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Pharmacological and psychosocial treatment of adults with gambling disorder: A meta-review

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Abstract:	BACKGROUND AND OBJECTIVES. Gambling Disorder (GD) is a major public health problem, leading to impaired socio-economical functioning and increased social costs. Although the research on this field has been rising over the years, approved treatment guidelines for GD are currently not available. The aim of this study was to systematically review the literature on the pharmacological and non-pharmacological treatment of adults with GD, to identify possible agreed-upon standards of care. METHODS. MEDLINE, PubMed, and Cochrane electronic databases were searched up to September 2018 for systematic reviews on pharmacological and non-pharmacological treatment of adults with GD. Twenty-three studies were eventually included in this meta-review. RESULTS. Studies reported promising results of opioid antagonists and mood stabilizers in reducing GD-related symptomatology. Lithium was particularly effective in gamblers with comorbid bipolar disorders. Cognitive Behavioural Therapy (CBT) was the most commonly used psychological intervention and reduced global severity, gambling frequency, and financial loss. Motivational Interviewing (MI) seemed to improve several GD domains, alone or in combination with CBT. Self Help Interventions (SHIs) showed some efficacy in promoting treatment-seeking, and in combination with other treatments. CONCLUSIONS. We found moderate evidence of effect for CBT, but lower evidence for pharmacotherapy and SHIs. Results suggested some efficacy for MI in the short- but not in the long-term. It is likely that certain interventions might be more effective than others on specific features of GD. Further studies are needed to compare the efficacy and acceptability of individual and combined psychosocial and pharmacological interventions, in order to deliver patient-tailored treatments.

Pharmacological and psychosocial treatment of adults with gambling disorder: A meta-review

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ABSTRACT

BACKGROUND AND OBJECTIVES. Gambling Disorder (GD) is a major public health problem, leading to impaired socio-economical functioning and increased social costs. Although the research on this field has been rising over the years, approved treatment guidelines for GD are currently not available. The aim of this study was to systematically review the literature on the pharmacological and non-pharmacological treatment of adults with GD, to identify possible agreed-upon standards of care.

METHODS. MEDLINE, PubMed, and Cochrane electronic databases were searched up to September 2018 for systematic reviews on pharmacological and non-pharmacological treatment of adults with GD. Twenty-three studies were eventually included in this meta-review.

RESULTS. Studies reported promising results of opioid antagonists and mood stabilizers in reducing GD-related symptomatology. Lithium was particularly effective in gamblers with comorbid bipolar disorders. Cognitive Behavioural Therapy (CBT) was the most commonly used psychological intervention and reduced global severity, gambling frequency, and financial loss. Motivational Interviewing (MI) seemed to improve several GD domains, alone or in combination with CBT. Self Help Interventions (SHIs) showed some efficacy in promoting treatment-seeking, and in combination with other treatments.

CONCLUSIONS. We found moderate evidence of effect for CBT, but lower evidence for pharmacotherapy and SHIs. Results suggested some efficacy for MI in the short- but not in the long-term. It is likely that certain interventions might be more effective than others on specific features of GD. Further studies are needed to compare the efficacy and acceptability of individual and combined psychosocial and pharmacological interventions, in order to deliver patient-tailored treatments.

1. INTRODUCTION

Gambling disorder (GD) features persistent and recurrent maladaptive patterns of gambling behavior, which ultimately lead to impaired socio-relational functioning (American Psychiatric Association, 2013). In the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5), GD has been classified in the "Substance-related and Addictive Disorders" (SAD) category because of its striking similarities to drug addiction in several respects, including neurobiological mechanisms, impaired cognitive abilities, genetic liabilities, and treatment response (Fauth-Bühler et al., 2017; Moccia et al., 2017; Pettorruso et al., 2018). Surveys indicate that GD prevalence in the general European population ranges from 0.12% to 5.8%, and similar rates have been reported worldwide (Calado and Griffiths, 2017). Evidence suggests that gender and age differences may account in GD pathophysiology and treatment, with male individuals and adolescents displaying an increased risk of developing maladaptive gambling conducts (Van Den Bos et al., 2013; Di Nicola et al., 2017). Psychiatric comorbidities, including mood, personality and substance use disorders are common in GD individuals. Of note, comorbid diseases often affect gambling treatment access and compliance, possibly by influencing the efficacy of pharmacological and psychological interventions (Lorains et al., 2011; Di Nicola et al., 2014). To date, a number of different treatment modalities, including psychosocial and pharmacological interventions, have been applied to GD, but no standardized practice guidelines are currently available. Psychopharmacological compounds, including antidepressants, mood stabilizers, and opioid receptors antagonists (though administered in an off-label regimen) have shown mixed results in improving GD outcomes (Grant et al., 2014; Goslar et al., 2018). Psychological therapies, such as cognitive-behavioral therapy (CBT) and motivational interviewing (MI), proved to be effective in reducing gambling behavior and other symptoms of GD. However, the durability of therapeutic gain is unknown and additional research is required to draw conclusions (Cowlishaw et al., 2012; Rash and Petry, 2014). Taken all together, these findings suggest a need for further systematic evaluation of current therapeutic approaches in GD, along with a closer

