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FULL-LENGTH REPORT

Antidepressant prescription as a risk factor for developing gambling disorder: A longitudinal registry-based study in Norway

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ABSTRACT

Objective: The association between depression and gambling disorder (GD) has been well-researched. However, prior research lacks consensus on the temporal association between depression and GD. Furthermore, the extant literature has not explored the nature of the aforementioned relationship using objective research methodology data and large-scale samples. The present study addressed these research gaps by investigating the longitudinal relationship between antidepressant prescriptions and the likelihood of developing GD using registry data over a period of 11 years (2008–2018). *Methods:* Data were derived from the Norwegian Patient Registry (NPR) that was matched with data from the Norwegian Prescription Registry (NorPD). The dataset comprised 27,420 individuals, where 5,131 were diagnosed with GD. A binary logistic regression analysis was conducted where individuals with GD were compared with 22,289 individuals matched on age and gender from NPR. *Results:* The results show that individuals with antidepressant prescriptions had higher odds of developing GD (OR = 2.80, 95% CI: 2.60–3.01, $p < 0.001$). Furthermore, males and older adults were found to have a higher likelihood of being diagnosed with GD. *Conclusions:* Depression is known to be one of the most common mental health disorders. The findings show that prior antidepressant prescription is associated with GD, which would be in accordance with the escape hypothesis because some individuals gamble to escape dysphoric feelings, such as depression. The study findings add to the existing knowledge on the temporal association of depression and GD. Furthermore, the results also have significant practical implications.

KEYWORDS

depression, gambling disorder, registry-based study, case-control study, longitudinal study

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INTRODUCTION

Depression is a common mental disorder in present society, and it is estimated that about 3.8% of the world's population suffer from depression (World Health Organization, 2023).

The disorder can be understood as the state where an individual displays symptoms characterized by low mood, as well as a lack of a positive affect coupled with varied associated behavioral (e.g., apathy), cognitive (e.g., problems concentrate), emotional (e.g., feeling of worthlessness), and physical (e.g., weight loss) symptoms (National Collaborating Centre for Mental Health, 2010). Depressed individuals often try to cope with their negative mental state through different coping strategies, for example through addictive behavior (Jacobs, 1986). One relevant addictive behavior is gambling, which by some is used for escaping from dysphoric feelings (Bilevicius et al., 2018). Such a getaway strategy could become persistent, repetitive, and lead to addictive behavior leading to harmful outcomes (e.g., personal, psychological, financial, social) (Giri et al., 2019). In some cases, this could lead to uncontrolled gambling, manifesting as problem gambling or even the more serious state, gambling disorder (GD).

The association between depression and problem gambling and GD has been well established. With regards to the association between depression and GD, different pathways may be relevant. First, depression may lead to escalation of problem gambling as a way of coping with a painful reality (Jacobs, 1986). In contrast, the second pathway is based on harmful consequences associated with GD that could result in depression (Kennedy et al., 2010). Finally, the two pathways may co-occur due to common risk factors (Chinneck, Mackinnon, & Stewart, 2016). The present research aims to provide a deeper exploration of the first pathway.

Extant literature has examined the relationship between depression and GD mainly using cross-sectional, longitudinal research, or systematic reviews. Most of the research based on cross-sectional research design has found the existence of a positive association between depression and GD (Cosenza, Ciccarelli, & Nigro, 2019; Martin, Usdan, Cremeens, & Vail-Smith, 2014; Molde, Pallesen, Bartone, Hystad, & Johnsen, 2009), although with some exceptions (Delfabbro, Lahn, & Grabosky, 2006; Pascual-Leone, Gomes, Orr, Kaploun, & Abeare, 2011). There have also been a few attempts at investigating the association between depression and problem gambling using longitudinal research design. However, there are mixed findings related to their association over time. Most of the longitudinal research has failed to demonstrate an association between depression and following problem gambling (Afifi, Nicholson, Martins, & Sareen, 2016; Chinneck et al., 2016; Edgerton et al., 2015, 2018) whereas others have found them to be positively associated over time (Bilevicius et al., 2018; Dussault et al., 2016).

