Berlin 2013, Dannon 2005b, Hollander 2000 and Mc Elroy 2008) did not relate to opioid antagonists and so the committee were content that their recommendations were based on studies in which no gambling industry funding had been received.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.16 to 1.5.19 and research recommendations on the role of pharmacological therapy alone, in combination or in people with comorbidities.

References – included studies

Effectiveness

Dowling 2022

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 of Systematic Reviews, Issue 9, 2022

Other

Beck 1961

Beck, A., Ward, C., Mendelson, M., Mock, J., Erbaugh, J., An Inventory for Measuring Depression, Archives of General Psychiatry, 561, 1961

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Lesieur 1987

Lesieur, H., Blume,S., The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers, American Journal of Psychiatry, 1184, 1987

Shaffer 1994

Shaffer, H., LaBrie, R., Scanlan, K., Cummings, T., Pathological gambling among adolescents: Massachusetts Gambling Screen (MAGS), Journal of Gambling Studies, 339, 1994

Spielberger 1970

Spielberger, C., Gorsuch, R., Lushene, R., STAI Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, 1970

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

See the Cochrane review protocol for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

Effectiveness searches

See Appendix 1 and Appendix 2 of the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Economics searches

Please note that a combined literature search was undertaken to cover the economics aspects of all the review questions in a single search.

Database: Applied Social Science Index and Abstracts (ASSIA)

Date of last search: 04/04/2023

#	Searches
	AB,TI (gambl* or betting or bet or bets or wager* or "gaming machine*" or "slot machine*" or "fruit machine*" or "poker machine*" or "lottery machine*" or "lotteries machine*" or "gaming terminal*" or "slot terminal*" or "fruit terminal*" or "poker terminal*" or "lottery terminal*" or "lotteries terminal*" or pokies or pokey or puggy or fruities)
AND	AB,TI(budget* OR cost* OR economic* OR pharmaco-economic* OR price* OR pricing* OR financ* OR fee OR fees OR expenditure* OR saving* OR "value for money" OR "monetary value" OR "resourc* allocat*" OR "allocat* resourc*" OR fund OR funds OR funding* OR funded OR ration OR rations OR rationing* OR rationed or "quality of life" or "quality adjusted life" or "disability adjusted life" or "short form or shortform" or "health year equivalent*" or "nottingham health profile*" or "sickness impact profile*" or "health status indicator*" or "health utilit*" or "utilit* valu*" or "utilit* measur*" or "willingness to pay" or "standard gamble*" or "time trade off" or "time tradeoff" or "duke health profile" or "functional status questionnaire" or "dartmouth coop functional health assessment*")
AND	Additional limits - Date: From January 2000

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Date of last search: 04/04/2023

#	Searches
#1	MeSH descriptor: [Gambling] this term only
#2	gambl*:ti,ab
#3	betting:ti,ab
#4	(bet or bets):ti,ab
#5	wager*:ti,ab
#6	((gaming or gambling or slot or fruit or poker or lottery or lotteries) near/5 (machine* or terminal*)):ti,ab
#7	(pokies or pokey or puggy or fruities):ti,ab
#8	((dice or card or cards or roulette or blackjack or poker or baccarat or crap or craps or keno or casino* or bingo or bookmaker* or "book maker" or bookie* or lottery or lotteries or lotto or "scratch card*" or scratchcard* or raffle or raffles or sweepstak* or "amusement arcade*" or slot or slots) near/5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)):ti,ab
#9	((game or games or gaming or gamer*) near/5 (money or monetization or monetisation or monetary)):ti,ab
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 with Cochrane Library publication date Between Jan 2000 and Mar 2022
#12	MeSH descriptor: [Economics] this term only
#13	MeSH descriptor: [Value of Life] this term only
#14	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#15	MeSH descriptor: [Economics, Hospital] explode all trees
#16	MeSH descriptor: [Economics, Medical] explode all trees
#17	MeSH descriptor: [Resource Allocation] explode all trees
#18	MeSH descriptor: [Economics, Nursing] this term only
#19	MeSH descriptor: [Economics, Pharmaceutical] this term only
#20	MeSH descriptor: [Fees and Charges] explode all trees