examination of clinical variables that could affect GD outcome. The aim of the present study was to systematically review the literature relevant to the pharmacological and non-pharmacological treatment of adults with GD, in order to identify possible agreed-upon standards of care for Gambling Disorder.

2. METHODS

MEDLINE, PubMed and Cochrane electronic databases were searched up to 6 September 2018 for systematic reviews on pharmacological and non-pharmacological treatment of adults with GD. Electronic databases were searched using the following syntax: (gambling OR gamble OR betting OR wagering) AND (Clinical Trial [ptyp] OR meta-analysis* OR metaanalysis* OR systematic review* OR review*). No language restrictions were applied. We included only systematic reviews or meta-analysis of psychological and/or pharmacological interventions for the treatment of pathological, problem gambling, or GD.

Two authors in a double-blind fashion examined every record. Disagreements about the selection of studies and data extraction were solved through discussion. References from the included papers were manually searched to identify other relevant studies. The quality of the systematic reviews was evaluated by using the AMSTAR-2 (Shea et al., 2017).

We initially identified 2840 potentially relevant studies. After having excluded duplicate citations based on abstracts and titles, we screened a total of 308 pertinent papers about pathological and problem gambling. Finally, we included 23 papers (see Figure 1 and Table 1, full list of references available as supplementary material), which we qualitatively analyzed to address the following clinical questions to our meta-review:

- What is the evidence for the efficacy of pharmacological treatments for individuals with gambling disorder?

- What is the evidence for the efficacy of cognitive-behavioral therapy for individuals with gambling disorder?
- What is the evidence for the efficacy of motivational interventions for individuals with gambling disorder?
- What is the evidence for the efficacy of self-help interventions for individuals with gambling disorder?

3. RESULTS

3.1 What is the evidence for the efficacy of pharmacological treatments for individuals with gambling disorder?

Overall, pharmacological interventions have been found to produce mixed results in reducing GD symptoms (Pallesen et al., 2007; Bartley et al., 2013; Mouaffak et al., 2017). Pallesen's group (2007) found all pharmacological treatments to be moderately efficacious for reducing any gambling symptoms in adults when compared with no treatment/placebo (SMD 0.78, 95%CI 0.64 to 0.92). However, a more recent meta-analysis by Bartley et al. (2013) found for all pharmacological treatments a small effect size compared to placebo for any gambling symptoms (SMD 0.22, 95%CI 0.08 to 0.36), with the 95%CI including a statistically significant, but clinically minor effect.

Research in psychopharmacology for GD has improved over time, and while the earliest systematic reviews had few RCTs included (e.g., Petry et al., 1999 included only two RCTs), the most recent systematic reviews comprised a reasonable number of RCTs (e.g., Grant et al., 2014 included 18 RCTs). However, no medications have been officially approved yet by the USA Food and Drug Administration or by the European Medicine Agency for the treatment of GD. This may be due to the fact that clinical results are sometimes divergent and they frequently have severe limitations (Labuzek, 2014). The Australian National Health and Medical Research Council (NHMRC) suggested three main classes of medications for the treatment of GD: opioid antagonists,

antidepressants and mood stabilizers (NHMCR, 2011). Other types of psychopharmacological agents that have been studied include olanzapine and N-acetylcysteine (Pickering et al., 2018).

