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Research Article

A Systematic Review of the Psychiatric-Adverse Effects associated with the Administration of Vilazodone

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ABSTRACT

Purpose: Vilazodone is a novel antidepressant used to treat Major Depressive Disorder (MDD). Available literature suggests that the efficacy and safety of Vilazodone have not yet been systematically assessed and described. This study aims to provide a critical overview of the literature on the psychiatric-adverse effects associated with Vilazodone administration, from January 2000 to January 2020, highlighting the effects, consistencies, knowledge gaps, current theories, and limitations of available understandings.

Findings: From an initial search of 124 articles, a total number of 7 full texts, that met the inclusion criteria, were included in the review. Several psychiatric-adverse effects were found to occur with the use of Vilazodone. The findings of this study suggested that these common psychiatric-adverse effects associated with the use of Vilazodone are not included in the Food and Drugs Administration registration document and Patient Information Leaflet.

Conclusions: Vilazodone has a wide range of psychiatric-adverse effects as apparent from reviewing published clinical trials. More considerable attention in research should be given to a broader range of psychiatric-adverse effects associated with Vilazodone, and further detailed clinical trials are required to establish the safety profile. The limited amount of evidence from included studies shows that there is scanty scientific data concerning the safety profile of Vilazodone in psychiatric practice. The review was registered with the Open Science Framework (https://doi.org/10.17605/OSF.IO/2M7HY).

Keywords: Generalized anxiety disorder, Major depressive disorder, Mental health, Pharmacovigilance, Post-marketing surveillance, Psychiatry, Vilazodone

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INTRODUCTION

Adverse Drug Reactions (ADRs) can affect patients irrespective of age or gender, ultimately impacting morbidity and mortality (Schellack N, *et al.*, 2018). ADRs have become a major global health problem that needs to be addressed (Szmulewicz A, *et al.*, 2016). According to a study, ADRs are identified as the 4th-6th prime cause of death in the United States with the contribution of more than 100 000 deaths annually (Pirmohamed M, *et al.*, 2004).

Vilazodone is a relatively new drug that was released onto the market in 2011, sold under the brand name Viibryd, used to treat Major Depressive Disorder (MDD) (Cruz MP, 2012). Currently, there are numerous effective antidepressants on the market that have been available much longer than Vilazodone. Vilazodone has an advantage because it offers a dissimilar mechanism that produces remission of depressive symptoms (Singh M, *et al.*, 2012). Vilazodone simultaneously acts as a Selective Serotonin Reuptake Inhibitor (SSRI) and a 5-Hydroxytryptamine (Serotonin) 1A receptor (5-HT1A-receptor) partial agonist and enhances serotonergic activity in the Central Nervous System (CNS) through selective inhibition of serotonin reuptake (Cruz MP, 2012).

Over the years, several other adverse effects, including diarrhoea, headache, nausea, vomiting, and insomnia, have been identified with the use of Vilazodone (Wang YQ, *et al.*, 2016). However, being a relatively new drug, it is not clear if all adverse effects have been identified. In recent times, new warnings were reported of the drug indicating the risk of psychiatric-adverse effects such as worsening depression and the emergence of suicidal ideation (Goldenberg MM, 2011). More than half of the adverse effects recorded on the World Health Organization (WHO) site, VigiAccess, were not indicated on the Patient Information Leaflet (PIL) and Food and Drugs Administration (FDA) approval documentation. The highest frequency of these undetected adverse effects was observed under psychiatric disorders, clearly indicating the need for continued post-marketing surveillance.

Psychiatric-adverse effects caused by SSRIs have received little attention in clinical studies and are not listed in the literature as part of the known or expected adverse effects (Sansone RA and Sansone LA, 2010). Information about an antidepressants' adverse effects at the time of marketing is generated only from pre-marketing trials and studies (Wang YQ, *et al.*, 2016). This may be due to the failure of clinical studies to systematically assess psychiatric-adverse effects (Hughes S, *et al.*, 2017). Post-marketing studies and monitoring will provide more information about a drugs' effects on patients in clinical contexts.

