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Research Article

Role of Bupropion in the Management of Internet Gaming Disorder: A Systematic Review

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ABSTRACT

This systematic review aims to summarize the role of bupropion in the management of internet gaming disorder (IGD) patients. Five electronic databases were searched without date restrictions until September 10, 2021. Four studies with a moderate risk of bias were included. Compared to escitalopram, bupropion showed better improvement in reducing addictive use of online gaming and IGD severity (low certainty). Compared with placebo or no treatment, bupropion was better in reducing addictive use of online gaming, IGD severity, and the total time of online game playing (low to moderate certainty). The combination of bupropion with cognitive behavior therapy (CBT) was superior to bupropion alone in reducing the addictive use of online gaming and the total time of online game playing (low certainty). Bupropion may be effective in improving IGD symptoms. However, there is an evident need for more extensive randomized controlled trials (RCTs) with better methodology and longer follow-up before more conclusions can be drawn.

Keywords: *bupropion, internet addiction, internet gaming disorder, treatment.*

Introduction

Playing games is an activity that can help humans explore, hone cognitive abilities, interact with others, and release stress [1]. Playing online games is a way to deal with stress due to social restrictions during the COVID-19 pandemic. However, the lifestyle changes due to the pandemic that require many people to spend time at home have increased Internet use, especially online games, which has sparked concerns over the overuse of online games [2-3].

Excessive activity in playing online games can cause various problems, including a decline in finances, work, family, and social relationships, and psychological issues [1,3-4]. The American Psychiatric Association then took this concern seriously, with the inclusion of Internet gaming disorder (IGD) in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), as a "condition requiring further study" in 2013 [5]. The World Health Organization also responded by including the diagnosis of gaming disorder in the International Classification of Disease, 11th edition (ICD-11) [6].

Many studies exist regarding IGD; however, many inconsistencies remain, especially in

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diagnosis. This is because the diagnostic criteria are still being debated. Some researchers stressed that there are similarities between IGD and other Internet-related problems, including online gambling disorder and Internet addiction, especially those related to brain functional connectivity as observed with functional magnetic resonance imaging (fMRI) [7-9]. Moreover, research on IGD is still very limited, especially in pharmacotherapy. Most studies on pharmacotherapy treatment of IGD did not use a randomized controlled trial (RCT) design in the form of case reports or only used a small number of samples [1,10].

Bupropion is one drug type that is often used in IGD therapy [1,7,10-12]. Bupropion (synonym: 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one, amfebutamone, $C_{13}H_{18}ClNO$) is an antidepressant that is also utilized in treating addiction disorders (e.g., nicotine or gambling addiction) [13,14]. Hydroxybupropion (HB), threohydrobupropion (TB), and erythro-hydrobupropion are the three active metabolites that are produced during the metabolism of bupropion (EB). The genetically variable enzyme cytochrome P450 2B6 is principally responsible for mediating the generation of HB (CYP2B6). Bupropion is metabolized by carbonyl reductase into TB and EB. In an animal model, TB and EB were found to be only about 20% as potent as bupropion. The primary active metabolite, HB, has almost half (~50%) the activity of the parent medication [15]. Bupropion inhibits the reuptake of dopamine (dopamine transporter/DAT inhibitor) and norepinephrine (norepinephrine transporter/NET inhibitor). DAT blockade of the striatum and nucleus accumbent causes an increase in dopamine in those areas, which leads to a reduced craving effect in people with addiction [16-18] (Figure 1).