#	Searches
#21	MeSH descriptor: [Budgets] explode all trees
#22	budget*:ti,ab
#23	cost*:ti,ab
#24	(economic* or pharmaco?economic*):ti,ab
#25	(price* or pricing*):ti,ab
#26	(financ* or fee or fees or expenditure* or saving*):ti,ab
#27	(value near/2 (money or monetary)):ti,ab
#28	resourc* allocat*:ti,ab
#29	(fund or funds or funding* or funded):ti,ab
#30	(ration or rations or rationing* or rationed):ti,ab
#31	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	MeSH descriptor: [Value of Life] this term only
#33	MeSH descriptor: [Quality of Life] this term only
#34	"quality of life":ti
#35	((instrument or instruments) near/3 "quality of life"):ab
#36	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#37	"quality adjusted life":ti,ab
#38	(qaly* or qald* or qale* or qtime* or "life year" or "life years"):ti,ab
#39	"disability adjusted life":ti,ab
#40	daly*:ti,ab
#41	(sf36 or "sf 36" or "short form 36" or "shortform 36" or "short form36" or shortform36 or "sf thirtysix" or sfthirtysix or "sfthirty six" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirtysix" or "short form thirty six"):ti,ab
#42	(sf6 or "sf 6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six" or shortform6 or "short form6"):ti,ab
#43	(sf8 or "sf 8" or "sf eight" or sfeight or "shortform 8" or "shortform 8" or shortform8 or "short form8" or "shortform eight" or "short form eight"):ti,ab
#44	(sf12 or "sf 12" or "short form 12" or "shortform 12" or "short form12" or shortform12 or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve"):ti,ab
#45	(sf16 or "sf 16" or "short form 16" or "shortform 16" or "short form16" or shortform16 or "sf sixteen" or sfsixteen or "shortform sixteen" or "short form sixteen"):ti,ab
#46	(sf20 or "sf 20" or "short form 20" or "shortform 20" or "short form20" or shortform20 or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty"):ti,ab
#47	(hql or hqol or "h qol" or hrqol or "hr qol"):ti,ab
#48	(hye or hyes):ti,ab
#49	(health* near/2 year* near/2 equivalent*):ti,ab
#50	(pqol or qls):ti,ab
#51	(quality of wellbeing or "quality of well being" or "index of wellbeing" or "index of well being" or qwb):ti,ab
#52	"nottingham health profile*":ti,ab
#53	"sickness impact profile":ti,ab
#54	MeSH descriptor: [Health Status Indicators] explode all trees
#55	(health near/3 (utilit* or status)):ti,ab
#56	(utilit* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)):ti,ab
#57	(preference* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)):ti,ab
#58	disutilit*:ti,ab
#59	rosser:ti,ab
#60	"willingness to pay":ti,ab
#61	"standard gamble*":ti,ab
#62	("time trade off" or "time tradeoff"):ti,ab
#63	tto:ti,ab
#64	(hui or hui1 or hui2 or hui3):ti,ab
#65	(eq or euroqol or "euro qol" or eq5d or "eq 5d" or euroqual or "euro qual"):ti,ab
#66	"duke health profile":ti,ab
#67	"functional status questionnaire":ti,ab
#68	"dartmouth coop functional health assessment*":ti,ab
#69	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68
#70	#11 and #31
#71	#11 and #69
#72	#70 or #71

Database: Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Date of last search: 04/04/2023

#	Searches
S1	TI (gambl* or betting or bet or bets or wager* or "gaming machine*" or "slot machine*" or "fruit machine*" or "poker machine*" or "lottery machine*" or "lotteries machine*" or "gaming terminal*" or "slot terminal*" or "fruit terminal*" or "poker terminal*" or "lottery terminal*" or "lotteries terminal*" or pokies or pokey or puggy or fruities) Limiters - Publication Year: 2000-
S2	TI (budget* OR cost* OR economic* OR pharmaco-economic* OR price* OR pricing* OR financ* OR fee OR fees OR expenditure* OR saving* OR "value for money" OR "monetary value" OR "resourc* allocat*" OR "allocat* resourc*" OR fund OR funds OR funding* OR funded OR ration OR rations OR rationing* OR rationed or "quality of life" or "quality adjusted life" or "disability adjusted life" or "short form or shortform" or "health year equivalent*" or "nottingham health profile*" or "sickness impact profile*" or "health status indicator*" or "health utilit*" or "utilit* valu*" or "utilit* measur*" or "willingness to pay" or "standard gamble*" or "time trade off" or "time tradeoff" or "duke health profile" or "functional status questionnaire" or "dartmouth coop functional health assessment*") Limiters - Publication Year: 2000-
S3	S1 and S2

Database: Embase

Date of last search: 04/04/2023

#	Searches
1	GAMBLING/
2	PATHOLOGICAL GAMBLING/
3	(gambl* not standard gamble).ti,ab.
4	betting.ti,ab.
5	(bet or bets).ti,ab.
6	wager*.ti,ab.
7	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
8	(pokies or pokey or puggy or fruities).ti,ab.
9	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.
10	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.
11	or/1-10
12	limit 11 to english language
13	limit 12 to yr="2000 -Current"
14	letter.pt. or LETTER/
15	note.pt.
16	editorial.pt.
17	CASE REPORT/ or CASE STUDY/
18	(letter or comment*).ti.
19	or/14-18
20	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
21	19 not 20
22	ANIMAL/ not HUMAN/
23	NONHUMAN/
24	exp ANIMAL EXPERIMENT/
25	exp EXPERIMENTAL ANIMAL/
26	ANIMAL MODEL/
27	exp RODENT/
28	(rat or rats or mouse or mice).ti.
29	or/21-28
30	13 not 29
31	HEALTH ECONOMICS/
32	exp ECONOMIC EVALUATION/
33	exp HEALTH CARE COST/
34	exp FEE/
35	BUDGET/
36	FUNDING/
37	RESOURCE ALLOCATION/
38	budget*.ti,ab.
39	cost*.ti,ab.
40	(economic* or pharmaco?economic*).ti,ab.
41	(price* or pricing*).ti,ab.
42	(financ* or fee or fees or expenditure* or saving*).ti,ab.
43	(value adj2 (money or monetary)).ti,ab.
44	resourc* allocat*.ti,ab.
45	(fund or funds or funding* or funded).ti,ab.
46	(ration or rations or rationing* or rationed).ti,ab.
47	or/31-46
48	SOCIOECONOMICS/

#	Searches
49	exp QUALITY OF LIFE/
50	quality of life.ti,kw.
51	((instrument or instruments) adj3 quality of life).ab.
52	QUALITY-ADJUSTED LIFE YEAR/
53	quality adjusted life.ti,ab,kw.
54	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.
55	disability adjusted life.ti,ab,kw.
56	daly*.ti,ab,kw.
57	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.
58	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.
59	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.
60	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.
61	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.
62	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.
63	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.
64	(hye or hyes).ti,ab,kw.
65	(health* adj2 year* adj2 equivalent*).ti,ab,kw.
66	(pqol or qls).ti,ab,kw.
67	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.
68	NOTTINGHAM HEALTH PROFILE/
69	nottingham health profile*.ti,ab,kw.
70	SICKNESS IMPACT PROFILE/
71	sickness impact profile.ti,ab,kw.
72	HEALTH STATUS INDICATOR/
73	(health adj3 (utilit* or status)).ti,ab,kw.
74	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
75	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.
76	disutilit*.ti,ab,kw.
77	rosser.ti,ab,kw.
78	willingness to pay.ti,ab,kw.
79	standard gamble*.ti,ab,kw.
80	(time trade off or time tradeoff).ti,ab,kw.
81	tto.ti,ab,kw.
82	(hui or hui1 or hui2 or hui3).ti,ab,kw.
83	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.
84	duke health profile.ti,ab,kw.
85	functional status questionnaire.ti,ab,kw.
86	dartmouth coop functional health assessment*.ti,ab,kw.
87	or/48-86
88	30 and 47
89	30 and 87
90	88 or 89