The purpose of this study was to evaluate the psychiatric-adverse effects associated with the use of Vilazodone and evaluate the factors that have been hypothesized as being responsible for these effects. The study further evaluates the need for post-marketing surveillance.

METHODS

Search strategy

The search strategy was developed by three reviewers (authors) and applied to identify published articles in a three-phase approach (Appendix 1) as previously done (Wiafe E, *et al.*, 2020). First, a limited search of Pubmed (Medline) was carried out. The text words and index terms contained in the titles and abstract of the articles obtained were analyzed. Secondly, all related keywords and index terms identified were used in all the

included databases. Thirdly, the reference section of selected articles was checked for additional related studies. We performed a systematic literature search in March 2020 using multiple literature databases, including Pubmed (Medline), Proquest Psychology Journals, Web of Science, Taylor and Francis Online Journals, PsychInfo, and Wiley Online Library. Additional searches were performed in Google Scholar. Studies were limited to articles published from January 2000 to January 2020 as the patent of Vilazodone for registration was only received in 2011. Studies were also limited to the English language because it is the only language of communication amongst the researchers. Filters were set to English, human studies, and studies in adolescents (12 years and older) and adults (18 yrs and older). Reference checking of included articles was also done to capture missing primary articles as a result of indexing errors. The bibliographic software (End Note), was used for the data management of retrieved references. All the results of the literature searches were imported into the EndNote program and duplicates were removed.

The text words and index terms such as Vilazodone, Viibryd, depression, 5-HT1A, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion were used in each database. The search terms were combined using the Boolean operators 'AND' and 'OR' as indicated in Appendix 1 (Higgins JP, *et al.*, 2016).

Study eligibility

The PICOS framework was used to set criteria to identify the potential studies. The inclusion criteria were study Population (adolescents aged >12 and adults aged >18 years who reported psychiatric-adverse effects whilst on Vilazodone), Intervention (Vilazodone irrespective of dose and duration), Comparator (including studies that compared psychiatric-adverse effects and outcomes of Vilazodone and other antidepressants), Outcomes (psychiatric-adverse effects caused by the administration of Vilazodone), and Study design (Randomized Controlled Trials (RCTs), case reports, cross-sectional studies, and cohort studies). We excluded studies that were not published in the English language, published before January 2000 and after January 2020, were not primary studies, and did not report any psychiatric-adverse effects and outcomes associated with Vilazodone.

Study selection

All the articles were retrieved independently from the included electronic databases by two of the reviewers (authors) and then exported to EndNote program. The articles were reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Moher D, *et al.*, 2009). Duplicates were identified and removed using EndNote program. Two of the reviewers independently reviewed all titles and abstracts to determine eligibility based on set criteria. With this, the two reviewers further evaluated the full texts of the articles identified for their final eligibility for data extraction. All disagreements were resolved in consultation with a third reviewer.

Quality assessment and data extraction

The critical evaluation of the articles for quality was undertaken by two reviewers employing the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies, JBI critical appraisal checklist for cohort studies, and JBI critical appraisal tool for Randomized Controlled Trials (Aromataris E and Munn Z, 2017). The articles were then scored based on their quality scores and classified as; less than 50% (low-quality studies), 50% to 75% (moderate-quality studies), or greater than 75% (high-quality studies). We did not predefine any study exclusion based on quality criteria. The results of this appraisal were used to show the possibility of bias in the design, conduct, and analysis of each study. We employed a predesigned data extraction form prepared in a Microsoft Excel® sheet. The data extraction form was piloted to ensure completeness and clarity. The following data were extracted: bibliographic information, study characteristics, participants' characteristics, treatment information, description of psychiatric-adverse effects, and outcome of interest. All disagreements in the course of extraction were resolved by discussion and consensus, with the inputs of an arbiter.

Data synthesis

Data were imported into SPSS Software for analysis. Frequency tables summarized categorical data, including sample characteristics, patient characteristics, and psychiatric-adverse effects outcomes. Psychiatric-adverse effects found from selected studies were listed in tables according to preferred terms based on the most commonly used coding system, the Medical Dictionary for Regulatory Activities (MedDRA) (Le Noury J, *et al.*, 2015) (Appendix 2). Using these terms, the impacts of psychiatric-adverse effects on Vilazodone were described. A narrative synthesis was done to describe and discuss the outcomes.