The present study attempted to overcome some of the shortcomings of extant literature. First, considering that there are mixed findings on the temporal association of depression and GD, the present study added new knowledge to the existing knowledge pool. Due to lack of availability of exact information regarding depression diagnosis, the present study used antidepressant prescription as a proxy for depression. There is little research investigating the association of antidepressant prescription with GD. Second, from a methodological perspective, prior research lacks objective investigation of the association between depression and GD. For example, cross-sectional designs are not suited for examining the temporal direction between depression and GD whereas self-reported data often suffer from non-response bias and self-report biases (such as social desirability and memory recall bias). In contrast, the present study examined the possibility of a proxy for depression (i.e., prescribed antidepressants) being a risk factor for GD. The registry-based research offers a varied set of advantages, such as (i) efficiency in terms of cost and time requirements, (ii) enabling investigation of associations over time, (iii) enhancement of the generalizability of the findings, (iv) being free from recall and selection bias, and (v) enabling studying the entire population of interest (Laugesen et al., 2021; Li et al., 2016). Finally, to the best of the authors' knowledge, the present study is the first to examine the association between using antidepressant prescriptions as a proxy for depression and GD.

MATERIALS AND METHODS

Data extraction

The data for the study came from the Norwegian Patient Registry (NPR) (Bakken, Ariansen, Knudsen, Johansen, & Vollset, 2020) and the Norwegian Prescription Registry (NorPD) (Norwegian Institute of Public Health, 2024). NPR covers all Norwegian public specialized health-care services at the individual level, including private health-institutions and specialists contracted by the regional health authorities from 2008 onwards (Bakken et al., 2020). NPR includes detailed information about a patient's care, treatment, and diagnosis for both inpatient and outpatient hospital care in Norway. In 2019 there were approximately 10.5 million treatments/consultations among 3.2 million patients in somatic institutions (Helsedirektoratet, 2020a), psychiatric institutions (Helsedirektoratet, 2020b), and private health institutions (Helsedirektoratet, 2020c) contracted by the regional health institutions combined. NorPD covers all prescription drugs dispensed from pharmacies at the individual level in Norway since 2004 (Norwegian Institute of Public Health, 2024). Drugs dispensed in hospitals, nursing homes and to animals in Norway are also included, but not at the individual level. The database contains detailed information of prescribed medication, dosage, etc. in Norway. In the present study, NPR identified the study group (patients with GD) and control population (illness controls) from the NPR. These populations were then matched with NorPD using the Norwegian personal identification for linking information of antidepressants prescriptions to NPR data.

Participants

The study comprised all patients who were diagnosed with GD (N = 5,131) and a control group consisting of patients

from NPR without GD (n = 22,289) in the observation period from January 2008 to December 2018. The inclusion criteria for the GD group were a GD diagnosis (F63.0 according to ICD-10) in the observation period and being 18 years or older when they received the GD diagnosis. The GD diagnosis was made by a qualified specialist at the specialized healthcare services. The illness controls consisted of patients registered in NPR. The control population was frequency-matched on gender and age with the study group. The frequency match was conducted by the NPR. The exclusion criteria for illness controls were the presence of a GD diagnosis in the observation period. No other exclusion criteria were set. Consequently, the illness control group reflected a general sample of patients who had received treatment at the specialized healthcare services.

Antidepressant prescriptions

Antidepressant prescriptions were defined as all Anatomical Therapeutic Chemical (ATC) classifications beginning with "N06". The observed prescription ATC classifications can be viewed in Table 1 and a full list of the ATC-classifications and brands can be viewed in Appendix Table A1).

Table 1. Antidepression prescriptions by ATC-code in the whole sample, GDs and illness controls