Database: Emcare

Date of last search: 04/04/2023

#	Searches
1	GAMBLING/
2	PATHOLOGICAL GAMBLING/
3	(gambl* not standard gamble).ti,ab.
4	betting.ti,ab.
5	(bet or bets).ti,ab.
6	wager*.ti,ab.
7	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
8	(pokies or pokey or puggy or fruities).ti,ab.
9	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.
10	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.

#	Searches
11	or/1-10
12	limit 11 to english language
13	limit 12 to yr="2000 -Current"
14	letter.pt. or LETTER/
15	note.pt.
16	editorial.pt.
17	CASE REPORT/ or CASE STUDY/
18	(letter or comment*).ti.
19	or/14-18
20	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
21	19 not 20
22	ANIMAL/ not HUMAN/
23	NONHUMAN/
24	exp ANIMAL EXPERIMENT/
25	exp EXPERIMENTAL ANIMAL/
26	ANIMAL MODEL/
27	exp RODENT/
28	(rat or rats or mouse or mice).ti.
29	or/21-28
30	13 not 29
31	HEALTH ECONOMICS/
32	exp ECONOMIC EVALUATION/
33	exp HEALTH CARE COST/
34	exp FEE/
35	BUDGET/
36	FUNDING/
37	RESOURCE ALLOCATION/
38	budget*.ti,ab.
39	cost*.ti,ab.
40	(economic* or pharmaco?economic*).ti,ab.
41	(price* or pricing*).ti,ab.
42	(financ* or fee or fees or expenditure* or saving*).ti,ab.
43	(value adj2 (money or monetary)).ti,ab.
44	resourc* allocat*.ti,ab.
45	(fund or funds or funding* or funded).ti,ab.
46	(ration or rations or rationing* or rationed).ti,ab.
47	or/31-46
48	SOCIOECONOMICS/
49	exp QUALITY OF LIFE/
50	quality of life.ti,kw.
51	((instrument or instruments) adj3 quality of life).ab.
52	QUALITY-ADJUSTED LIFE YEAR/
53	quality adjusted life.ti,ab,kw.
54	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.
55	disability adjusted life.ti,ab,kw.
56	daly*.ti,ab,kw.
57	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.
58	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.
59	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.
60	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.
61	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.
62	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.
63	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.
64	(hye or hyes).ti,ab,kw.
65	(health* adj2 year* adj2 equivalent*).ti,ab,kw.
66	(pqol or qls).ti,ab,kw.
67	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.
68	NOTTINGHAM HEALTH PROFILE/
69	nottingham health profile*.ti,ab,kw.
70	SICKNESS IMPACT PROFILE/
71	sickness impact profile.ti,ab,kw.

#	Searches
72	HEALTH STATUS INDICATOR/
73	(health adj3 (utilit* or status)).ti,ab,kw.
74	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
75	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.
76	disutilit*.ti,ab,kw.
77	rosser.ti,ab,kw.
78	willingness to pay.ti,ab,kw.
79	standard gamble*.ti,ab,kw.
80	(time trade off or time tradeoff).ti,ab,kw.
81	tto.ti,ab,kw.
82	(hui or hui1 or hui2 or hui3).ti,ab,kw.
83	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.
84	duke health profile.ti,ab,kw.
85	functional status questionnaire.ti,ab,kw.
86	dartmouth coop functional health assessment*.ti,ab,kw.
87	or/48-86
88	30 and 47
89	30 and 87
90	88 or 89

Database: Health Information Management Consortium (HMIC)

Date of last search: 04/04/2023

#	Searches
1	GAMBLING/
2	GAMBLERS/
3	GAMBLING MACHINES/
4	AMUSEMENT ARCADES/
5	CASINOS/
6	BOOKMAKERS/
7	LOTTERIES/
8	NATIONAL LOTTERY/
9	(gambl* not standard gamble).ti,ab.
10	betting.ti,ab.
11	(bet or bets).ti,ab.
12	wager*.ti,ab.
13	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
14	(pokies or pokey or puggy or fruities).ti,ab.
15	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.
16	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.
17	or/1-16
18	limit 17 to yr="2000 -Current"
19	exp ECONOMICS/
20	exp COSTS/
21	exp FEES/
22	exp BUDGETS/
23	RESOURCE ALLOCATION/
24	budget*.ti,ab.
25	cost*.ti,ab.
26	(economic* or pharmaco?economic*).ti,ab.
27	(price* or pricing*).ti,ab.
28	(financ* or fee or fees or expenditure* or saving*).ti,ab.
29	(value adj2 (money or monetary)).ti,ab.
30	resourc* allocat*.ti,ab.
31	(fund or funds or funding* or funded).ti,ab.
32	(ration or rations or rationing* or rationed).ti,ab.
33	or/19-32
34	"QUALITY OF LIFE"/
35	QUALITY-ADJUSTED LIFE YEARS/
36	HEALTH STATUS MEASURES/
37	HEALTH SERVICE INDICATORS/
38	quality of life.ti.