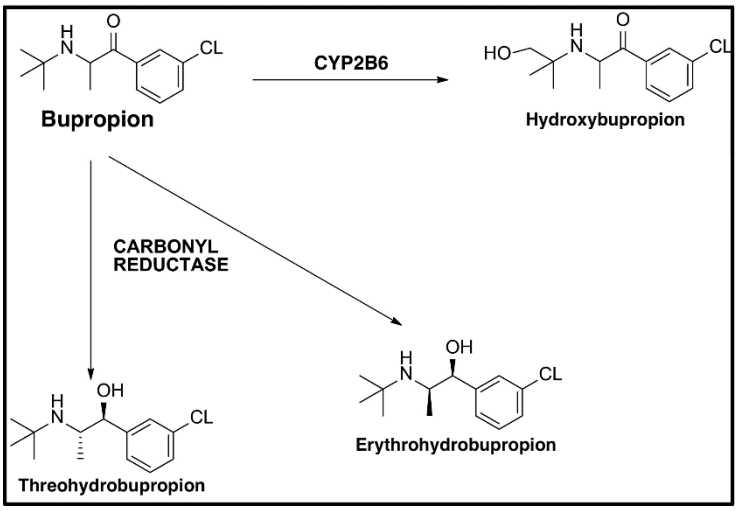

Figure 1. *Metabolic pathways of bupropion. Bupropion is metabolized by CYP2B6 to form hydroxybupropion and by carbonyl reductase to form threohydrobupropion and erythrohydrobupropion. CYP, cytochrome P450* [19]

Neuroimaging studies have suggested that brain region activation in response to online video game cues is similar to that observed in patients with substance dependence and pathological gambling, such as the anterior cingulate, the dorsolateral prefrontal cortex, the parahippocampus, the nucleus accumbens, and the orbitofrontal cortex [18, 20-23]. To shed more light on the use of pharmacotherapies in managing IGD patients, a systematic review was performed, with a particular focus on bupropion. The ultimate goal of IGD treatment is to reduce withdrawal and other unpleasant mood states while not gaming, as well as to lessen internet gaming-related behaviors that interfere with self-care, relationships, jobs, education, or other life obligations. Although there are gaps in our understanding of IGD,

some studies have found similarities between IGD's psychopathology and that of other Internet-related disorders, such as Internet addiction and online gambling disorder, especially when it comes to brain functional connectivity (as measured by fMRI). It is well known that bupropion is the drug of choice for treating addiction disorders, such as nicotine and gambling addiction. Dopamine (dopamine transporter/DAT inhibitor) and norepinephrine (norepinephrine transporter/NET inhibitor) reuptake are both inhibited by bupropion. Dopamine levels in the striatum and nucleus accumbens rise as a result of DAT blockage, which reduces the craving effect in addicts. The antidepressive properties of bupropion provide additional benefits, as depression is one of the withdrawal symptoms of IGD [9,16,24].

Currently, there is no "officially approved" pharmacological therapy for Internet Gaming Disorder (IGD) nor a "gold standard" approach to treating IGD. Thus, this systematic review aims to summarize the role of bupropion in the management of IGD patients. Based on our findings in this systematic review, we found that bupropion has the potential to be the drug of choice for treating IGD.

Methods

Study design

A systematic review of the scientific literature was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The protocol was registered in the international database PROSPERO of the National Institute for Health and Research with the code CRD42021276994.

Eligibility criteria

The eligibility criteria were based on the planned population, intervention, control, outcome, and study design elements outlined in Table 1.

Table 1. Eligibility criteria of included study

Criteria	Inclusion	Exclusion
Population	IGD patients (based on DSM-5 criteria or confirmed by experts) alone or with other psychiatric comorbidities. There are no demographic restrictions.	Involving patients with Internet-related problems other than IGD, such as addiction to the Internet, porn, social media, online and gambling; healthy individuals.
Intervention	Bupropion in various preparations and doses, alone or in combination with other therapies.	Using drugs other than bupropion.
Comparison	Psychopharmaceutical or other psychotherapy, placebo, or blank control.	No control group.
Outcome	Main outcome: changes in clinical signs and symptoms of the IGD were measured by psychometrics (e.g., YIAS, IGDS, CGI, etc.) and total time spent playing online games Secondary outcome: improvement of clinical signs and symptoms that may accompany IGD patients (e.g., depression, anxiety, etc.). Brain functional connectivity (FC) changes were assessed using functional magnetic resonance imaging (fMRI).	No outcome data.
Study design	Clinical trial (randomized or not), published in English. No publication date restriction.	Case study, review, editorial, news, letter, research, textbook, no published text in English.

IGD: Internet gaming disorder, DSM-5: Diagnostic and Statistical Manual of Mental Disorders, YIAS: Young's Internet Addiction Scale, IGDS: Internet Gaming Disorder Scale, CGI: Clinical Global Impression, fMRI: functional magnetic resonance imaging.