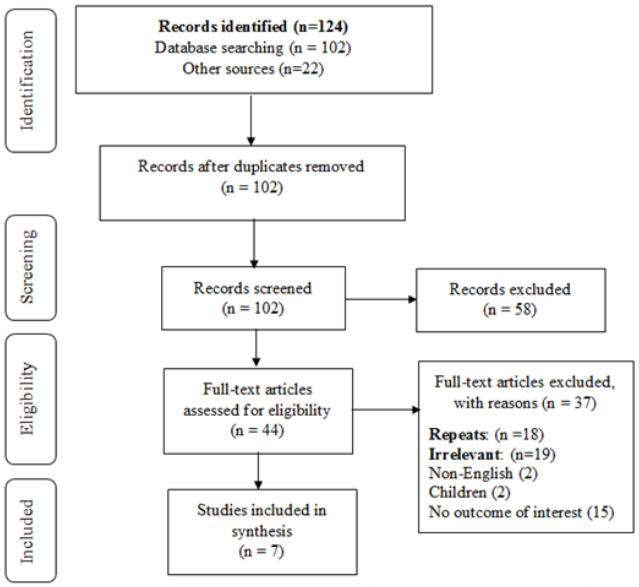

Figure 1: PRISMA 2009 flow diagram (Moher D, *et al.*, 2009)

RESULTS

Search findings and analysis

Search results: The data collection process for this systematic review began on the 26th of March, 2020. The process involved a four-part search which yielded a total of 124 articles. As shown in the PRISMA flow chart *(Figure 1)*, upon deduplication, the articles were reduced to 102. The abstract of each article was screened according to the set eligibility criteria, following which 58 were excluded. This left a total of 44 potentially eligible studies, which were subjected to full-text assessment. The full-text assessment stage excluded 37 articles (with reasons indicated in the PRISMA flow diagram), and 7 studies were finally included in the review. Inter-rater agreement in the title/abstract screening process was substantial (kappa=0.79; %agreement=96.8%) and moderate during full-text article screening (kappa=0.6; %agreement=84.4%).

Quality assessment/risk of bias

Using the JBI levels of evidence, one cross-sectional study (Hughes S, *et al.*, 2017), one cohort study (Robinson DS, *et al.*, 2015), and five RCTs were included in the review (Croft HA, *et al.*, 2014; Durgam S, *et al.*, 2016; Gommoll C, *et al.*, 2015; Khan A, *et al.*, 2009; Mathews M, *et al.*, 2015). Appraisal of individual studies using the JBI critical appraisal method is shown in the supplementary information (Appendix 3 A-C). To summarize, the cross-sectional study was of the highest quality (100%). The prospective cohort study was of moderate quality (50%-75%) and all the RCTs were of high quality (>75%).

Analysis of findings

Study characteristics: The articles that were selected were all published between 2009 and 2017, with the majority (n=6) of the studies conducted only after Vilazodone was released onto the market in 2011. All included studies were published primary studies: RCTs (n=5), open-label cohort study (n=1), and a cross-sectional study (n=1). Amongst the 5 RCTs, 3 were Phase IV trials and 2 were Phase III trials. Most of the studies took place over 8-10 weeks (n=6). The dose range of Vilazodone for all the included studies was 10-40 mg *(Table 1)*.

Demographic and patient characteristics: All studies took place in the USA, also being the country with the highest rate of use of Vilazodone. One study had a component of data collected from Mexico (Gommoll C, *et al.*, 2015). The main objectives of all the included studies were indicative of the evaluation of the safety and efficacy of Vilazodone for either the management of Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD). Most of the studies (n=6) included a population age group of between 18-70 years. The mean age for all included studies was 38 years. The mean percentage for the race group which accounted for the highest population of patients who were administered Vilazodone were Whites (76%). Females (65%) accounted for the greater proportion of patients who received Vilazodone *(Table 2)*.