#	Searches
39	((instrument or instruments) adj3 quality of life).ab.
40	quality adjusted life.ti,ab.
41	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
42	disability adjusted life.ti,ab.
43	daly*.ti,ab.
44	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
45	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab.
46	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab.
47	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
48	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
49	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
50	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
51	(hye or hyes).ti,ab.
52	(health* adj2 year* adj2 equivalent*).ti,ab.
53	(pqol or qls).ti,ab.
54	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
55	nottingham health profile*.ti,ab.
56	sickness impact profile.ti,ab.
57	(health adj3 (utilit* or status)).ti,ab.
58	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
59	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
60	disutilit*.ti,ab.
61	rosser.ti,ab.
62	willingness to pay.ti,ab.
63	standard gamble*.ti,ab.
64	(time trade off or time tradeoff).ti,ab.
65	tto.ti,ab.
66	(hui or hui1 or hui2 or hui3).ti,ab.
67	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
68	duke health profile.ti,ab.
69	functional status questionnaire.ti,ab.
70	dartmouth coop functional health assessment*.ti,ab.
71	or/34-70
72	18 and 33
73	18 and 71
74	72 or 73

Database: International Health Technology Assessment Database (INAHTA)

Date of last search: 04/04/2023

#	Searches
	All:(gamble or gambler or gamblers or gambling or gambled or betting or bet or bets or wager or wagers)
	AND Publication Year: 2000-2022

Database: MEDLINE ALL

Date of last search: 04/04/2023

#	Searches
1	GAMBLING/
2	(gambl* not standard gamble).ti,ab.
3	betting.ti,ab.
4	(bet or bets).ti,ab.
5	wager*.ti,ab.
6	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
7	(pokies or pokey or puggy or fruities).ti,ab.
8	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.

#	Searches
9	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.
10	or/1-9
11	limit 10 to english language
12	limit 11 to yr="2000 -Current"
13	LETTER/
14	EDITORIAL/
15	NEWS/
16	exp HISTORICAL ARTICLE/
17	ANECDOTES AS TOPIC/
18	COMMENT/
19	CASE REPORT/
20	(letter or comment*).ti.
21	or/13-20
22	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
23	21 not 22
24	ANIMALS/ not HUMANS/
25	exp ANIMALS, LABORATORY/
26	exp ANIMAL EXPERIMENTATION/
27	exp MODELS, ANIMAL/
28	exp RODENTIA/
29	(rat or rats or mouse or mice).ti.
30	or/23-29
31	12 not 30
32	ECONOMICS/
33	VALUE OF LIFE/
34	exp "COSTS AND COST ANALYSIS"/
35	exp ECONOMICS, HOSPITAL/
36	exp ECONOMICS, MEDICAL/
37	exp RESOURCE ALLOCATION/
38	ECONOMICS, NURSING/
39	ECONOMICS, PHARMACEUTICAL/
40	exp "FEES AND CHARGES"/
41	exp BUDGETS/
42	budget*.ti,ab.
43	cost*.ti,ab.
44	(economic* or pharmaco?economic*).ti,ab.
45	(price* or pricing*).ti,ab.
46	(financ* or fee or fees or expenditure* or saving*).ti,ab.
47	(value adj2 (money or monetary)).ti,ab.
48	resourc* allocat*.ti,ab.
49	(fund or funds or funding* or funded).ti,ab.
50	(ration or rations or rationing* or rationed).ti,ab.
51	ec.fs.
52	or/32-51
53	"VALUE OF LIFE"/
54	QUALITY OF LIFE/
55	quality of life.ti,kf.
56	((instrument or instruments) adj3 quality of life).ab.
57	QUALITY-ADJUSTED LIFE YEARS/
58	quality adjusted life.ti,ab,kf.
59	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.
60	disability adjusted life.ti,ab,kf.
61	daly*.ti,ab,kf.
62	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.
63	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.
64	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.
65	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.
66	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.
67	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.
68	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.
69	(hye or hyes).ti,ab,kf.

#	Searches
70	(health* adj2 year* adj2 equivalent*).ti,ab,kf.
71	(pqol or qls).ti,ab,kf.
72	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.
73	nottingham health profile*.ti,ab,kf.
74	sickness impact profile.ti,ab,kf.
75	exp HEALTH STATUS INDICATORS/
76	(health adj3 (utilit* or status)).ti,ab,kf.
77	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.
78	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.
79	disutilit*.ti,ab,kf.
80	rosser.ti,ab,kf.
81	willingness to pay.ti,ab,kf.
82	standard gamble*.ti,ab,kf.
83	(time trade off or time tradeoff).ti,ab,kf.
84	tto.ti,ab,kf.
85	(hui or hui1 or hui2 or hui3).ti,ab,kf.
86	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.
87	duke health profile.ti,ab,kf.
88	functional status questionnaire.ti,ab,kf.
89	dartmouth coop functional health assessment*.ti,ab,kf.
90	or/53-89
91	31 and 52
92	31 and 90
93	91 or 92

Database: NHS Economic Evaluation Database (NHS EED)

Date of last search: 04/04/2023

#	Searches
1	MeSH DESCRIPTOR GAMBLING IN NHSEED
2	(gambl*) TI IN NHSEED
3	(betting) IN NHSEED
4	(bet or bets) IN NHSEED
5	(wager*) IN NHSEED
6	(((gaming or gambling or slot or fruit or poker or lottery or lotteries) near5 (machine* or terminal*))) IN NHSEED
7	(pokies or pokey or puggy or fruities) IN NHSEED
8	(((dice or card or cards or roulette or blackjack or poker or baccarat or crap or craps or keno or casino* or bingo or bookmaker* or book maker or bookie* or lottery or lotteries or lotto or scratch card* or scratchcard* or raffle or raffles or sweepstak* or amusement arcade* or slot*) near5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose))) IN NHSEED
9	(((game or games or gaming or gamer*) near5 (money or monetization or monetisation or monetary))) IN NHSEED
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Database: PsycInfo