ATC-classification	Prescribed medication in the sample					
	All (N = 88,775)		GD (n = 35,957)		Control (n = 52,818)	
	N	%	N	%	n	%
N06AA04	708	0.8%	140	0.4%	568	1.1%
N06AA06	1,135	1.3%	241	0.7%	894	1.7%
N06AA09	8,161	9.2%	2,199	6.1%	5,962	11.3%
N06AA10	262	0.3%	109	0.3%	153	0.3%
N06AA12	189	0.2%	107	0.3%	82	0.2%
N06AB03	2,773	3.1%	1,441	4.0%	1,332	2.5%
N06AB04	4,965	5.6%	2,022	5.6%	2,943	5.6%
N06AB05	2,572	2.9%	894	2.5%	1,678	3.2%
N06AB06	7,705	8.7%	3,666	10.2%	4,039	7.6%
N06AB08	303	0.3%	176	0.5%	127	0.2%
N06AB10	27,370	30.8%	10,704	29.8%	16,666	31.6%
N06AF03	59	0.1%	0	0.0%	59	0.1%
N06AG02	88	0.1%	27	0.1%	61	0.1%
N06AX01	*	0.0%	*	0.0%	*	0.1%
N06AX02	*	0.0%	*	0.0%	*	0.0%
N06AX03	5,115	5.8%	2,030	5.6%	3,085	5.8%
N06AX11	9,617	10.8%	4,061	11.3%	5,556	10.5%
N06AX12	3,557	4.0%	1,762	4.9%	1,795	3.4%
N06AX16	11,969	13.5%	5,611	15.6%	6,358	12.0%
N06AX18	91	0.1%	47	0.1%	44	0.1%
N06AX21	1,401	1.6%	443	1.2%	958	1.8%
N06AX26	695	0.8%	276	0.8%	419	0.8%

Note. * if $n \leq 5$ in All, GD or Illness control, only % is reported. ATC = Anatomical Therapeutic chemical. GD = gambling disorder (study population). Control = Illness control group. % GD = number of GDs/total number in a row.

Design and procedure

The study employed a case-control design because the study group was matched with the illness control group. The study investigated whether individuals diagnosed with GD had a larger likelihood of getting prescription for antidepressants (see Table 1 for ATC classifications), acting as a proxy for depression, prior to receiving their first GD diagnosis compared to the control group. Consequently, only patients with GD having an antidepressant prescription prior to the origination of GD were considered for the analysis (see Fig. 1).

Statistical analysis

A binary logistic regression was chosen to investigate the nature of the longitudinal association between depression and GD. The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to examine if depression (indicated by antidepressant prescription) was associated with the likelihood of developing GD. In the GD group, individuals were considered exposed if they received antidepressant prescriptions prior to the emergence of the GD diagnosis. The median time from study start to GD diagnosis was 81 months (IQR = 39–111) and median time from study start to first antidepressant prescription in the GD group was 24 months (IQR = 5–59). The maximum time from study start to antidepressants was also set to 81 months in the control group in order to obtain comparable exposure times across the two groups. Using this cut-off of 81 months resulted in a median time of 27 months (IQR = 5–53) from study start to antidepressant prescription in the control group as compared to a median of 47 months (IQR = 12–85) if the entire study period (2008–2018) was taken into consideration. However, using the latter would substantially underestimate the association between antidepressant prescription and subsequent GD diagnoses. The participant flow for the study is visualized in Fig. 1.

Ethics

The study was approved by the Regional Committee for Medical and Health-Related Research Ethics in Western Norway (no. 30393).

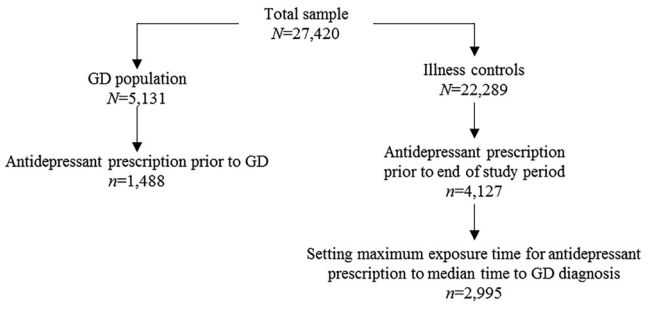

Fig. 1. Participant flow

RESULTS

The original control group sample comprised 17,641 males (79.1%) and 4,648 females (20.9%) within the age range of 18–88 years, with the mean age of 41.2 years (SD = 11.8 years). On the other hand, the GD population comprised 4,195 males (81.8%) and 936 females (18.2%), ranging from 18 to 88 years, with a mean age of 40.4 years (SD = 11.6 years). For those who were prescribed antidepressants prior to receiving a GD diagnosis (n = 1,488, see Fig. 1), the median time between depressant prescription to GD diagnosis was 37 months (IQR 13–72 months). The results of the binary logistic regression are presented in Table 2. The results showed that individuals with a prior antidepressant prescription had 2.80 greater odds of developing GD compared to those without prior antidepressant prescription (95% CI: 2.60–3.01). Females had 0.78 times the odds of developing GD compared to males (95% CI: 0.72–0.85). Finally, for every passing year, the odds of developing GD increased by 1% (95% CI: 1.01–1.01).