Data sources and search strategy

Literature was explored on electronic databases from PubMed, PsycINFO, SpringerLink, Cochrane, and ScienceDirect, with the keywords of "bupropion" *and* ("internet gaming" or "online gaming" or "video game" or "gaming" or "game") *and* ("disorder" or "addiction" or "problem" or "excessive"). The automatic filter feature on the electronic database was inactivated. The two authors independently performed the search protocol on September 10, 2021. Search results were saved using the Zotero® app and then imported into Covidence to eliminate duplication [26].

Study selection

First, the two authors independently selected titles and abstracts to search for potential studies and resolved disagreements by discussion. Second, the full text of potential studies was searched and selected based on inclusion and exclusion criteria. Both authors selected the full text independently. Studies that were excluded were then recorded along with their reasons. The results of the search were then reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams, using the R package and ShinyApp for producing PRISMA 2020 compliant flow diagrams [27] and the Covidence for the selection process [26].

Study risk of bias assessment

Before inclusion in the review, the included studies were assessed by two independent reviewers (AYS and IT) for methodological validity using the RoB 2 for the randomized controlled trial (RCT) studies and ROBINS-I for non-randomized studies [28-29]. The two reviewers resolved disagreements through discussion. The results collected by the critical appraisal were reported in narrative form, and "traffic light" plots were produced with the ROBVIS tool [30].

Data extraction and synthesis

The collected data were extracted independently by two reviewers using Covidence software, and the results were cross-checked [26]. The extracted data include the authors, country of origin, participant characteristics, methods of diagnosing IGD, intervention characteristics, main and secondary outcomes reported, and study design. A meta-analysis was not planned because of the anticipated diversity of included studies. Instead, the data were synthesized qualitatively and presented in narrative and tabular form.

Certainty of evidence assessment

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to perform an overall assessment of the quality of the evidence for each comparison group, and the GRADEpro GDT software was used to produce Summary of Findings (SoF) tables [31-32]. A four-point rating scale was used to rate the quality of the evidence (high, moderate, low, and very low) based on the following criteria: study limitation (risk of bias), inconsistency of results, imprecision, indirectness of evidence, and publication bias [31]. The SoF tables present the main outcome results narratively.

Result and Discussion

Study selection

The database searches found 283 references, i.e., PubMed (n = 9), SpringerLink (n = 197), Cochrane (n = 5), ScienceDirect (n = 62), and PsycINFO (n = 10). A total of 218 articles remained after removing duplicate references, and 190 were excluded after reading titles and abstracts. Thus, 28 studies were selected for the full-text screening and applying the eligibility criteria, excluding 24 studies. Of the 24 studies excluded during the full-text screening, nine were book chapter(s) [33-41], nine were review articles [42-47], one was a case report study [48], three were not using bupropion [23, 49-50], and two were using non-IGD population [44-45]. Finally, four studies were selected

for qualitative analysis [51-54]. The process of identification, selection, and exclusion of studies is shown in the PRISMA flow diagram below (Figure 2).

Study characteristics

All four studies were randomized controlled trials (RCT) [51-54]. All of the studies were conducted in South Korea, which included a total of 314. The number of participants in each study ranged from 30 to 119 [51-54]. Three studies included only male participants [51-53]. One study did not report the participant's sex [54]. The age of participants in the three studies ranged from 13 to 45 years [51-53], while the age range of participants in the other study was not reported (mean age only) [54].

The operational definitions of IGD varied between the studies. One study used DSM-V IGD classification [53]. The other studies used these criteria to define IGD: (1) extensive gameplay time (more than 4 h per day/30 h per week), (2) a score of more than 50 on the YIAS, and (3) impaired behaviors or distress due to a maladaptive pattern of online gameplay. These criteria were based on DSM-IV criteria for substance abuse [51,52,54]. Three studies used IGD patients with MDD as a comorbid [51,52,54].