Date of last search: 04/04/2023

#	Searches
1	GAMBLING/
2	GAMBLING DISORDER/
3	(gambl* not standard gamble).ti,ab.
4	betting.ti,ab.
5	(bet or bets).ti,ab.
6	wager*.ti,ab.
7	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
8	(pokies or pokey or puggy or fruities).ti,ab.
9	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.
10	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.
11	or/1-10
12	limit 11 to english language
13	limit 12 to yr="2000 -Current"
14	(letter or editorial or comment reply).dt. or case report/

#	Searches
15	(letter or comment*).ti.
16	or/14-15
17	exp randomized controlled trial/
18	random*.ti,ab.
19	or/17-18
20	16 not 19
21	animal.po.
22	(rat or rats or mouse or mice).ti.
23	or/20-22
24	13 not 23
25	ECONOMICS/
26	HEALTH CARE ECONOMICS/
27	exp "COSTS AND COST ANALYSIS"/
28	RESOURCE ALLOCATION/
29	budget*.ti,ab.
30	cost*.ti,ab.
31	(economic* or pharmaco?economic*).ti,ab.
32	(price* or pricing*).ti,ab.
33	(financ* or fee or fees or expenditure* or saving*).ti,ab.
34	(value adj2 (money or monetary)).ti,ab.
35	resourc* allocat*.ti,ab.
36	(fund or funds or funding* or funded).ti,ab.
37	(ration or rations or rationing* or rationed).ti,ab.
38	or/25-37
39	"QUALITY OF LIFE"/
40	"HEALTH RELATED QUALITY OF LIFE"/
41	quality of life.ti.
42	((instrument or instruments) adj3 quality of life).ab.
43	quality adjusted life.ti,ab.
44	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
45	disability adjusted life.ti,ab.
46	daly*.ti,ab.
47	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
48	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab.
49	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab.
50	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
51	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
52	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
53	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
54	(hye or hyes).ti,ab.
55	(health* adj2 year* adj2 equivalent*).ti,ab.
56	(pqol or qls).ti,ab.
57	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
58	nottingham health profile*.ti,ab.
59	sickness impact profile.ti,ab.
60	(health adj3 (utilit* or status)).ti,ab.
61	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
62	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
63	disutilit*.ti,ab.
64	rosser.ti,ab.
65	willingness to pay.ti,ab.
66	standard gamble*.ti,ab.
67	(time trade off or time tradeoff).ti,ab.
68	tto.ti,ab.
69	(hui or hui1 or hui2 or hui3).ti,ab.
70	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
71	duke health profile.ti,ab.
72	functional status questionnaire.ti,ab.
73	dartmouth coop functional health assessment*.ti,ab.
74	or/39-73
75	24 and 38

#	Searches
76	24 and 74
77	75 or 76
78	limit 77 to ("0100 journal" or "0110 peer-reviewed journal")

Database: Social Care Online

Date of last search: 04/04/2023

#	Searches
	AllFields: 'gamble or gambler or gamblers or gambling or gambled or betting or bet or bets or wager or wagers or "gaming machine" or "slot machine" or "fruit machine" or "poker machine" or "lottery machine" or "lotteries machine" or "gaming terminal" or "slot terminal" or "fruit terminal" or "poker terminal" or "lottery terminal" or "lotteries terminal" or pokies or pokey or puggy or fruities'
	AND AllFields: 'budget or cost or economic or pharmaco-economic or price or pricing or finance or fee or fees or expenditure or saving or "value for money" or "monetary value" or "allocate resource" or "resource allocation" or fund or funds or funding or funded or ration or rations or rationing or rationed' or "quality of life" or "quality adjusted life" or "disability adjusted life" or "short form or shortform" or "health year equivalent" or "sickness impact profile" or "health status indicator" or "health utility" or "utility value" or "utility measure" or "standard gamble" or "time trade off" or "time tradeoff"'
	AND PublicationYear:'2000 2020'

Database: Social Policy and Practice (SPP)

Date of last search: 04/04/2023

#	Searches
1	(gambl* not standard gamble).ti,ab.
2	betting.ti,ab.
3	(bet or bets).ti,ab.
4	wager*.ti,ab.
5	((gaming or gambling or slot or fruit or poker or lottery or lotteries) adj5 (machine? or terminal?)).ti,ab.
6	(pokies or pokey or puggy or fruities).ti,ab.
7	((dice or card? or roulette or blackjack or poker or baccarat or crap or craps or keno or casino? or bingo or bookmaker? or book maker or bookie? or lottery or lotteries or lotto or scratch card? or scratchcard? or raffle or raffles or sweepstak* or amusement arcade? or slot?) adj5 (money or monetization or monetisation or monetary or currency or currencies or cryptocurrency or cryptocurrencies or reward* or win or wins or winning* or loss or losses or lose)).ti,ab.
8	((game or games or gaming or gamer?) adj5 (money or monetization or monetisation or monetary)).ti,ab.
9	or/1-8
10	limit 9 to yr="2000 -Current"
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	or/11-19
21	quality of life.ti.
22	((instrument or instruments) adj3 quality of life).ab.
23	quality adjusted life.ti,ab.
24	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
25	disability adjusted life.ti,ab.
26	daly*.ti,ab.
27	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
28	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab.
29	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab.
30	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
31	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
32	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
33	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
34	(hye or hyes).ti,ab.

