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Review article

Pharmacotherapy of impulse control disorders: A systematic review

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ABSTRACT

There are currently no evidence-based treatment recommendations for impulse control disorders, which include intermittent explosive disorder (IED), kleptomania and pyromania. Therefore, this systematic review sought to identify all randomized controlled trials (RCTs) that investigated pharmacological treatments for impulse control disorders, to evaluate their efficacy and tolerability. Searches were conducted within MEDLINE, PsychINFO, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Eight studies were included, six investigated pharmacotherapies for IED, while two investigated management for kleptomania. For the treatment of IED, oxcarbazepine and fluoxetine were the most efficacious. Importantly, divalproex was not superior to placebo in decreasing IED symptoms and was associated with significant adverse effects. In the treatment of kleptomania, only naltrexone was effective. The existing data suggest that the pharmacological treatment for impulse control disorders is an understudied area of psychiatry. Much of the current research on impulse control disorders focuses on management with anticonvulsants and antidepressants. Further studies conducted on these interventions in this population may yield promising results.

1. Introduction

Impulse control disorders are defined under the Diagnostic and Statistical Manual of Mental Disorders (DSM)−5 chapter, Disruptive, Impulse Control and Conduct Disorders. The DSM-5 category of impulse control disorders includes intermittent explosive disorder (IED), kleptomania, and pyromania (American Psychiatric Association, 2013a). DSM-IV classified impulse control disorders slightly differently and included several other related disorders under the impulse control disorders umbrella, particularly trichotillomania, excoriation, pathologic gambling, and compulsive disorders such as compulsive shopping (American Psychiatric Association, 2000).

Impulse control disorders as defined by the DSM-5 are characterized by five stages of symptomatic behavior. The behavior begins with an increased sense of tension or arousal, which is followed by a failure to resist the urge to act. During the act, the arousal peaks; and as the act is completed, a sense of relief or release is felt. Lastly, the patient may feel a sense of remorse or guilt for their actions (American Psychiatric Association, 2013b).

While many psychiatric disorders include impulsivity as a diagnostic feature, impulsivity is a core characteristic of impulse control disorders. Impulsivity can be conceptualized as the failure to resist a desire or temptation that is potentially harmful to oneself. Impulsive individuals often underestimate the risks and harms associated with their actions and lack the ability to delay gratification. The literature suggests that the biological basis for impulsive behavior may be rooted in altered serotonergic function. Specifically, it seems that decreased serotonergic transmission may result in diminished impulse control (Masaki et al., 2006; Catharine A Catharine A Winstanley et al., 2004; Catharine A Catharine A. Winstanley et al., 2004.).

While impulse control disorders were once thought to be quite uncommon, recent investigations have suggested that their prevalence in the general population is significant. Papers published on the prevalence of IED in the United States reported a weighted lifetime prevalence of 6.9% in the general population (Coccaro, 2012). The National Comorbidity Survey Replication Adolescent Supplement found an incidence of

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7.8% in adolescents ("National Comorbidity Survey: Adolescent Supplement (NCS-A), 2001-2004,"). The incidence of kleptomania is less studied, but a paper by Goldman et al. suggested an incidence of 0.3–0.6% in the general population (Goldman, 1991). Pyromania is also less frequently discussed in the literature, with one estimate suggesting a prevalence of 1% in a sample of college students (Odlaug and Grant, 2010). As such, it is possible that the morbidity and disease burden associated with impulse control disorders has been underestimated.