Psychiatric-adverse effect outcomes: A double-blind placebo-controlled trial was conducted over ten weeks by Durgam S, *et al.* to test the efficacy of Vilazodone amongst adolescent patients aged 12-17 years old. Adverse effects that led to the discontinuation of the drug included nightmares (Vilazodone at 30 mg/day, n=2; Placebo, n=0), suicidal ideation (Vilazodone at 15 mg/day and 30 mg/day, n=4; Placebo, n=1), and depression (Vilazodone at 15 mg/day and 30 mg/day, n=4; Placebo, n=0). In the study by Croft HA, *et al.*, anxiety (n=2; 0.8%) was recorded with Vilazodone use, higher than Placebo (n=1; 0.4%). Irritability was also recorded but was lower than the Placebo (Vilazodone=0.4%, Placebo=0.8%).

Khan A, *et al.* reported that abnormal dreams recorded with the administration of Vilazodone (n=14; 6%) were higher than the placebo (n=4; 1.7%). In the submission by Gommoll C, *et al.*, 2015, abnormal dreams were more associated with the use of Vilazodone (n=10; 5%) in comparison to the Placebo (n=3; 1.5%). The open-label cohort study by Robinson *et al.* reported psychiatric-adverse effects such as abnormal dreams (n=62; 10.4%), anxiety (n=36; 6%), and suicidal ideation (n=5; 0.8%) associated with the administration of Vilazodone.

According to Hughes S, *et al.* online user reviews of two older antidepressants: Escitalopram and Duloxetine, and 2 newer antidepressants: Vilazodone and Vortioxetine, with few completed clinical studies and less post-marketing experience, were studied for differences in their adverse effects profiles (Hughes S, *et al.*, 2017). The final sample consisted of 3,243 user reviews on the four drugs: Escitalopram (n=2,359; 72.7%); Vilazodone (n=394; 12.1%); Duloxetine (n=305; 9.4%); and Vortioxetine (n=185; 5.7%) from three health websites (Hughes S, *et al.*, 2017). The recruited patients reported 57% of psychiatric-adverse effects, 41.4% of gastrointestinal effects, and 28.4% of sleep effects with the administration of Vilazodone (Hughes S, *et al.*, 2017). The psychiatric-adverse effects demonstrated moderate to substantial relationships with patients' satisfaction with Vilazodone, whereas gastrointestinal, metabolic, or sexual adverse effects were minimally related (Hughes S, *et al.*, 2017). Vilazodone users reported the highest rates of abnormal dreams (25.6%), aggression or increased anger (10.7%), aggravated depression and crying (11.7%), sleep paralysis (5.1%), agitation (7.6%), and confusion (6.3%) in comparison to the other antidepressants (Hughes S, *et al.*, 2017). Worsened anxiety was a highly reported psychiatric-adverse effect amongst the users of Vilazodone.

Table 1: Study characteristics of included studies

Studies	Design	Groups (n)	Duration	Functional tests	Dose range	Summary of the main objective	Inclusion Population	Summary of findings (psychiatric adverse effects)
Khan A, *et al.*	RCT Double-blind	n=481 Vilazodone 40 mg=235 Placebo=233	8 weeks	HAM-A MADRS CGI-I CGI-S HDRS 17 HDRS 21 HARS	Vilazodone 10 mg once daily for seven days, 20 mg for the next seven days, and 40 mg for the duration of the study	To evaluate the safety of Vilazodone in patients with MDD	Adults with MDD who had an ongoing major depressive episode lasting ≥ 4 weeks and ≤ 2 years, and had an HDRS-17 total score ≥ 22	Abnormal dreams
Croft HA, *et al.*	RCT Double-blind Phase IV	n=797 Vilazodone 40 mg=253 Vilazodone 20 mg=292 Placebo=252	8 weeks	C-SSRS MADRS CGI-S HAM-A	Vilazodone 10 mg once daily for seven days, 20 mg for the next seven days, and 40 mg for the duration of the study	To assess the efficacy, safety, and tolerability of Vilazodone in patients with MDD	Adults with MDD who had an ongoing major depressive episode lasting ≥ 8 weeks and up to 12 months, and had a MADRS total score ≥ 26	Anxiety, irritability, depression, and suicidal ideation