The RCTs suggested that some medications could be more efficacious than others. Opioid antagonists, especially naltrexone and nalmefene, have demonstrated mixed degrees of efficacy in treating GD (Dell'Osso et al., 2005; Mouaffak et al., 2017). Mouaffak et al. (2017) found that naltrexone was significantly more efficacious than placebo in reducing GD symptoms when treating individuals suffering from behavioral addictions in general (SMD –0.27, 95%CI –0.51 to – 0.03), but not when treating pathological gamblers (SMD –0.22, 95%CI -0.53 to 0.09). These results are not consistent with those of another meta-analysis by Bartley et al. (2013), in which opioid antagonists were significantly more efficacious than placebo in reducing GD symptoms, with a small effect size (SMD 0.22, 95% CI 0.03 to 0.41).

Some systematic reviews analyzed RCTs on SSRIs (Grant & Kim, 2002; Dell'Osso et al., 2005; Achab et al., 2011). Five randomised, double-blind, placebo-controlled trials with SSRIs have been conducted (Hollander et al., 2000; Blanco et al., 2002; Kim et al., 2002; Grant et al., 2003; Saiz-Ruiz et al., 2005), two of which showing SSRIs to be significantly superior to placebo (Hollander et al., 2000; Kim et al., 2002). Bartley et al. (2013) merged data from trials on SSRIs (Hollander et al., 2000; Blanco et al., 2002; Kim et al., 2002; Grant et al., 2003; Saiz-Ruiz et al., 2005) and bupropion (Black 2007). According to these Authors, antidepressants were not significantly associated with a reduction in gambling severity (SMD 0.18, 95% CI -0.06 to 0.42).

Regarding mood stabilizers, promising avenues for future research are held in the treatment of GD. Pallesen et al. (2007) found a moderate effect size for lithium versus placebo in reducing GD symptoms in patients with comorbid bipolar spectrum disorder (Cohen's d= 0.58). Bartley et al. (2013) found a non-significant moderate effect size for topiramate versus placebo in reducing GD symptoms in individuals with GD (SMD 0.40, 95%CI -0.21, 1.01).

Achab et al. (2011) raised some doubts about the generalizability of the results on mood stabilizers for GD, and larger trials are required before reaching any reasonable conclusion about their effect.

Some pathological gamblers with specific comorbidities may benefit more from certain pharmacological interventions than others (Dell'Osso, 2005). For example, in the meta-analysis by Pallesen et al. (2007), the proportion of male participants was negatively related to the magnitude of the effect sizes (unstandardised beta (B) 0.019, standard error for unstandardised beta (SEB) 0.004, $p<0.01$) when performing a regression analysis (Pallesen et al. 2007). Moreover, therapeutic effects appeared dose- and symptomatology-related. In three different studies (Grant, 2002; Grant et al., 2003; Mouaffak et al., 2017) the administered daily dose of naltrexone varied from 25 to 250 mg in conditions in which the urge of gambling was dominant. Overall, the results showed a considerable reduction in gambling severity (90.9% of patients responded to naltrexone) when naltrexone was (1) used as monotherapy; (2) used in patients with no comorbidity. The selected studies did not report specific results about a proper drug dosing, and clear clinical guidelines are not available.

3.2 What is the evidence for the efficacy of cognitive behavioral therapy for individuals with gambling disorder?

Many psychological interventions have been studied for the treatment of individuals with GD. All psychological interventions pooled together have been associated with reduced gambling symptoms, when compared to standard care or no treatment (SMD 2.01, 95% CI 1.90 to 2.13) (Pallesen et al., 2005). However, evidence suggested that only 10% of individuals with GD contact the helpline service to get assistance (Lucchini & Griffiths, 2015) and that less than 10% of pathological gamblers were in treatment at any one time (Cunningham, 2005). Among face-to-face treatments (FTFTs), CBT proved to be the most commonly reported intervention (Gooding & Tarrier, 2009; Chebli et al., 2016; Chrétien 2017; Goslar et al., 2017). Australian clinical guidelines for screening, assessment, and treatment in problem gambling (PGRCT, 2011) suggested individual or group CBT for the treatment of gambling symptoms (level B of recommendation [NHMRC, 2009]).