There are currently no evidence-based treatment recommendations for IED, kleptomania and pyromania. Attempts at treating these disorders often involve utilizing recommendations from treatment protocols for other conditions. The vast majority of the papers published on the treatment of impulse control disorders are case reports and therefore, provide little in the way of generalizable treatment suggestions. This review seeks to provide a summary of randomized controlled trials (RCTs) investigating pharmacological treatments for impulse control disorders. We have specifically chosen to focus on IED, kleptomania and pyromania from the DSM-5 category of Disruptive, Impulse Control and Conduct Disorders (American Psychiatric Association, 2013a). Other disorders in that category include oppositional defiant disorder (ODD), conduct disorder (CD) and antisocial personality disorder (ASPD). However, comprehensive systematic reviews investigating pharmacological management have already been published for these disorders (Khalifa et al., 2020; Pringsheim et al., 2015). As a result, there was little benefit in including ODD, CD and ASPD in the scope of this review. The objective of this review is to evaluate the efficacy and tolerability of current pharmacotherapeutic options for the treatment of impulse control disorders.

2. Methods

2.1. Search strategy and selection criteria

A systematic literature review for all original studies that investigated the efficacy and tolerability of pharmacotherapy options in impulse control disorders was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guideline for reporting (Liberati et al., 2009). We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42021255178). Criteria for literature searches and inclusion criteria were determined a priori and followed for all methods.

We developed a search strategy tailored to each database using search terms such as "Intermittent explosive disorder", "kleptomania", "pyromania", "fire-setting", "arson", "shoplift", "theft" and "impulse control". Please refer to Appendix 1 in the Online Supplement for the full search strategy. The search was limited to RCTs on samples of human participants of any age engaged in pharmacological treatment for an impulse control disorder. The disorders that were considered in this review were intermittent explosive disorder, kleptomania, and pyromania. Only English full-text studies in any setting from peer-reviewed journals or clinical trial registers were eligible for inclusion.

Electronic searches were conducted within the following databases to April 2021: MEDLINE, PsychINFO, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE. Searches were also performed in the following trials registers: The International Standard Randomised Controlled Trial Number (ISRCTN) registry, The US National Institutes of Health Ongoing Trials Register, The Australian New Zealand Clinical Trials Registry, and The World Health Organization International Clinical Trials Registry platform. Reference lists and cited articles of included records were scanned to collect additional records and ensure that all relevant studies were captured.

2.2. Outcomes

Outcomes of interest were participant or parent-reported global assessment of condition severity at the conclusion of treatment, assessed using a published scale; adverse events, stratified by severity and organ system involvement; mortality; quality of life using a validated scoring tool; investigator or physician-rated global assessment of condition severity at the conclusion of treatment, assessed using a published scale.

2.3. Selection process and data collection

Title and abstract screening, full-text review and data extraction was conducted independently by four reviewers to identify studies for full-text review. Any discrepancies raised during the screening process were resolved through consensus. Agreement among the four investigators at this stage was calculated using the κ statistic. Should the publication have met all eligibility criteria, data such as the study characteristics, study design, setting, population demographics, diagnostic criteria used, and pharmacotherapy characteristics was extracted. Reference lists of included papers were also assessed to collect additional records and ensure that all relevant studies were captured. If eligible studies did not report data necessary for inclusion in the systematic review, efforts were made to contact the corresponding authors directly.

2.4. Risk of bias

Risk of bias was assessed using the Cochrane Risk of Bias Tool 2.0 for each of the domains: (a) risk of bias arising from the randomization process, (b) effect of assignment to intervention, (c) effect of adhering to intervention, (d) missing outcome data, (e) risk of bias in measurement of the outcome, (f) risk of bias in selection of the reported result (Sterne et al., 2019). Final risk of bias ratings for each of the studies was determined through consensus.

3. Results

Following duplicate removal we identified 11,167 articles, of which 11,109 were excluded based on title and abstract screen. Of the 58 studies assessed for full text screening, eight RCT studies met our inclusion criteria and were included in the final review. (Fig. 1).

A summary of each included RCT characteristics, pharmacotherapy used, and their key features is captured in (Table 1) (Coccaro et al., 2009, 2015; Coccaro and Lee, 2019; Grant et al., 2009; Hollander et al., 2003; Koran et al., 2007; Mattes, 2005, 2008). The eight studies included a total of 583 subjects and seven unique pharmacotherapies. Mean age was reported in six studies, ranging from 33.6 to 49.6 years. All studies reported the percentage of males assessed, with 59.44% of the studies' subjects being men (range 28–87.5%, SD 21.9).