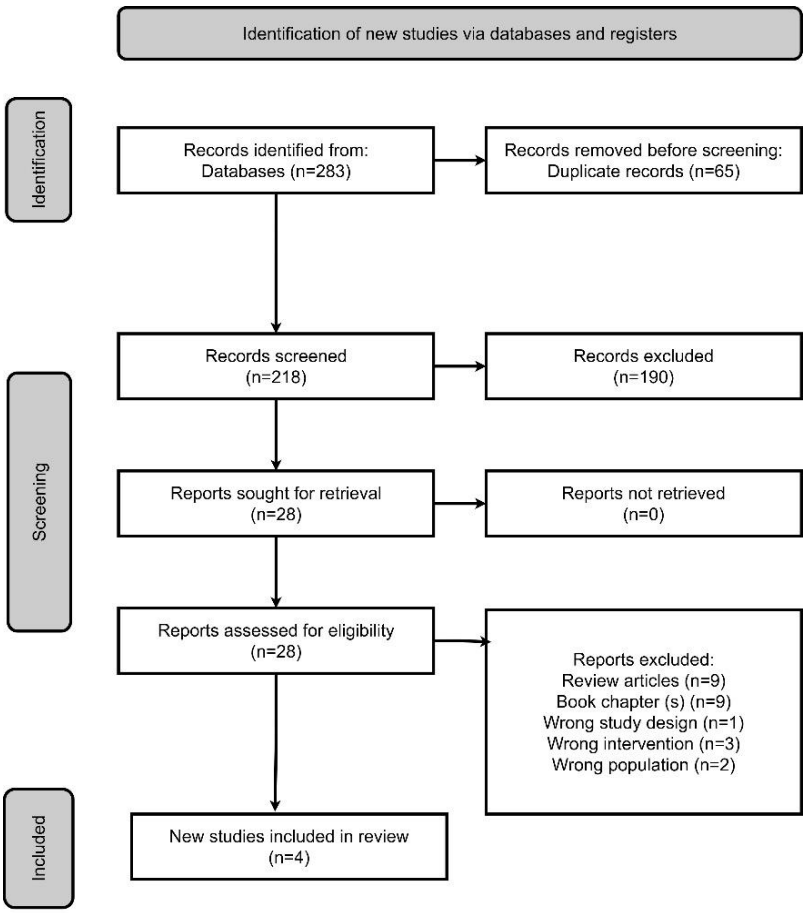

Figure 2. PRISMA flow diagram

All of the studies used the Young Internet Addiction Scale (YIAS) to address addictive use of the Internet (specifically Internet gaming) and Beck's Depression Inventory (BDI) to assess depression symptom severity [51-54]. Two studies assessed total playing time (hours/week) pre- and post-intervention [51-52]. Other diagnostic tools used between the studies were varied. The Clinical Global Impressions-Severity Scale (CGI-S) was used in two studies [51,53]. The Korean version of attention-deficit hyperactivity disorder (ADHD)

Rating Scale (K-ARS) and the Behavioral Inhibition and Activation Scales (BIS/BAS) were used in two studies [53-54]. One study assessed changes in brain FC using functional magnetic resonance imaging (fMRI) [54].

The dosage of bupropion used in all studies was consistent: an initial dose of 150 mg/day subsequently increased (during the first week or after one week of therapy) to 300 mg/day [51-54]. Three studies used bupropion sustained release (SR) formulation [51,53,54], while the formulation used in the remaining study was not reported [52]. The treatment duration in each study ranged from 6 to 12 weeks [51-54]. Table 2 presents a summary of the key characteristics of each study.

Table 2. Key characteristics of included studies

Lead author and year	Country	Population description	Age range (years)	Assessment of IGD	Intervention	Number of participants (intervention & comparison group)	Main outcome of IGD	Secondary outcome	Study design
Han DH, Renshaw PF [51]	South Korea	Male with problematic online game play and MDD	13–42	(1) excessive game play time (more than 4 h per day/30 h per week), (2) a score of more than 50 on the YIAS, and (3) impaired behaviors or distress due to a maladaptive pattern of online game play	8 weeks bupropion + education (bupropion SR 150 mg/day increased to 300 mg/day during the first week of treatment) or placebo + education	N = 50 (25 bupropion, 25 placebo)	YIAS, G-time, CGI-S	BDI	RCT
Kim et al. [52]	South Korea	Male with problematic online game play and MDD	13–18	(1) Excessive game play (more than 4 h per day/30 h per week), (2) a score of more than 50 on the YIAS, and (3) maladaptive behaviors or distress due to a problematic online game play	8 weeks of bupropion only (150 mg/day for 1 week followed by 300 mg/day for 7 weeks) and 8 weeks of bupropion + CBT (eight-session group CBT, once a week)	N = 65 (32 bupropion + CBT and 33 bupropion only)	YIAS, G-time	BDI, BAI, Life-SS, School-PBS	RCT
Song et al. [53]	South Korea	Male IGD patients	13–45	DSM-5	Bupropion SR (150 mg/day and increased to	N = 119 (44 bupropion, 42	YIAS, CGI-S	BDI, K-ARS, BIS/BAS	RCT