CBT is based on cognitivism and behaviorism paradigms. According to cognitivism, mental disorders are triggered by unhealthy beliefs (Ellis, 1958; Beck, 1967), while for behaviorism most human traits

and actions are learned (Watson, 1920) so that gambling disorder can be considered a learned behavior. Therefore, CBT aims to modify cognitions and behaviors that lead to pathological gambling.

A recent meta-analysis by Goslar et al. (2018), showed the efficacy of FTFTs versus no treatment in GD. In particular, face-to-face CBT was proven effective in reducing global severity (SMD 0.31, 95% CI 0.86 to 2.06), gambling frequency (SMD 0.15, 95% CI 0.48 to 1.08) and financial loss (SMD 0.11, 95% CI 0.44 to 0.86). On the contrary, both global severity and financial loss appeared not significantly changed after self-guided CBT, while gambling frequency was still positively affected by the treatment, even if with smaller effect sizes (SMD 0.09, 95% CI 0.06 to 0.42) (Goslar et al., 2018). In a previous meta-analysis, CBT resulted to have robust effects both at the short-term (0-3 months) (SMD -0.72, 95% -0.92 to -0.49), after twelve month of follow up (SMD -0.40, 95% CI -0.7 to -0.08) and after twenty-four months of follow-up (SMD -0.81, 95% CI -1.16 to -0.47) (Gooding & Tarrier, 2009). Although the results of these studies were promising, the short-term results appeared more encouraging than the long-term results (Gooding & Tarrier, 2009; Cowlishaw, 2012; Goslar et al., 2018). A recent Cochrane review, updated from a previous one including only 4 RCTs (Oakley-Browne, 2000), examined 14 studies and indicated insufficient evidence for the maintenance of effect for CBT in reducing gambling behavior when compared to no treatment (which included wait-list or assessment-only controls). In fact, lack of statistically significant efficacy at 9 to 12 months follow up was evidenced in three domains, such as gambling severity (SMD -0.11, 95% CI -0.43 to 0.22), financial loss (SMD -0.15, 95% CI -0.47 to 0.18), and frequency of gambling (SMD -0.12, 95% CI 0.45 to 0.20), whereas the same three domains were significantly effective for CBT at the short-term evaluation (0-3 months). Remarkably, follow-up data were available only for one RCT (Cowlishaw et al., 2012).

Mindfulness-enhanced cognitive behavioral therapy (M-CBT) also was explored for the treatment of GD. In a controlled pilot study, M-CBT was tested for GD, showing efficacy for gambling symptoms

at post-treatment (SMD 1.14; 95%CI 0.13 to 2.16) (Toneatto et al., 2014). M-CBT still needs further research before being considered in standard practice.

3.3 What is the evidence for the efficacy of motivational interventions for individuals with gambling disorder?

Alternative psychological therapies for GD are characterized by changes in behavior and are considered as an avenue to engage problem or at-risk gamblers (Diskin & Hodgins, 2009; Yakovenko et al., 2015). There is evidence for the efficacy of motivational approaches in the treatment of GD (Potenza 2002; Cowlishaw et al., 2012). Australian clinical guideline for screening, assessment, and treatment in problem gambling (PGRCT, 2011) suggested Motivational Interviewing (MI) for the treatment of gambling symptoms (level B of recommendation [NHMRC, 2009]). MI is a brief intervention (i.e., 2-4 sessions) aimed at managing the patient's ambivalence about change through reflective listening, understanding, and empathy (De Giorgi, 2018). MI originates from Rogers' person-centered counseling, through the integration of cognitive and behavioral strategies (Rogers, 1951; Miller, 1991). MI can be delivered, both in clinical trials and in clinical practice, alone or in combination with other brief interventions, such as CBT (Toneatto & Ladouceur 2003; Chrétien, 2017; Pickering, 2018; De Giorgi, 2018).

Meta-analyses seem to confirm the supposed efficacy of MI on the distinct gambling disorder domains, even if with slightly different results. According to a systematic review performed by the Cochrane Collaboration (Cowlishaw et al., 2012), the intervention was found efficacious only in reducing financial loss at 0-3 months post-treatment (3 trials included; SMD -0.41, 95% CI -0.75 to -0.07) and the frequency of gambling at 9-12 months follow-up (1 trial included; SMD 0.53, 95% CI -1.04 to -0.02). Yakovenko et al. (2015), instead, found the MI efficacious in reducing gambling frequency at all time points up to the 12 months follow-up, and financial loss at post-treatment (SMD -0.23, 95% CI -0.41 to -0.05). Control conditions of included trials varied from assessment only to providing a CBT-based workbook and to control interviews using SCID-II modules (Cowlishaw et

al. 2012; Yakovenko et al. 2015). Individual moderators of intervention outcome were not analyzed by meta-analyses (Cowlishaw et al. 2012; Yakovenko et al. 2015).