Six of the identified studies investigated pharmacotherapy for IED, while the remaining two studies investigated management for kleptomania. Despite a thorough search of the literature, we were unable to identify any RCTs investigating pharmacotherapy for pyromania. The interventions employed in these papers were quite variable, however, they were largely dominated by SSRIs and anticonvulsants. Five of six studies investigating IED used the Overt Aggression Scale Modified (OAS-M) as their main measure of symptom severity (Coccaro, 2020). The two studies exploring pharmacotherapy for kleptomania primarily utilized the Yale Brown Obsessive Compulsive Scale Modified for Kleptomania (K-YBOCS) (Goodman et al., 1989).

3.1. Risk of bias

For the risk of bias assessment using the Cochrane Risk of Bias Tool 2.0, each of the five domains were rated as either low risk, some concerns, or high risk. Two of the included studies were classified to have a high risk of bias and six studies were classified to have some concern regarding their risk of bias (Fig. 2) (Higgins et al., 2019). Common areas in which RCT studies were assessed as higher risk were the domains, "bias arising from the randomization process" and "bias in the selection

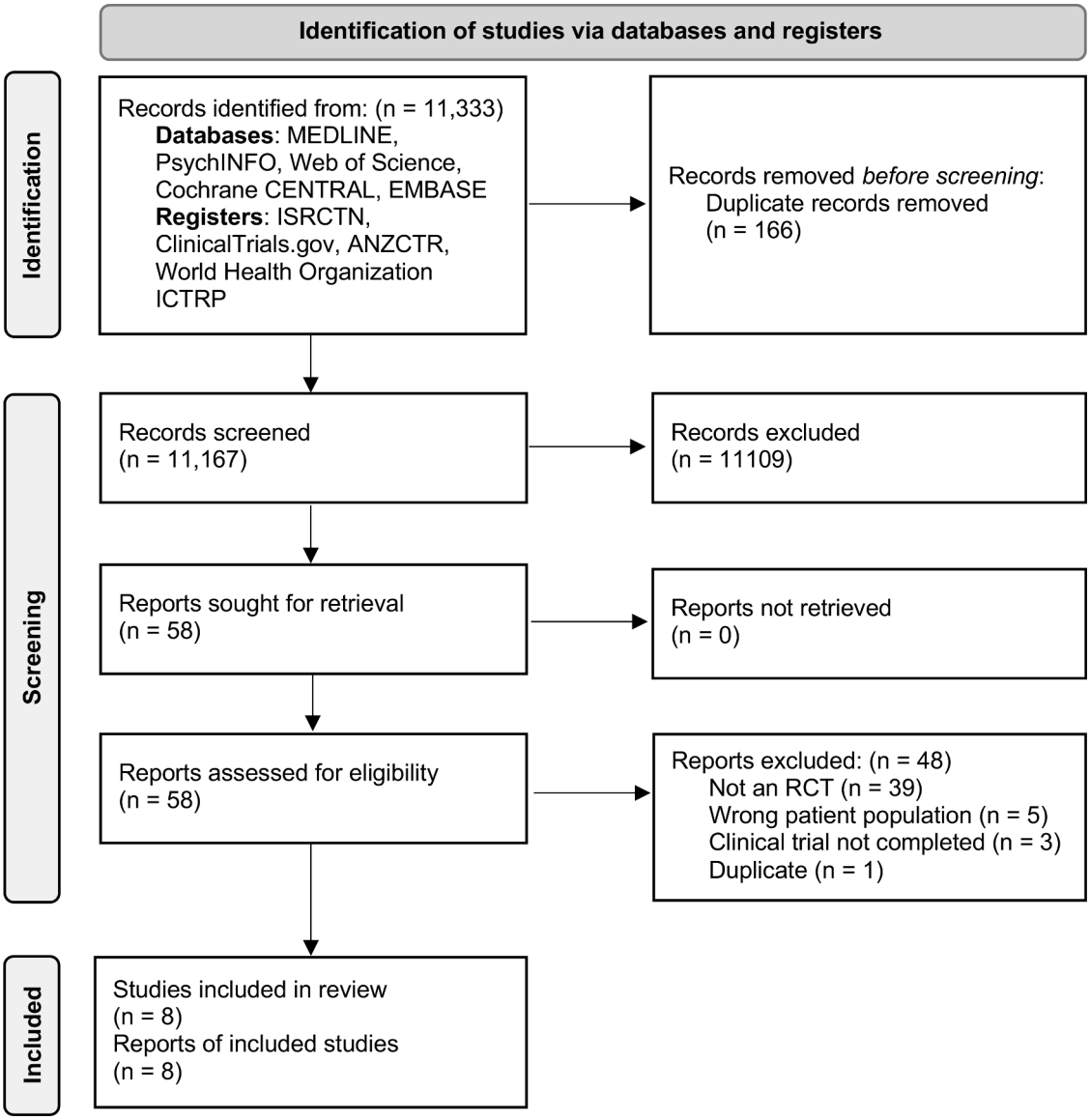

Fig. 1. PRISMA flow diagram.

Table 1
Study and population baseline characteristics.

Study	Disorder	Intervention	Dose (mg)	Sample size	Mean age	Sex (% male)	Diagnostic criteria	Severity scale	Length of administration (weeks)
Coccaro 2019	IED	Lorcaserin	20[a]	10	33.6	50	DSM-5	Taylor Aggression Paradigm	1
Coccaro 2015	IED	Fluoxetine, Divalproex	20–60, 500–2500	90	N/A	50	DSM-5	OAS-M	12
Coccaro 2009	IED	Fluoxetine	20–60	100	36.8	77	DSM-IV	OAS-M	12
Mattes 2008	IED	Levetiracetam	250–1500[b]	40	45.4	87.5	DSM-IV	OAS-M	10
Mattes 2005	IED	Oxcarbazepine	150–2400	48	41.7	81	Coccaro revised criteria	OAS-M	10
Hollander 2003	IED	Divalproex	500	246	40.3	73	DSM-IV	OAS-M	12
Grant 2009	Kleptomania	Naltrexone	50–150	25	N/A	28	DSM-IV	K-YBOCS	8
Koran 2007	Kleptomania	Escitalopram	10–20	24	49.6	29	DSM-IV	K-YBOCS	17

[a] Lorcaserin was only administered once to all patients. [b] Levetiracetam was given twice daily.