Lead author and year	Country	Population description	Age range (years)	Assessment of IGD	Intervention	Number of participants (intervention & comparison group)	Main outcome of IGD	Secondary outcome	Study design
					300 mg/day during the first week) or escitalopram (10 mg/day and increased to 20 mg/day during the first week) for 6 weeks	escitalopram, 33 no medication)			
Nam et al. [54]	South Korea	Patients with problematic Internet game play and MDD	NR (mean age for bupropion group 22.9 ± 1.9)	(1) Excessive Internet game play of more than 4 h per day or 30 h per week, (2) YIAS scores of more than 50, and (3) maladaptive and disruptive behavior in general life due to excessive Internet game play	Bupropion SR (150 mg/day followed by 300 mg/day during the first week) or escitalopram (10 mg/day followed by 20 mg/day during the first week) for 12 weeks	N = 30 (15 bupropion, 15 escitalopram)	YIAS	BDI, K-ARS, BIS/BAS, brain FC (fMRI)	RCT

IGD, Internet gaming disorder; YIAS, Young's Internet Addiction Scale; CBT, cognitive behavior therapy; MDD, major depressive disorder; G-time, mean total time of online game playing (hour/week); BDI, Beck's Depression Inventory; BAI, Beck's Anxiety Inventory; Life-SS, Modified Student's Life Satisfaction Scale; School-PBS, Modified-School Problematic Behavior Scale; RCT, randomized controlled trial; SR, sustained release; CGI-S, Clinical Global Impression-Severity Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; K-ARS, Korean version of attention-deficit hyperactivity disorder (ADHD) Rating Scale; BIS/BAS, Behavioral Inhibition and Activation Scales; NR, not reported; FC, functional connectivity; fMRI, functional magnetic resonance imaging

IGD, Internet gaming disorder; YIAS, Young's Internet Addiction Scale; CBT, cognitive behavior therapy; MDD, major depressive disorder; G-time, mean total time of online game playing (hour/week); BDI, Beck's Depression Inventory; BAI, Beck's Anxiety Inventory; Life-SS, Modified Student's Life Satisfaction Scale; School-PBS, Modified-School Problematic Behavior Scale; RCT, randomized controlled trial; SR, sustained release; CGI-S, Clinical Global Impression-Severity Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; K-ARS, Korean version of attention-deficit hyperactivity disorder (ADHD) Rating

Scale; BIS/BAS, Behavioral Inhibition and Activation Scales; NR, not reported; FC, functional connectivity; fMRI, functional magnetic resonance imaging.

Risk of bias within studies

Of the four RCT studies, one was classified as low risk of bias (RoB) [51] and three as moderate RoB [52-54]. The RoB was related to concerns about the randomization process [52-54] and deviations from the intended intervention (due to unclear blinding) [52-53]. We decided to include all of the studies. Table 3 summarizes the overall RoB level and the effect direction plot. The results of each assessed item are shown in the "traffic light" plots in the supplementary article Table 1.

Table 3. Effect direction plot of bupropion for IGD patients pre- and posttreatment

Study	Study Design	RoB	YIAS	CGI-S	G-time	BDI	K-ARS	BIS/ BAS	BAI	Life -SS	School -PBS
Han and Renshaw [52]	RCT	Low	▲	▲	▲	▲					
Kim et al. [53]*	RCT	Mod	▲		▲	▲			▼	▲	▲
Song et al. [54]	RCT	Mod	▲	▲		▲	▲	▲			
Nam et al. [55]	RCT	Mod	▲			▲	▲	▲			

Explanations: upward arrow ▲ = positive health impact, downward arrow ▼ = negative health impact, sideways arrow ◀▶ = no change/mixed effects/conflicting findings

Sample size: Final sample size (individuals) in the intervention group: large arrow ▲ > 300; medium arrow ▲ 50–300; small arrow ▲ < 50

RoB, risk of bias; YIAS, Young's Internet Addiction Scale; CGI-S, Clinical Global Impression-Severity Scale; G-time, mean total time of online game playing (hour/week); BDI, Beck's Depression Inventory; K-ARS, Korean version of attention-deficit hyperactivity disorder (ADHD) Rating Scale; BIS/BAS, Behavioral Inhibition and Activation Scales; BAI, Beck's Anxiety Inventory; Life-SS, Modified Student's Life Satisfaction Scale; School-PBS, Modified-School Problematic Behavior Scale; RCT, randomized controlled trial