Gommoll C, *et al.*	RCT Double-blind Phase: III	n=673 Vilazodone 40 mg=225 Vilazodone 20 mg=227 Placebo=221	10 weeks	C-SSRS HAM-A CGI-I CGI-S	Vilazodone 20-40 mg	To evaluate the safety and efficacy of Vilazodone in patients with GAD	Participants with HAMA total score ≥ 20, HAMA items 1 and 2 scores ≥ 2, and CGI-S score ≥ 4	Abnormal dreams and suicidal ideation
Mathews M, *et al.*	RCT Double-blind Phase: IV	n=1133 Vilazodone 40 mg=291 Citalopram 40 mg=289 Placebo=290	10 weeks	C-SSRS MADRS HAM-A CGI-I CGI-S	Vilazodone 10 mg once daily for seven days, 20 mg for the next seven days, and 40 mg for the duration of the study	To evaluate the safety and efficacy of Vilazodone 20-40 mg in patients with MDD	Adults with MDD who had an ongoing major depressive episode lasting ≥ 8 weeks and up to 12 months, and had a MADRS total score ≥ 26	Suicidal ideation
Robinson DS, *et al.*	Open-Label multicentre safety trial cohort study	n=599	52 weeks	MADRS CGI C-SSRS	Vilazodone titrated from 10-40 mg over ten days	To assess the safety and tolerability of Vilazodone in patients with MDD	Adult patients with a 17-item Hamilton Rating Scale for Depression score of 18 or greater received Vilazodone according to a fixed-titration schedule to reach a dose of 40 mg/d continued up to 1 year.	Abnormal dreams, anxiety, and suicidal ideation
Durgam S, *et al.*	RCT Double-blind study	n=529 Vilazodone 15 mg=175 Vilazodone 30 mg=180 Placebo=174	10 weeks	C-SSRS CDRS-R CGI-S	Vilazodone 15-30 mg	To evaluate the safety, efficacy, and tolerability in adolescent patients with MDD	Patients aged 12-17 years with a diagnosis of MDD for a minimum of 6 weeks with the Children's Depression Rating Scale-Revised (CDRS-R) total score C 40 and a Clinical Global Impressions-Severity (CGI-S) score C 4.	Nightmares, suicidal ideation, depression, suicidal attempt, anxiety, depressive symptoms, impulsive behaviour, irritability, mental status change, suicidal ideation, and suicidal behaviour
Hughes S, *et al.*	Cross Sectional Study	n=3243 Escitalopram=2359 Vilazodone=394 Duloxetin=305 Vortioxetine=185		N/A	Vilazodone 10 mg	To examine the adverse effects among online users and reviews of two older and two newer antidepressants	Included article based on online user reviews for 4 antidepressants from three websites: the professional health portals WebMD and Everyday health, and ask a patient.	Abnormal dreams, agitation, aggression or increased anger, aggravated depression, crying, anxiety, confusion, depersonalization, emotional numbing, sleep paralysis, suicidal ideation or attempt

Table 2: Demographic and patient characteristics

Author	Year	Country	Age	Mean age	Race	Gender
Khan A, *et al.*	2009	USA	18-70 years	41 years	77% Whites	59% female
						41% male
Croft HA, *et al.*	2015	USA	18-70 years	39 years	80% Whites	68% female
						32% male
Gommoll C, *et al.*	2015	USA and Mexico	18-70 years	40 years	81% Whites	69% female
						31% male
Mathews M, *et al.*	2015	USA	18-70 years	41 years	71% Whites	57% female
						43% male
Robinson DS, *et al.*	2015	USA	18-70 years	42 years	80% Whites	68% female
						32% male
Durgam S, *et al.*	2016	USA	12-17 years	15 years	67% Whites	59% female
						41% male
Hughes S, *et al.*	2017	USA	19-75 years	47 years	"Missing"	77% female
						23% male