DISCUSSION

The present study examined whether depression, using antidepressant prescription as a proxy, was a risk factor for developing GD using a case-control longitudinal research design. The research was based on objective registry data from 2008 to 2018 that comprised 5,131 individuals diagnosed with GD and 22,289 controls.

The results showed that having antidepressant prescriptions was associated with increased risk of being diagnosed with a GD diagnosis. This suggests that depression or other conditions for which antidepressants are prescribed increase the likelihood of GD. This finding is consistent with the prior literature (Bilevicius et al., 2018; Dussault et al., 2016). In accordance with Jacobs' general theory of addiction (Jacobs, 1986) and Khantzian's self-medication hypothesis (Khantzian, 1997), individuals may engage in addictive behaviors such as gambling with the intention of temporarily escaping from painful emotions (Chinneck et al., 2016; Rømer Thomsen, Callesen, Linnet, Kringelbach, & Møller, 2009). In this regard, Bilevicius et al. (2018) and Arias-de la Torre et al. (2021) have reported that depressed young adults engage in gambling and drinking to regulate negative emotions. Moreover, Vaughan and Flack (2022) reported that the association between depression and GD was conditional (i.e., whether the depressed individual views gambling as a solution for managing their negative emotional state). This could possibly explain the longitudinal association between antidepressant prescription and GD attested to in the present study. Afifi et al. (2016), Chinneck et al. (2016), Edgerton et al. (2015), and Edgerton et al. (2018) found no support that depression was a risk factor for subsequent gambling problems. Indeed, Afifi et al. (2016) found a reverse temporal association where gambling problems were associated with the onset of mental health disorders and substance use disorders later. Similarly, Chineck et al. (2016) found that neither disorder was a risk factor for the other and suggested that the co-occurrence between depression and gambling problems is likely to be explained by third common factors, such as substance abuse. Therefore, different contextual factors or research-related methodological factors may possibly explain the contrasting results. For example, apart from regional differences, instruments, and sample sizes, the longitudinal studies that did not find that depressive symptoms were a risk factor for problem gambling were all based on the Manitoba Longitudinal Study of Young Adults consisting of young adults aged 18–20 years in 2007, and who were followed for five years (Afifi et al., 2016; Chinneck et al., 2016; Edgerton et al., 2015, 2018) whereas the present study consisted of all patients diagnosed with GD with a follow-up period of 11 years. The difference in age between the current population and the sample in other studies may explain the inconsistencies in findings because younger age is in itself a risk factor for GD and because younger individuals will have less time in which they possibly could have received a depression diagnosis. Consequently, developing depression before GD might be less common among younger individuals.

However, not all agree that antidepressant prescription is a reliable proxy for depression diagnosis. Several other psychiatric disorders, such as anxiety and bipolar disorders are quite often treated with antidepressants, and are also closely linked to the development of problem gambling (Kessler et al., 2008). Antidepressants are also commonly used for off-label purposes such as treatment of eating disorders, sleep problems, smoking cessation, and chronic pain management (Skånland & Cieślar-Pobuda, 2019). For example, a Canadian study reported that only 55% of antidepressant prescriptions were related to depression (Wong et al., 2016), and another study found that 27% of those receiving antidepressant prescriptions lacked a depressive diagnosis (Simon et al., 2014).