#	Searches
35	(health* adj2 year* adj2 equivalent*).ti,ab.
36	(pqol or qls).ti,ab.
37	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
38	nottingham health profile*.ti,ab.
39	sickness impact profile.ti,ab.
40	(health adj3 (utilit* or status)).ti,ab.
41	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
42	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
43	disutilit*.ti,ab.
44	rosser.ti,ab.
45	willingness to pay.ti,ab.
46	standard gamble*.ti,ab.
47	(time trade off or time tradeoff).ti,ab.
48	tto.ti,ab.
49	(hui or hui1 or hui2 or hui3).ti,ab.
50	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
51	duke health profile.ti,ab.
52	functional status questionnaire.ti,ab.
53	dartmouth coop functional health assessment*.ti,ab.
54	or/21-53
55	10 and 20
56	10 and 54
57	55 or 56

Database: Social Science Citation Index (SSCI)

Date of last search: 04/04/2023

#	Searches
	(gambl* or betting or bet or bets or wager* or "gaming machine*" or "slot machine*" or "fruit machine*" or "poker machine*" or "lottery machine*" or "lotteries machine*" or "gaming terminal*" or "slot terminal*" or "fruit terminal*" or "poker terminal*" or "lottery terminal*" or "lotteries terminal*" or pokies or pokey or puggy or fruities) and (budget* OR cost* OR economic* OR pharmaco-economic* OR price* OR pricing* OR financ* OR fee OR fees OR expenditure* OR saving* OR "value for money" OR "monetary value" OR "resourc* allocat*" OR "allocat* resourc*" OR fund OR funds OR funding* OR funded OR ration OR rations OR rationing* OR rationed or "quality of life" or "quality adjusted life" or "disability adjusted life" or "short form or shortform" or "health year equivalent*" or "nottingham health profile*" or "sickness impact profile*" or "health status indicator*" or "health utilit*" or "utilit* valu*" or "utilit* measur*" or "willingness to pay" or "standard gamble*" or "time trade off" or "time tradeoff" or "duke health profile" or "functional status questionnaire" or "dartmouth coop functional health assessment*") (Title) Timespan: 2000-01-01 to 2022-03-24

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

See Results of the search – figure 1 from the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

See the Characteristics of included studies tables from the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

See the Data and analyses tables from the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

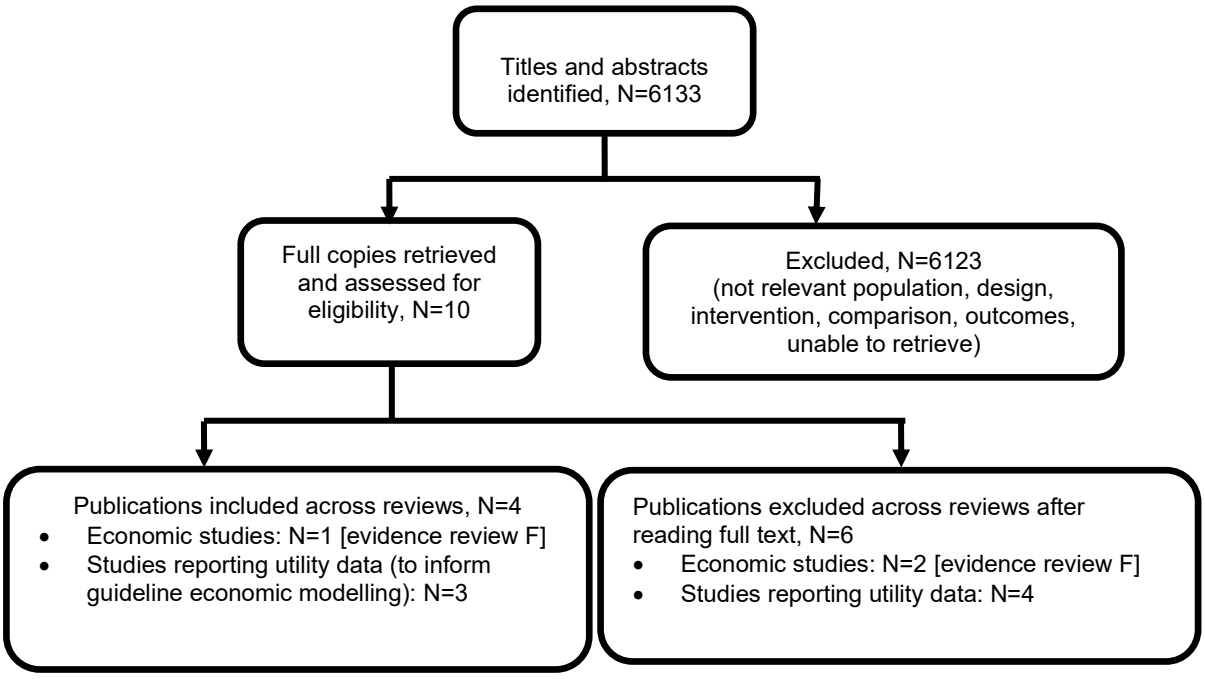
See the Summary of findings tables from the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Appendix G Economic evidence study selection

Economic evidence study selection for: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

A global health economics search was undertaken for all areas covered in the guideline. **Figure 1** shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people experiencing harmful gambling, their families, friends and others close to them, and studies reporting gambling-related health state utility data.

Figure 1: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

No economic evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

No economic modelling was undertaken for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

Excluded effectiveness studies

See the Characteristics of excluded studies table of the Cochrane review for Pharmacological interventions for the treatment of disordered and problem gambling at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008936.pub2/full

Excluded economic studies

No economic evidence was reviewed at full text and excluded from this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of pharmacological interventions for people who participate in harmful gambling (including those with comorbid conditions)?

K.1.1 Research recommendation

What is the effectiveness and cost-effectiveness of combination pharmacological therapy for the treatment of gambling-related harms?

K.1.2 Why this is important

The evidence for single pharmacological therapies for the treatment of harmful gambling showed there was little evidence of benefit for many of the medications tested. However, in other compulsive disorders, there is known to be benefit from combination therapy and therefore evidence to identify if this is the case with harmful gambling may increase the number of treatment options.