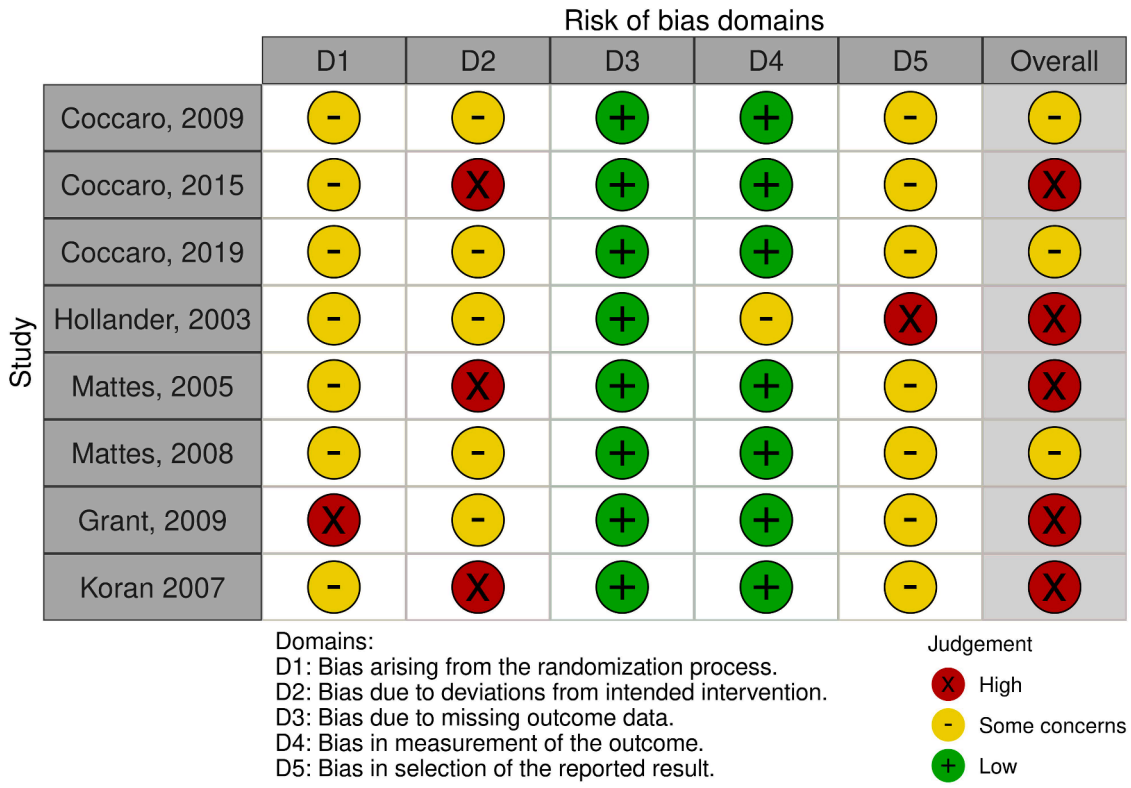

Fig. 2. Assessment of risk of bias using Cochrane Risk of Bias Tool 2.0.

of the reported result".

3.2. Outcomes of the review

Intermittent Explosive Disorder: IED was by far the most researched of the impulse control disorders. Of the eight RCTs included in this review, six of them investigated IED pharmacotherapy. The interventions attempted for IED included lorcaserin, fluoxetine, divalproex, levetiracetam and oxcarbazepine.

Anticonvulsants: Divalproex was an intervention investigated by Coccaro et al. (2015) and Hollander et al. (2003) Both studies found no statistically significant treatment difference between divalproex and placebo on OAS-M scores in patients with IED. Similarly, Mattes et al. (2008) did not find levetiracetam to be significantly different from placebo on any of their outcome measures for impulsivity and aggression. However, in their 2005 study, Mattes et al. found the oxcarbazepine group to be statistically better than placebo in terms of total aggression, verbal aggression, and aggression against objects.

Antidepressants: Fluoxetine was the only antidepressant tried as an intervention for IED. It was employed by Coccaro et al. (2015) and Coccaro et al. (2009). In their 2009 paper, Coccaro et al. found a statistically significant reduction in impulsive aggressive behavior in the fluoxetine treatment group compared to placebo. Meanwhile, in their 2015 study, Coccaro et al. did not find any anti-aggressive efficacy to be demonstrated by fluoxetine. However, Coccaro et al. (2015) postulated that the reason for the lack of significant difference between treatment groups may have been due to their sample not possessing high enough OAS-M irritability scores. In a subgroup analysis of patients above OAS-M aggression scores of 15 and OAS-M irritability scores of 6 Coccaro et al. (2015) found a significant effect favoring fluoxetine over placebo.

Lorcaserin: The 2019 Coccaro et al. study employed lorcaserin as an intervention to reduce aggression and impulsivity in patients with IED. They were able to find a decrease in impulsive aggression in the lorcaserin treatment group, however, the reduction was not statistically significant.