As aforementioned, the association between antidepressant prescription and GD has not undergone extensive research. Moreover, the limited research that exists suggests a link between antidepressants and GD (Menon, Cribb, Sarris, & Ng, 2018; Toneatto, Skinner, & Dragonetti,

Table 2. Binary logistic regression predicting the onset of gambling disorder after depression* in the time-period from 2008 to 2018

Predictor	OR	95% CI	p-value
Age in 2008	1.01	[1.01, 1.01]	<0.001
Gender			
Male (reference)	1.00	–	
Female	0.78	[0.72, 0.85]	<0.001
Depression*			
No (reference)	1.00	–	
Yes	2.80	[2.60, 3.01]	<0.001

Note. OR = Odds ratios. CI = Confidence intervals.
Total$_n$ = 27,420. Gambling disorder (GD)$_N$ = 5,131.
Illness controls$_n$ = 22,289.
*Measured as antidepressant prescription.

2002). Some classes of antidepressants (e.g., selective serotine reuptake inhibitors) have been found to trigger impulse control and maladaptive decision-making due to changes in serotonin levels in the brain. As such the present study findings are consistent with the limited extant literature. However, the findings of the present study should be corroborated with registry data in terms of the temporal associations between depression diagnosis (and not only antidepressant prescriptions as a proxy) and GD. Moreover, the advantage of using antidepressant prescriptions as a proxy for depression is that those being prescribed antidepressants for depression by their GP are included, whereas registry data on depression diagnosis normally only include those receiving treatment by specialized care.

Study implications

The findings of the present study have theoretical as well as practical implications. From the theoretical perspective, the study adds clarity on the temporal association between antidepressant prescriptions and GD. To the best of the authors' knowledge, the present study is the first to examine the longitudinal association between them using registry-based data through the use of antidepressants as a proxy for depression. The investigation of depression and GD through the lens of antidepressants being a proxy for depression also adds a new perspective to the existing understanding on the association.

From the perspective of practical implications, the findings could assist healthcare service providers, such as psychologists and psychiatrists. Because depression has been found to be a risk factor for developing GD, different early intervention and targeted prevention approaches could be developed. Such strategies could be helping people suffering from depression to avoid engaging in gambling behavior, especially to the level where it starts becoming problematic in nature. For example, strategies could entail distracting their mental attention to other interests or helping them realize that money spent on gambling instead could be used on something more meaningful in the future (Delfabbro et al., 2006). Another strategy could be the introduction of counter-cognitions intending to make them aware of the true odds of winning when engaged in gambling (Delfabbro et al., 2006). Additional strategies could be aimed at bringing them mentally and emotionally close to their friends and family during depressive periods of their life, as this could also moderate the association of depression with GD (Dussault et al., 2016; Edgerton et al., 2018).

Limitations and strengths

The longitudinal research design, together with the use of registry-based data, represent the biggest strengths of the present study. As aforementioned, the use of health registry data is a major methodological asset since it can avoid bias related to selection, non-response, and self-reporting. Furthermore, the use of a large sample size is another strength of the present study.

Despite the strengths, the research also suffers from some limitations that should be mentioned. First, registry-based data has the tendency to suffer from limited data quality in terms of validity (Laugesen et al., 2021). For example, the correctness of the positive predictive value denoting the probability that the person under question has actually been found to be suffering from depression. Second, the exact information on diagnosis of depression was not available in the present dataset. The present data provides information on when the study sample was first prescribed antidepressants during the considered study period. It should be noted that antidepressants are recommended in other situations (e.g., pain, sleep problems, etc.) in addition to depression. The present study assumed antidepressant prescription as a proxy for an individual suffering depression. Not all individuals getting an antidepressant prescription will have depression and far from all experiencing depression will get an antidepressant prescription. Therefore, the magnitudes of the associations observed in the present study involve some degree of uncertainty. Consequently, future research should continue to investigate the relationship between GD and different operationalizations and proxies of depression for comparison, such as diagnosis of depression only, and diagnoses of depression with other psychiatric disorders (e.g. anxiety disorders, and bipolar disorder).

Furthermore, depression is often a time-limited disorder that may last for a specific time period, such as six months or one year (National Collaborating Centre for Mental Health, 2010). Therefore, it is possible that individuals who got the GD diagnosis and who had prior depression, had remitted from depression before the presence of the GD. Additionally, depression is also recurrent in nature. Consequently, it could be relevant that the study sample might have suffered from one or more depressive episodes during the considered study period of 11 years. Such information could also have a confounding influence on the nature of the temporal association between depression and GD. It should also be acknowledged that there was no cut-off, either in terms of duration of the prescription or dosage of the antidepressant, in order to include use of antidepressants as a proxy for depression. Third, individuals' demographic characteristics may confound the association between antidepressant prescription and GD. The present study only took the influence of age and gender into consideration.