Concerning the comparative efficacy between MI and CBT for GD, clinical trials found no significant differences in terms of both efficacy on gambling symptoms and adherence to the treatment (Carlbring et al., 2010; Oei et al., 2010).

3.4 What is the evidence for the efficacy of self-help interventions for individuals with gambling disorder?

In the treatment of GD, self-help interventions (SHIs) may be useful in reducing the barriers associated with seeking professional treatment and in addition to traditional interventions (Petry, 1999; Marchica, 2016). Carlbring and Smit (2008) reported a high effect size for SHIs compared to a wait-list control group in reducing gambling symptoms (SMD 1.36). Other studies (Hodgins et al., 2001, Hodgins et al., 2009) introduced the use of telephone helplines in combination with self-help workbooks, but without finding significant improvement in gambling symptoms (Goslar et al., 2017). Danielsson et al. (2014) reported no effect for FTFT versus phone-delivered intervention in reducing financial loss, while FTFT was more effective in reducing total hours spent in gambling (Danielsson, 2014).

Other SHIs included internet-delivered therapy or online interventions. Many trials seemed to report positive results for Internet-delivered therapy, and its efficacy did not seem limited to GD (Raylu, 2008; Gainsbury, 2011; Chebli, 2016). According to a systematic review by Chebli et al. (2016), Internet-delivered therapy was efficacious in reducing GD, and treatment effects were sustained up to the three years follow-up. The authors found that the implementation of Internet-delivered therapy and the addition of telephone consultations were time-efficient and cost-effective, with dropout rates which were similar or even superior to the dropout rates found in the studies investigating FTFTs. Chebli et al. (2016), based their conclusions on three non-comparative studies and one RCT.

A meta-analysis by Goslar et al. (2017) showed inferior effect sizes for SHIs compared with no treatment than FTFTs compared to no treatment, both in the short- and in the long-term. In particular, at short-term, SHIs had a low effect size, with no significant difference versus no treatment for the reduction of global severity (SHIs: SMD 0.30, 95% CI –0.02 to 0.63), while FTFTs had a significantly large effect size versus no treatment (SMD 1.15, 95% CI 0.63 to 1.67). Results were similar for the reduction of frequency for SHIs versus no treatment (SMD 0.12, 95% CI 0.02 to 0.22), and FTFTs versus no treatment (SMD 0.74, 95% CI 0.48 to 0.99) and for financial loss for SHIs versus no treatment (SMD 0.13, 95% CI 0.05 to 0.22) and FTFTs versus no treatment (SMD 0.67, 95% CI 0.47 to 0.87) (Goslar et al., 2017).

Although self-help, telephone and/or Internet treatments along with self-help workbooks seemed to achieve expanded accessibility (Rash & Petry, 2014; Danielsson et al., 2014; Yakovenko et al., 2015), it remains unclear whether or when such interventions can be deemed as appropriate. The negative results of the trials could be due to the fact that the majority of SHIs included resources processed within a brief, single session, which brought limited treatment benefit when compared to controls. Moreover, individuals with comorbid personality disorders or psychological problems and comprehensive interpersonal difficulties could respond less to SHIs, while individuals less educated may require assistance in learning and practicing skills (Raylu, 2008). On the other hand, SHIs tended to benefit individuals with high motivation, resourcefulness, education, and whose personality is characterized by functional, active, focused, stable, mechanical and determined traits (Raylu, 2008). Since SHIs have shown to be efficacious for some outcomes, notwithstanding their limited effect sizes, further studies would be needed in order to identify outcome predictors and sub-groups of gamblers more susceptible to benefit from certain types of SHIs (Goslar et al., 2018).

4. DISCUSSION

We found moderate evidence of effect for CBT for individuals with GD, while lower evidence was found for pharmacological interventions and SHIs. We found some effect for MI in the short-term, while no effect was proven in the long-term.