Adverse effects: The reporting of adverse events was not consistent between studies, with some studies providing very detailed data, and others providing almost none. Both the 2019 and 2015 papers by Coccaro et al. did not discuss adverse events in their manuscript. In their 2009 study, Coccaro et al. found that sexual dysfunction, sleep disturbance, nausea/vomiting, jitteriness/restlessness were statistically more common in the fluoxetine group than placebo, with 4 of the patients in the fluoxetine group withdrawing from the study Hollander et al. (2003). stated that compared to placebo, depression, increased appetite, asthenia, tremor, nausea, and nervousness were more common in the divalproex group. The most frequent reasons for discontinuation from the Hollander et al. study were abnormal lab values, which included, increased liver function tests, hyperkalemia, and hyperglycemia. 21 patients in the divalproex group withdrew due to adverse events compared to four in the placebo group ($p<0.001$). The 2008 study by Mattes et al. reported sedation, dizziness, and headache to be the most common adverse events in their study. Five patients dropped out of the levetiracetam group due to suicidal ideation, increased irritability, sedation, and depressed mood, while only one patient dropped out of the placebo group due to depressed mood. In their 2005 study, Mattes et al. reported that adverse events were minor and that six patients dropped out of the oxcarbazepine group while three patients dropped out of the placebo group.

Kleptomania: Only two of the included studies investigated interventions for kleptomania. The interventions employed for kleptomania were naltrexone and escitalopram.

Antidepressants: Koran et al. found no statistically significant differences between the escitalopram group and placebo in the double-blind portion of their experiment. The did however, report significant changes in the K-YBOCS and other symptom severity measures when conducting an open label trial with escitalopram.

Naltrexone: Grant et al. showed naltrexone to be superior to placebo in the treatment of kleptomania on all outcome measures, including the K-YBOCS.

Adverse effects: Koran et al. (2007) reported that the most common adverse events were nausea, insomnia, somnolence and diarrhea. No subjects withdrew for adverse events. Grant et al. found no statistical difference in adverse events between groups. Nausea was the most common adverse event and caused one subject to withdraw from the naltrexone group.

4. Discussion

4.1. Conclusions about treatment efficacy

The conclusions that can be drawn from this review are limited by the quality of the evidence. Given that this review only examined eight RCTs, often using modest sample sizes, it is difficult to make concrete treatment recommendations for impulse control disorders. A meta-analysis was not conducted due to the small number of studies included in the review, coupled with the fact that not all RCTs provided enough data for quantitative analysis. Nevertheless, a qualitative assessment of the literature demonstrates that some interventions showed more promise than others.

For the treatment of IED oxcarbazepine and fluoxetine were the most efficacious. Mattes et al. 2005 found oxcarbazepine to be helpful in reducing total aggression, verbal aggression, and aggression against objects. In their 2009 paper Coccaro et al. found fluoxetine to be effective in decreasing impulsive aggression; however, this was not entirely corroborated by the findings in their 2015 paper. More research is required to be able to assess the true efficacy of these two agents for the treatment of IED. Perhaps most significantly, divalproex, an intervention assessed by both Coccaro et al. (2015) and Hollander et al. (2003), was not effective at reducing symptoms of IED in either study. This is a significant finding, as previous studies have reported that divalproex can decrease impulsivity in patients with borderline personality disorder (Hollander et al., 2001; 2005). There has also been some evidence to suggest that divalproex can decrease impulsive aggression in adolescents with mood lability and disruptive behavior (Barzman et al., 2007; Donovan et al., 2000). Moreover, Hollander et al. (2003) found that divalproex was effective in decreasing OAS-M aggression and irritability scores for patients with a primary diagnosis of a cluster B personality disorder. However, this finding was not replicated in patients with IED. This suggests that the underlying mechanism for impulsive aggression and irritability in IED populations may be different than that of patients with cluster B personality disorders. Of note, divalproex had significant adverse effects when compared to many of the other interventions employed for IED. Therefore, the harms of using divalproex in IED patients were substantial and the clinical benefits were negligible.

In the treatment of kleptomania, only naltrexone was effective Grant et al. (2009). found a very promising effect size for naltrexone in their RCT; however, the generalizability of their findings is limited by their small sample size.