* Outcomes included in this plot were from bupropion only group

Effect of bupropion in clinical symptoms of IGD

Supplementary article Table 2 presents the complete summary of the results of each study (including pre-post-intervention data and comparison of each treatment group where available). We made a post hoc decision to divide the included studies into three comparison groups, i.e., (1) bupropion vs. escitalopram [53,54], (2) bupropion vs. placebo or no treatment [51.53], and (3) bupropion vs. bupropion + CBT combination [52].

Clinical symptoms pre-post-bupropion treatment

The scores of all clinical symptom scales related to IGD after bupropion treatment showed improvement in all studies. Bupropion significantly reduced mean total online game playing time, YIAS score, and CGI-S score, and the results were consistent across studies. Bupropion also significantly reduced BDI score, BIS/BAS score, K-ARS score, and School-PBS score and increased Life-SS score [51-54]. Interestingly, the BAI score increased after bupropion treatment [52]. Table 3 presents the effect direction plot of each study outcome pre- and post-bupropion treatment.

<u>Bupropion vs. escitalopram:</u> Two studies compared bupropion with escitalopram.

Both studies showed significant improvement in YIAS, BDI, and BIS/BAS scores in both treatment groups [53,54]. One study showed a significant difference in YIAS score between the two groups in favor of bupropion ($p = 0.02$) [53], while the other study showed no significant difference ($p = 0.35$) [54]. One study assessed the CGI-S score. The result showed that both treatments were effective, with a significant difference in favor of bupropion ($p = 0.02$) [53]. No significant difference in BDI score was

observed between the two groups in both studies [53-54]. The BIS/BAS score showed no significant difference between the two groups in one study [53], while the other study showed a significant difference in favor of bupropion [54]. The K-ARS score in both studies showed significant differences in favor of bupropion [53-54]. Table 4 summarizes findings for the main outcome of bupropion vs. escitalopram.

Table 4. Summary of findings

Bupropion compared to escitalopram for internet gaming disorder			
Patient or population: Internet gaming disorder Setting: South Korea Intervention: bupropion Comparison: escitalopram			
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Addictive use of online gaming assessed with: YIAS follow-up: range 6–12 weeks	Both interventions were effective in improving YIAS score. One study showed significant difference in favor of bupropion. One study showed no difference between groups	116 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Severity of IGD assessed with: CGI-S follow-up: 6 weeks	Both interventions were effective in improving CGI-S score. Significant difference between both groups in favor of bupropion	86 (1 RCT)	⊕⊕◯◯ Low[a,b]
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.			
Explanations a. Downgraded due to study limitations because of unclear or inadequate allocation concealment and/or blinding b. Downgraded due to below optimal information size (small sample size) YIAS, Young's Internet Addiction Scale; RCT, randomized controlled trial; IGD, Internet gaming disorder; CGI-S, Clinical Global Impression-Severity Scale			

Bupropion vs. placebo or no treatment: Two studies compared bupropion with placebo or no treatment.

In both studies, it was shown that bupropion was significantly more effective than placebo or no treatment concerning improvement in YIAS, CGI-S, and BDI scores (all $p < 0.01$) [51,54]. In one study, bupropion was superior to placebo in reducing the total time of online game playing ($p < 0.01$) [51]. Table 5 summarizes findings for the main outcome of bupropion vs. placebo or no treatment.

Table 5. Summary of findings

Bupropion compared to placebo or no treatment for Internet gaming disorder			
Patient or population: Internet gaming disorder Setting: South Korea Intervention: bupropion Comparison: placebo or no treatment			
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Addictive use of online gaming assessed with: YIAS follow-up: range 6–8 weeks	Two studies showed that bupropion significantly improved YIAS score compared to placebo/no treatment	130 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Severity of IGD assessed with: CGI-S follow-up: range 6–8 weeks	Two studies showed that bupropion significantly improved CGI-S score compared to placebo/no treatment	130 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Mean total time of online game playing (hour/week) follow-up: 8 weeks	One study showed that bupropion significantly reduced total time of online game playing compared to placebo	50 (1 RCT)	⊕⊕⊕◯ Moderate[b]
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.			
Explanations a. Downgraded due to study limitations because of unclear or inadequate allocation concealment and/or blinding b. Downgraded due to below optimal information size (small sample size) YIAS, Young's Internet Addiction Scale; RCT, randomized controlled trial; IGD, Internet gaming disorder; CGI-S: Clinical Global Impression-Severity Scale			