Regarding pharmacological interventions, we did not find a clear hierarchy between drugs to be used in GD therapy: all pharmaceutical classes - antidepressants, mood stabilizers, and antipsychotic agents - showed inconsistent results and, when effective, mixed degrees of efficacy in RCTs. The paucity of head-to-head studies rendered the comparison across medication even more difficult. Some studies indicated some medications to be more effective in a particular subgroup of individuals with GD with specific comorbidities (i.e., lithium for individuals with GD and comorbid bipolar disorder). Therefore, the generalization of the results was problematic. More experimental evidence is needed to determine in which cases pharmacological treatment for GD would be appropriate, and if so, which drug would be considered the first choice and in which group of individuals.

Among psychological interventions, a growing body of evidence has demonstrated the efficacy of both CBT and MI in the therapy of gambling disorders, even if some questions remain open. While, on the one hand, FTFTs seemed to be more effective than SHIs, it is not clear whether these results are maintained when considering the cost-effectiveness ratio. Follow-up data are scarce, and, in general, it seems that the good results obtained at the end of treatment were not maintained in the long-term; finally, help-seeking rates for psychotherapeutic treatments were low, and so were the attendance and acceptability. Self-help approaches such as telephone support, self-help workbooks, and internet-delivered interventions can help overcome some barriers to treatment access and therefore do represent a promising horizon. RCTs on SHIs were powered on superiority for reducing gambling symptoms when compared to wait-list controls, or sometimes on non-inferiority for reducing gambling symptoms when compared to FTFTs. However, since these interventions have been often offered in combination (e.g., telephone support plus self-help workbooks), and some

showed to be more efficacious in selected sub-categories of gamblers, it is still to understand in which subtypes of patients SHIs are the most appropriate, and whether they should be implemented alone or in combination to traditional treatments.

This review followed a strict systematic search protocol; however, it is not without limitations. We could not evaluate studies not included in the selected systematic reviews and meta-analyses. However, the search and selection of studies have been comprehensive, and we are confident not to have lost significant evidence. Moreover, the number of systematic reviews retrieved was small, with a small sample size, which limited our confidence in the evidence. Besides, although selected studies demonstrated multidimensional treatment measures, there was large variability in the range of outcomes used and inconsistency in specific measurement methods, particularly in the assessment of gambling behaviour. This issue has been previously raised in GD literature (Pickering et al., 2018), and supports the need to introduce a clear and uniform definition of GD treatment outcomes across intervention trials.

5. CONCLUSIONS

Current studies support the short-term efficacy of CBT and MI for GD. Overall, no evidence of efficacy was found for pharmacological interventions for GD. There is a body of evidence more substantial and consistent on the efficacy of psychosocial interventions compared to pharmacological treatments. Further studies are needed to compare and rank the efficacy and acceptability of both individual and combined psychosocial and pharmacological interventions.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the bibliographic search, screening, and selection processes.

Table

Table 1. Characteristics of the systematic reviews included in the meta-review.