K.1.3 Rationale for research recommendation

Table 4: Research recommendation rationale

Importance to 'patients' or the population	There are few evidence-based pharmacological options that are known to be effective and cost-effective for treating harmful gambling and so evidence of effectiveness and cost-effectiveness for combination therapy would increase treatment options.
Relevance to NICE guidance	NICE guidelines provide limited advice on pharmacological options for treating harmful gambling due to a paucity of evidence.
Relevance to the NHS	NHS specialist gambling clinics are currently being set up nationwide and a broader range of therapeutic options is likely to improve success rates.
National priorities	Treatment of harmful gambling is a national priority for the Office for Health Improvement and Disparities.
Current evidence base	No evidence for combination therapies was identified as part of this evidence review.
Equality considerations	None known.

NHS: National Health Service; NICE: National Institute for Health and Care Excellence

K.1.4 Modified PICO table

Table 5: Research recommendation modified PICO table

Population	People aged 18 years or older, currently participating in harmful gambling.
Intervention	Combination therapy with any combination of: • Antidepressants (including serotonin reuptake inhibitors)

	• Mood stabilisers and anticonvulsants • Opioid antagonists (for example, naltrexone) • Atypical antipsychotics (for example, olanzapine) • Other pharmacological treatments that do not belong within these 4 general categories
Comparator	• Interventions compared with each other • An appropriate 'non-intervention' (for example, placebo)
Outcome	**Critical** • Gambling behaviour (measured for example by reduction in money spent, time spent, frequency) • Severity of gambling symptoms (as measured by standard measurement tools, for example, clinical global impression rating scale (CGI), SOGS, or Massachusetts Gambling Screen) • Cost-effectiveness (including resource use measurements and QALY estimations using a validated preference-based measure such as the EQ-5D or SF-6D) **Important** • Severity of secondary symptoms such as depression and anxiety (measured by validated instruments such as the Spielberger State-Trait Anxiety Inventory or the Beck Depression Inventory) • Occurrence of clinical diagnoses of pathological gambling (operationalised according to a clinician administered diagnostic interview (for example, DSM criteria))
Study design	Randomised controlled trial
Timeframe	End of treatment and then 6 and 12 months follow up

DSM: Diagnostic and statistical manual of mental disorders; EQ-5D: European Quality of Life 5 dimension; SF-6D; Short-Form 6-Dimension health index; SOGS: South Oaks Gambling Screen; QALY: Quality adjusted life years

K.1.5 Research recommendation

What is the effectiveness and cost-effectiveness of pharmacological treatment for gambling-related harms in people with comorbidities (for example, depression, anxiety or other addictions)?

K.1.6 Why this is important

The evidence for single pharmacological therapies for the treatment of harmful gambling showed there was little evidence of benefit for many of the medications tested. However, the population included in these studies was primarily people without comorbidities or other addictions and did not consider that pharmacological therapy may have a differential effect in different sub-types of people experiencing harmful gambling.

K.1.7 Rationale for research recommendation

Table 6: Research recommendation rationale

Importance to 'patients' or the population	People experiencing harmful gambling may often be suffering from comorbidities such as depression and anxiety or other addictions. These differences may impact on the effectiveness of treatment and so evidence about effectiveness in these different groups will support better tailoring of treatment to individuals.
Relevance to NICE guidance	NICE guidelines provide limited advice on which groups of people will benefit most from pharmacological treatment and this information will allow more specific recommendations to be made.
Relevance to the NHS	NHS specialist gambling clinics are currently being set up nationwide and a better tailoring of therapeutic options to individuals is likely to improve success rates.
National priorities	Treatment of harmful gambling is a national priority for the Office for Health Improvement and Disparities.
Current evidence base	No subgroup analysis by comorbidities or personality types was available as part of this evidence review.
Equality considerations	People with co-morbid mental health conditions may be at a greater risk of experiencing harmful gambling, and accessing treatment for this condition if they do. It is important to determine if the effectiveness of pharmacological treatment is the same in this population in order to ensure they are receiving the most appropriate treatment for them and prevent a furthering of health inequalities.

NHS: National Health Service; NICE: National Institute for Health and Care Excellence

K.1.8 Modified PICO table

Table 7: Research recommendation modified PICO table

Population	**Inclusion** People aged18 years and older, currently participating in harmful gambling and with comorbid mental health conditions. **Exclusion** People with a diagnosis of Parkinson's disease.
Intervention	Pharmacological therapy (either monotherapy or combination) with any of: • Antidepressants (including serotonin reuptake inhibitors) • Mood stabilisers and anticonvulsants • Opioid antagonists (for example, naltrexone)

	• Atypical antipsychotics (for example, olanzapine) • Other pharmacological treatments that do not belong within these 4 general categories
Comparator	• Interventions compared with each other • An appropriate 'non-intervention' (for example, placebo)
Outcome	**Critical** • Gambling behaviour (measured for example by reduction in money spent, time spent, frequency) • Severity of gambling symptoms (as measured by standard measurement tools, for example, clinical global impression rating scale (CGI), SOGS, or Massachusetts Gambling Screen) • Cost-effectiveness (including resource use measurements and QALY estimations using a validated preference-based measure such as the EQ-5D or SF-6D) **Important** • Severity of secondary symptoms such as depression and anxiety (measured by validated instruments such as the Spielberger State-Trait Anxiety Inventory or the Beck Depression Inventory) • Occurrence of clinical diagnoses of pathological gambling (operationalised according to a clinician administered diagnostic interview (for example, DSM criteria))
Study design	Randomised controlled trial
Timeframe	End of treatment and then 6 and 12 months follow up
Additional information	Pre-planned stratification by comorbidities, personality types.