Bupropion vs. bupropion + CBT combination: One study compared bupropion as the only treatment with a combination of bupropion and CBT

Both treatments improved total online game playing time, YIAS, BDI, Life-SS, and School-PBS scores. Significant differences were seen in favor of the bupropion + CBT combination ($p \leq 0.01$) except for the Life-SS score (no difference between groups, $p = 0.11$). The BAI score in the bupropion group was increased, while the BAI score in the bupropion + CBT was decreased [52]. Table 6 summarizes findings for the main outcome of bupropion vs. bupropion + CBT combination.

Table 6. Summary of findings

Bupropion compared to bupropion + CBT for Internet gaming disorder			
Patient or population: Internet gaming disorder Setting: South Korea Intervention: bupropion Comparison: bupropion + CBT			
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Addictive use of online gaming assessed with: YIAS follow-up: 8 weeks	Both interventions were effective in improving YIAS score. Significant difference between both groups in favor of bupropion + CBT	65 (1 RCT)	⊕⊕◯◯ Low[a,b]
Mean total time of online game playing (hour/week) follow-up: 8 weeks	Both interventions were effective in reducing total time of online game playing. Significant difference between both groups in favor of bupropion + CBT	65 (1 RCT)	⊕⊕◯◯ Low[a,b]
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.			
Explanations a. Downgraded due to study limitations because of unclear or inadequate allocation concealment and/or blinding b. Downgraded due to below optimal information size (small sample size) CBT, cognitive behavior therapy; YIAS, Young's Internet Addiction Scale; RCT, randomized controlled trial			

Effect of bupropion in brain functional connectivity: One study assessed brain FC after 12-week bupropion therapy using fMRI.

The results showed decreased functional correlations between five pairs of regions: left precuneus to left insular ($F = 4.12$, $p = 0.04$), right precuneus to left insular ($F = 4.67$, $p = 0.03$), right parietal cortex to left parietal cortex ($F = 4.64$, $p = 0.03$), left insular to right insular ($F = 4.79$, $p = 0.03$), and left dACC (dorsal anterior cingulate cortex) to right dACC ($F = 7.16$, $p = 0.01$). Improvement in YIAS scores was positively correlated with the decreased functional correlation between the right dACC and the left insular in all patients. Improvement in BIS-BAS scores was positively correlated with decreased functional correlation within the right dACC and the left insular in all patients [54].

Posttreatment follow-up and adverse event: Two studies assessed changes in the outcomes during the posttreatment phase, both at a 4-week posttreatment period [51-52]. Han and Renshaw reported that no significant differences in the bupropion group were observed in YIAS scores, mean total time of online game playing, and CGI-S scores, while the BDI scores were increased. No significant changes in all outcomes were observed in the placebo group [51]. Kim et al. reported that no changes

in both bupropion and bupropion + CBT groups were observed in the mean total time of online game playing, YIAS, BDI, BAI, Life-SS, and School-PBS scores [52]. The adverse events reported in all studies were nausea + headache (N = 6), headache + palpitation (N = 4), and palpitation only (N = 1) [51,52,54].

This systematic review aimed to assess the role of bupropion in the management of IGD. In addition to the main clinical symptom in IGD, the results in this study also assessed depressive symptoms, impulsivity, inattention, problematic behaviors, life satisfaction, and brain FC as the secondary outcome. We grouped the included studies into three comparison groups, namely, (1) bupropion vs. escitalopram [53,54], (2) bupropion vs. placebo or no treatment [51,53], and (3) bupropion vs. bupropion + CBT combination [52].

Main Findings

This review included 4 RCTs and consisted of 264 IGD patients. All studies were conducted in South Korea. This confirms previous reports suggesting that South Korea considered IGD to be the main health issue and has established large-scale projects to deal with the issue. Most patients were males, probably because of their greater tendency for some underlying mental health issues such as personality issues, impulsivity, attention problems, and risk-taking. It also seems that many games were made to be more appealing to males than females (e.g., competition, war, violence, sexualized images of women, and crude humor) [1,9].