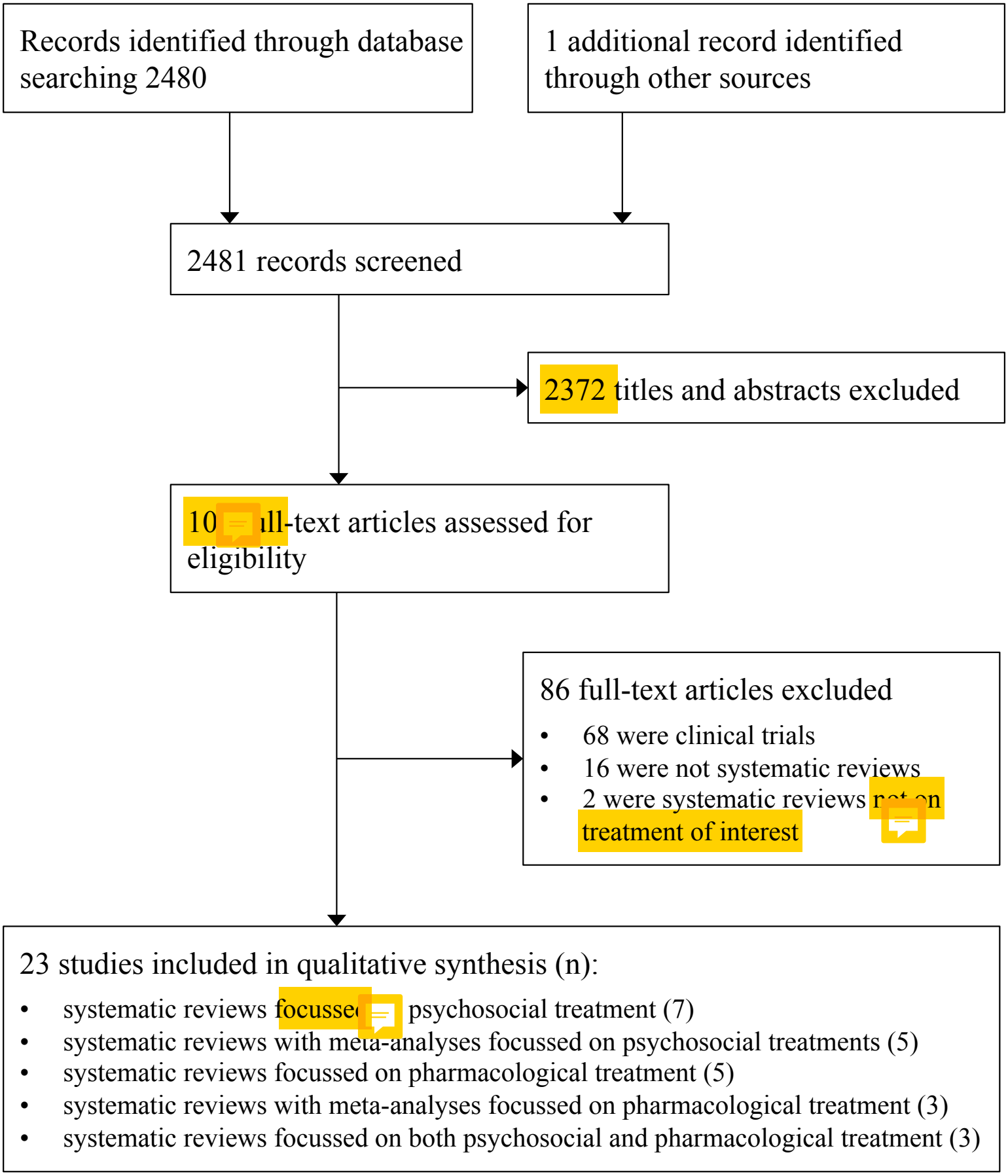
Study	Type of studies included	Study design	Population	Intervention	Comparison	Primary outcomes	AMSTAR-2
Achab, 2011	27 studies: 18 controlled trials, 9 open label trials	Systematic review	1.102 adult pathological gamblers	Pharmacological treatment (antidepressants, mood stabilizers, and antipsychotic agents)	Any pharmacological treatment	Efficacy, acceptability and tolerability	+
Bartley, 2013	14 RCTs	Systematic review and meta-analysis	1024 pathological gamblers	Pharmacological treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Placebo	Efficacy	+
Chebli, 2016	3 non-comparative studies and 1 RCT	Systematic review	901 adolescent or adult pathological gamblers	Internet based intervention	Any	Efficacy, acceptability	+ + +
Chrétien, 2017	39 studies (case studies, multiple case studies, experimental, quasi-experimental)	Systematic review	2.757 pathological gamblers	CBT, Cognitive restructuring	No comparison, no treatment	Efficacy in thoughts restructuring	+ +
Cowlishaw, 2012	12 RCTs	Systematic review	1245 adult pathological gamblers	CBT, Integrative therapy, motivational interviewing, other psychological therapy	10 of 14 studies compared the intervention with a wait-list control, 2 trials compared assessment only, 2 trials compared the intervention with gamblers anonymous referral	Efficacy	+ + + +
Danielsson, 2014	74 studies (2 RCTs involving pathological gamblers)	Systematic review	142.165 smokers or problem drinkers or adults affected by pathological gambling (406 pathological gamblers)	Technology-based support via telephone or web	Any technology based support	Efficacy	+
Dell'Osso, 2005	13 studies (RCTs, open label, case report)	Systematic review	398 pathological gamblers	Pharmacological treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Placebo, other pharmacological treatment	Efficacy and tolerability	+
Gainsbury, 2011	9 RCTs (1 of them involving pathological gamblers)	Systematic review	12.596 adults or adolescents affected by addictive disorders (66 adult pathological gamblers)	Internet-based therapy	Telephone counseling or waiting list	Efficacy, quality of life	+ +