There may also be other significant demographic factors, such as education, socio-economic status, marital status, and other health-related variables that may have confounded this relationship effect, such as drinking alcohol, smoking cigarettes. Due to unavailability of this information from the health registries for this project, the present study was unable to take into consideration their influence on the association between antidepressant prescription and GD. Consideration of such information could further contribute to adding robustness to the study findings. Finally, it is highly likely that the number of people diagnosed with GD does not reflect the actual number of people suffering from gambling problems during the study time period. A recent prevalence study from Norway estimated that approximately

23,000 individuals aged between 16 and 74 years have a gambling problem (Pallesen et al., 2023), and a meta-analysis showed that approximately only 1 in 5 individuals with problem gambling seek help (Bijker, Booth, Merkouris, Dowling, & Rodda, 2022). Therefore, it seems conceivable that patients with GD included in the present study only represent a small subset of all those who suffer from GD in Norway. However, the advantage of using the NPR is that the records are based on validated and officially registered diagnoses.

Similarly, it is likely that the actual number of people suffering from depression is higher than the number of people receiving antidepressant medication. Consequently, the cases that have been captured using registry data are likely to be representative of the most severe cases suffering from GD and depression which could influence the generalizability of the present study's findings.

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Appendix

Table A1. Antidepression prescriptions by brand in the whole sample, GDs and controls

ATC-code	Brand	All *n*	GD *n*	Illness Control *n*	% GD
N06AA04	*Anafranil*	663	103	560	15.5%
	Klomipramin	45	37	8	82.2%
N06AA06	*Surmontil*	1,135	241	894	21.2%
N06AA09	*Amitriptylin*	*	*	*	100.0%
	Sarotex	8,160	2,198	5,962	26.9%
N06AA10	*Noritren*	262	109	153	41.6%
N06AA12	*Sinequan*	189	107	82	56.6%
N06AB03	*Fluoxetin*	2,579	1,330	1,249	51.6%
	Fontex	194	111	83	57.2%
N06AB04	*Cipramil*	356	165	191	46.3%
	Citalopram	4,609	1,857	2,752	40.3%
N06AB05	*Paroxetin*	1,213	355	656	29.3%
	Seroxat	1,359	539	1,022	39.7%
N06AB06	*Sertralin*	3,529	1,785	1,744	50.6%
	Zoloft	4,176	1,881	2,295	45.0%
N06AB08	*Fevarin*	303	176	127	58.1%
N06AB10	*Cipralex*	8,613	3,119	5,494	36.2%
	Escitalopram	18,757	7,585	11,172	40.4%
N06AF03	*Nardil*	59	0	59	0.0%
N06AG02	*Aurorix*	42	4	38	9.5%
	Moclobemid	46	23	23	50.0%
N06AX01	*5-HTP douglas*	*	*	*	2.7%
N06AX02	*L-Tryptophan*	*	*	*	0.0%
N06AX03	*Miansein*	306	141	165	46.1%
	Tolvon	4,809	1,889	2,920	39.3%
N06AX11	*Mirtazapin*	1,331	660	671	49.6%
	Remeron	8,286	3,401	4,885	41.0%
N06AX12	*Wellbutrin*	3,444	1,711	1,733	49.7%
	Zyban	113	51	62	45.1%
N06AX16	*Efexor*	881	433	448	49.1%
	Venlafaxin	10,471	4,898	5,573	46.8%
	Venlazid	467	219	248	46.9%
	Venlix	150	61	89	40.7%
N06AX18	*Edronax*	91	47	44	51.6%
N06AX21	*Cymbalta*	962	299	663	31.1%
	Duloxetin	439	144	295	32.8%
N06AX26	*Brintellix*	695	276	419	39.7%

Note. * if $n \leq 5$ in all, GD or Illness control, only % GD is reported.