4.2. Pharmacological basis

The studies included in this review employed different pharmacological agents and thereby different mechanisms to alter serotonergic and GABAergic neurotransmission. Historically, impulsivity has been associated with a deficiency in serotonergic neurotransmission in the central nervous system (Masaki et al., 2006; Catharine A Catharine A Winstanley et al., 2004; Catharine A Catharine A. Winstanley et al., 2004.). Upon further study, the relationship has been found to be more complex; still, decreased activity at most 5-HT receptor subclasses is linked to increased impulsivity. Recent studies have also reported a negative association between impulsivity and GABA levels in the brain (Ende et al., 2015; Li et al., 2020). Patients with increased impulsivity were found to have lower concentrations of GABA, and higher concentrations of glutamate within their brains (Ende et al., 2015). The three serotonergic agents used in the included studies were fluoxetine, escitalopram and lorcaserin. Fluoxetine and escitalopram act on the 5-HT transporter to increase serotonin in synapses, while lorcaserin directly agonies the 5-HT2c receptor to increase serotonergic effect. However, given the fact that lorcaserin and escitalopram were not effective in decreasing impulsivity in IED and kleptomania patients respectively, our findings were not adequately explained by the hypothesis that impulsivity is driven by a deficiency in serotonergic transmission. Moreover, divalproex and levetiracetam were the two GABAergic agents used to treat IED and neither was superior to placebo in decreasing impulsivity or aggression. Therefore, the results of our review were not able to support the theory that increasing GABA neurotransmission in the brain decreases impulsivity. At this time, a clear biological basis for our results cannot be established.

4.3. Study duration

It is important to note that none of the included studies administered the intervention for an extended duration. Most studies delivered their intervention for 12 or fewer weeks. While that may be enough to generate a maximal treatment response in some studies on depression and anxiety, we do not have sufficient data to indicate whether the same holds true for impulse control disorders. In future studies, it may be interesting to investigate the impact of a longer treatment duration on changes in symptom severity scales.

4.4. Current challenges and future directions

This review also highlights that there is currently a paucity of evidence on pharmacotherapy of impulse control disorders, as only eight papers were highlighted in a very extensive search of the literature. Of these eight papers, the vast majority of studies evaluated the impact of pharmacotherapy on IED. There were no papers evaluating potential pharmaceutical management for pyromania. Nevertheless, the few studies analyzed in this review show some promise for pharmacologic management of impulse control disorders. In particular, oxcarbazepine and naltrexone may be worth further investigating as treatments for IED and kleptomania respectively.

4.5. Strengths and limitations of the review

A thorough search of the literature was conducted, spanning four databases and five RCT registries. This review included only double blind RCTs, thereby ensuring a high level of methodological rigor. This review had a strong and specific inclusion and exclusion criteria that allowed for strong inter-rater reliability within the screening process.

Nevertheless, the sample sizes of the papers included were quite small. Five of the included studies had sample sizes under 50, which made it difficult for them to obtain sufficient power. There were not enough studies on any given intervention to be able to make specific therapeutic recommendations for clinicians. The diagnostic criteria used to recruit participants for the studies varied slightly, as some studies used the DSM-IV criteria for IED and kleptomania while others used the DSM-5 criteria for the same disorders.

Author contributions

Talha Tahir: Conceptualization, Methodology, Project administration, Validation, Writing- Original draft preparation, Reviewing and Editing, Visualization

Melanie Mitsui Wong: Conceptualization, Methodology, Validation, Writing- Original draft preparation, Reviewing and Editing, Visualization

Muhammad Maaz: Methodology, Data Curation, Formal analysis

Roshan Naufal: Investigation (Title and abstract screening, Full text screening, Data extraction)

Rabia Tahir: Investigation (Title and abstract screening, Full text screening, Data extraction), Writing- Reviewing & Editing

Yedishtra Naidoo: Project administration, Supervision, Writing- Reviewing and Editing

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114499.

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