Gooding, 2009	25 clinical trials	Systematic review and meta-analysis	1.326 adult pathological gamblers	Cognitive therapy, motivational interviewing and imaginal desensitization	Treatment as usual, no treatment or waiting list; or another form of treatment	Efficacy	+++
Goslar, 2017	27 RCTs	Systematic review and meta-analysis	3.879 adult pathological gamblers	All types of psychological face-to-face and self-guided treatments for disordered gambling	Face-to-face treatments compared with self-guided treatments	Efficacy	+++
Grant, 2014	18 RCTs	Systematic review	1708 pathological gamblers	Pharmacological treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Placebo	Efficacy	+
Labuzek, 2014	23 clinical trials	Systematic review	1110 adult pathological gamblers	Pharmacological treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Any	Efficacy and tolerability	+
Marchica, 2016	2 RCTs and 4 clinical trials	Systematic review	778 adult problem or at-risk gamblers	Personalized feedback intervention	Any	Efficacy, classification of outcome measures	+
Mouaffak, 2017	6 RCTs (3 of them involving pathological gamblers)	Systematic review and meta-analysis	356 adults affected by behavioral addictions (135 pathological gamblers)	Naltrexone	Placebo	Efficacy, acceptability and tolerability	+++
Oakley-Browne, 2000	4 RCTs	Systematic review and meta-analysis	262 adult pathological gamblers	Any psychosocial intervention	Any	Efficacy, acceptability, tolerability	++++
Pallesen, 2007	15 clinical trials	Systematic review and meta-analysis	597 pathological gamblers	Pharmacological treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Placebo, pretreatment, other pharmacological treatment	Efficacy, classification of outcome measures	+
Pallesen, 2005	22 clinical trials	Systematic review and meta-analysis	1434 adolescent and adult pathological gamblers	Any psychosocial intervention	No treatment	Efficacy, classification of outcome measures	+
Petry, 1999	1 observational study and 7 clinical trials	Systematic review	228 adult pathological gamblers	Family and marital therapy, cognitive behavioral therapy, clomipramine, fluvoxamine	Any	Efficacy	+
Pickering, 2018	17 RCTs and 17 comparative designs	Systematic review	4.889 adult pathological gamblers	Any psychological and pharmacological treatment	Any	Efficacy, classification of outcome measures	+++

Potenza, 2002	5 RCTs	Systematic review	217 problem or pathological gamblers	Pharmacological Treatment (antidepressant, mood stabilizers, and antipsychotic agents)	Placebo	Efficacy and safety	+
Raylu, 2008	Clinical trials	Systematic review	Problem gamblers	Self-help treatments	Placebo, no treatment, waiting list	Efficacy, acceptability	+
Toneatto, 2003	11 RCTs	Systematic review	579 pathological gamblers	Any psychological and pharmacological treatment	Any	Efficacy, acceptability, tolerability	+
Yakovenko, 2015	8 RCTs	Systematic review and meta-analysis	627 adult pathological gamblers	Motivational interviewing	No treatment	Efficacy	+ +

Legend: AMSTAR-2: + Critically low quality; + + Low quality; + + + Moderate quality; + + + + High quality; CBT= cognitive behavioral therapy, RCTs= randomized controlled trials.

Figure


Records identified through database searching 2480
1 additional record identified through other sources
2481 records screened
2372 titles and abstracts excluded
10 ıll-text articles assessed for eligibility
86 full-text articles excluded
• 68 were clinical trials
• 16 were not systematic reviews
• 2 were systematic reviews not on treatment of interest
23 studies included in qualitative synthesis (n):
• systematic reviews focusse psychosocial treatment (7)
• systematic reviews with meta-analyses focussed on psychosocial treatments (5)
• systematic reviews focussed on pharmacological treatment (5)
• systematic reviews with meta-analyses focussed on pharmacological treatment (3)
• systematic reviews focussed on both psychosocial and pharmacological treatment (3)

Supplemental Data File (References)