DSM: Diagnostic and statistical manual of mental disorders; EQ-5D: European Quality of Life 5 dimension; SF-6D; Short-Form 6-Dimension health index; SOGS: South Oaks Gambling Screen; QALY: Quality adjusted life years

K.1.9 Research recommendation

What is the effectiveness and cost-effectiveness of pharmacological treatment with and without psychological therapy for the treatment of gambling-related harms?

K.1.10 Why this is important

Limited evidence is available for the effectiveness of pharmacological therapies to treat harmful gambling and most of this evidence is based on people who are not currently receiving any other treatment. However, in clinical practice most people will continue with psychological therapy (usually CBT) at the same time as pharmacological therapy. It is not known if pharmacological therapies are therefore effective and cost-effective when used alone in people who have not responded adequately to psychological therapies or when used as adjunctive therapy, in addition to psychological therapies..

K.1.11 Rationale for research recommendation

Table 8: Research recommendation rationale

Importance to 'patients' or the population	People experiencing harmful gambling may wish to try psychological therapies such as CBT as the first line of treatment, but if this is unsuccessful and leading to the desired reduction in harmful gambling, pharmacological therapy may provide an alternative or additional adjunctive therapy.
Relevance to NICE guidance	NICE guidelines provide limited advice on which groups of people will benefit most from pharmacological treatment and this information will allow more specific recommendations to be made.
Relevance to the NHS	NHS specialist gambling clinics are currently being set up nationwide and a better tailoring of therapeutic options to individuals is likely to improve success rates.
National priorities	Treatment of harmful gambling is a national priority for the Office for Health Improvement and Disparities.
Current evidence base	No evidence was identified on the effectiveness of pharmacological therapy where there is an inadequate response to psychological therapies alone.
Equality considerations	None known.

CBT: Cognitive behavioural therapy; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

K.1.12 Modified PICO table

Table 9: Research recommendation modified PICO table

Population	People aged 18 years or older, currently participating in harmful gambling, who have not responded adequately to group or individual CBT and who are being switched to or started on adjunctive pharmacological therapy.
Intervention	Pharmacological therapy with any of: • Antidepressants (including serotonin reuptake inhibitors) • Mood stabilisers and anticonvulsants • Opioid antagonists (for example, naltrexone) • Atypical antipsychotics (for example, olanzapine) • Other pharmacological treatments that do not belong within these 4 general categories
Comparator	• Placebo • CBT plus pharmacological therapy • CBT alone (or with an appropriate 'non-intervention' such as placebo)
Outcome	**Critical**

	• Gambling behaviour (measured for example by reduction in money spent, time spent, frequency) • Severity of gambling symptoms (as measured by standard measurement tools, for example, clinical global impression rating scale (CGI), SOGS, or Massachusetts Gambling Screen) • Cost-effectiveness (including resource use measurements and QALY estimations using a validated preference-based measure such as the EQ-5D or SF-6D) **Important** • Severity of secondary symptoms such as depression and anxiety (measured by validated instruments such as the Spielberger State-Trait Anxiety Inventory or the Beck Depression Inventory) • Occurrence of clinical diagnoses of pathological gambling (operationalised according to a clinician administered diagnostic interview (for example, DSM criteria))
Study design	Randomised controlled trial
Timeframe	End of treatment and then 6 and 12 months follow up
Additional information	Pre-planned stratification by nature and number of psychological therapies previously received.

DSM: Diagnostic and statistical manual of mental disorders; EQ-5D: European Quality of Life 5 dimension; SF-6D; Short-Form 6-Dimension health index; SOGS: South Oaks Gambling Screen; QALY: Quality adjusted life years

Appendix L Methodological limitations

The methodological limitations of the Cochrane review (Dowling 2022) have been assessed using the ROBIS tool to assess risk of bias in systematic reviews.

ROBIS tool to assess risk of bias in systematic reviews

Domain 1: Study eligibility criteria

1.1 Did the review adhere to pre-defined objectives and eligibility criteria? Yes

1.2 Were the eligibility criteria appropriate for the review question? Yes

1.3 Were eligibility criteria unambiguous? Yes

1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (for example, date, sample size, study quality, outcomes measured? Yes

1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (for example, publication status or format, language, availability of data)? Yes

Concerns regarding specification of study eligibility criteria: LOW concern

Domain 2: Identification and selection of studies

2.1 Did the search include an appropriate range of databased/electronic sources for published and unpublished reports? Yes

2.2 Were methods additional to database searching used to identify relevant reports? Probably no

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes

2.4 Were restrictions based on date, publication format, or language appropriate? Yes

2.5 Were efforts made to minimise error in selection of studies? Yes

Concerns regarding methods used to identify and/or select studies: LOW concern

Domain 3: Data collection and study appraisal

3.1 Were efforts made to minimise error in data collection? Yes

3.2 Were sufficient study characteristics available for both review authors and reader to be able to interpret the results? Yes

3.3 Were all relevant study results collected for use in the synthesis? Yes

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? Yes

3.5 Were efforts made to minimised error in risk of bias assessment? Yes

Concerns regarding methods used to collect data or appraise studies: LOW concern

Domain 4: synthesis and findings

4.1 Did the synthesis include all studies that it should? Probably yes

4.2 Were all pre-defined analyses reported or departures explained? Yes

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? Yes

4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? Yes

4.5 Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses? Yes

4.6 Were biases in primary studies minimal or addressed in the synthesis? Yes

Concerns regarding the synthesis and findings: LOW concern

Risk of bias in the review

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? Yes

B. Was the relevance of identified studies to the review's research question appropriately considered? Yes

C. Did the reviewers avoid emphasising results on the basis of statistical significance? Yes

Risk of bias in the review: LOW concern