The results showed that bupropion reduced not only the severity of IGD symptoms but also depressive symptoms, impulsivity, inattention, and problematic behaviors and increased life satisfaction. Compared to escitalopram, bupropion showed better improvement in reducing addictive use of online gaming and IGD severity (low certainty). Bupropion was better than placebo or no treatment in reducing the addictive use of online gaming, IGD severity, and the total time of online game playing (low to moderate certainty). The combination of bupropion with CBT was superior to bupropion alone in reducing the addictive use of online gaming and the total time of online game playing (low certainty). The results of this study were consistent with the previous reviews regarding the treatment of IGD, suggesting that bupropion effectively reduced the symptoms of IGD [7,12, 55, 56].

The positive effects of bupropion are likely caused by its dual action as dopamine and norepinephrine reuptake inhibitors. As previously mentioned, neuroimaging studies have suggested that brain region activation in response to online video game cues is similar to that observed in patients with addictive disorders. Increased dopamine release induced by bupropion within the brain reward system can reduce negative emotions due to withdrawal symptoms and reduce craving for addictive behaviors. Meanwhile, increased noradrenergic activity induced by bupropion is associated with reduced impulsivity in patients with MDD [16,35,54]. Nam et al. reported that bupropion decreased FC within the default mode and salience networks. This reduced brain connectivity, which was more significant than the changes after escitalopram administration, was associated with improvement in excessive Internet game playing (decreased YIAS score) and impulsivity (decreased BIS/BAS score) [54].

Only two studies assessed changes in the outcomes during posttreatment follow-up, both in a 4-week period. Overall, no significant changes were observed in all main outcomes during this period [51,52]. We believed that a short follow-up period was not enough for the relapse of IGD in both bupropion and comparison groups. This lack of follow-up measures makes it impossible to assess bupropion's long-term effects. Regarding the safety issue, bupropion was generally safe, and no serious adverse events were reported. The most common adverse events reported were nausea and headache in six participants, which were relatively few [51,52,54].

Limitations

Several limitations in this study need to be considered. First, due to a relatively small number of studies and to capture more comprehensive data about the role of bupropion in IGD, broader review questions were used, resulting

in the heterogeneity of the population (especially in defining IGD), comparators, and outcome measures. A lack of standardized definitions and measures of IGD also caused the heterogeneity. Second, this study only included articles that were published in English. Since IGD has been an international issue, this might have excluded some relevant studies. Third, participants were mostly male adolescents or young adults from South Korea. It is unclear how well these participants represent the target population of people with IGD. Fourth, the included studies were often limited by randomization bias, unclear blinding, small sample size, and short follow-up duration, making it challenging to create strong evidence.

Implications

This review article leads to the findings on the role of bupropion in reducing IGD severity and mitigating some of the symptoms associated with excessive online gaming. Due to its dual-action mechanism, bupropion could reduce the addictive use of online gaming, depressive symptoms, impulsivity, inattention, and problematic behaviors associated with IGD. This finding deals with the limited literature on pharmacotherapies for IGD. For clinicians, this critical review might be considered as part of a comprehensive treatment plan for managing IGD patients. In addition, this study also contributes to the theoretical understanding of IGD. The limited but promising evidence for bupropion suggests further research targeting the neurobiological underpinnings of gaming addiction. As gaming addiction evolves, the potential role of pharmacological interventions will also rise, highlighting the importance of a multidisciplinary and personalized approach to addressing this modern mental health challenge.

For future research, it is important to create more homogeneity in the design of studies, utilize more reliable measures, improve methodology (proper randomization and blinding), use a larger sample size (including female patients), and have a longer follow-up duration. The collaboration of policymakers and funders is important to establish diagnostic criteria and measures to improve the quality of future studies and provide effective treatment. This review helps by presenting evidence from which rational decisions can be made, especially in the pharmacological treatment of IGD.

Conclusion

Despite its limitations, this review indicates that bupropion therapy, compared to escitalopram or placebo or no treatment, may have a better improvement in IGD symptoms. The combination with CBT may further improve this effect. Bupropion may also reduce depressive symptoms, impulsivity, inattention, and problematic behaviors and increase life satisfaction.

Conflict of interest

We have no conflict of interest.

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