Based on C-SSRS findings, as reported by Durgam S, *et al.* suicidal ideation (Placebo, 33.3%; Vilazodone 15 mg/day, 36.0%; Vilazodone 30 mg/day, 31.1%) and suicidal behaviour (Placebo, 1.8%; Vilazodone 15 mg/day, 1.1%; Vilazodone 30 mg/day, 1.1%) were recorded. Suicidal ideation with the use of Vilazodone 15 mg, was recorded as the highest in comparison to the placebo. The incidence of suicidal ideation during double-blind treatment in a study by Mathews M, *et al.* was also determined by the C-SSRS scale. The results showed that suicidal ideation was higher in the Placebo group (24.2%) relative to the active treatment groups (Vilazodone 20 mg/day, 17.4%; Vilazodone 40 mg/day, 18.1%; Citalopram, 16.3%). In a study by Gommoll C, *et al.*, 2015 where suicidal ideation was assessed with the C-SSRS scale, suicidal ideation was also reported more often amongst patients in the Placebo group (8%) compared with the Vilazodone (20-40 mg/day) group (6%). Suicidal ideation, according to the C-SSRS scale in the study by Croft HA, *et al.* (2014) was found to be 19% with the use of Vilazodone to the Placebo (21%). The details of these findings are expanded in *Tables 3 and 4*.

Table 3: Psychiatric-adverse effects of Vilazodone from reviewed studies

Psychiatric-adverse effect	Groups (n)			
Khan A, *et al.*				
	Vilazodone 40 mg		Placebo	
	n=235		n=233	
Abnormal dreams	14 (6.0%)		4 (1.7%)	
Croft HA, *et al.*				
	Vilazodone 40 mg		Placebo	
	n=255		n=253	
Anxiety	2 (0.8%)		1 (0.4%)	
Irritability	1 (0.4%)		2 (0.8%)	
Depression	0		2 (0.8%)	
Suicidal ideation based on C-SSRS scale	19%		21%	
Gommoll C, *et al.*				
	Vilazodone 20-40 mg		Placebo	
	n=200		n=198	
Abnormal dreams	10 (5%)		3 (1.5%)	
Suicidal ideation based on C-SSRS scale	6%		8%	
Mathews M, *et al.*				
	Vilazodone 20 mg	Vilazodone 40 mg	Citalopram 40 mg	Placebo
	n=288	n=284	n=280	n=281
Suicidal ideation based on C-SSRS scale	17.40%	18.10%	16.30%	24.20%
Robinson DS, *et al.*				
	Vilazodone 40 mg			
	n=599			
Abnormal dreams	62 (10.4%)			
Anxiety	36 (6.0%)			
Suicidal ideation	5 (0.8%)			

Durgam S, *et al.*				
		Vilazodone 15 mg	Vilazodone 30 mg	Placebo
		n=175 (%)	n=180 (%)	n=171 (%)
Nightmare		0	2 (1.1)	0
Suicidal ideation		2 (1.1)	2 (1.1)	1 (0.6)
Depression		3 (1.7)	1 (0.6)	0
Suicidal attempt		0	1 (0.6)	0
Anxiety		1 (0.6)	0	0
Depressive symptoms		1 (0.6)	0	1 (0.6)
Impulsive behaviour		0	0	1 (0.6)
Irritability		1 (0.6)	0	0
Mental status change		1 (0.6)	0	0
Suicidal ideation based on C-SSRS scale		36%	31.10%	33%
Suicidal behaviour based on C-SSRS scale		1.10%	1.10%	1.80%
Hughes S, *et al.*				
Abnormal dreams	18 (5.9)	135 (5.7)	101 (25.6)	5 (2.7)
Agitation	10 (3.3)	70 (3.0)	30 (7.6)	20 (10.8)
Aggression or increased anger	8 (2.6)	56 (2.4)	42 (10.7)	10 (5.4)
Aggravated depression, crying	26 (8.5)	123 (5.2)	46 (11.7)	20 (10.8)
Anxiety	27 (8.9)	240 (10.2)	53 (13.5)	29 (15.7)
Confusion	16 (5.2)	100 (4.2)	25 (6.3)	10 (5.4)
Depersonalization	14 (4.6)	157 (6.7)	13 (3.3)	5 (2.7)
Emotional numbing	25 (8.2)	253 (10.7)	16 (4.1)	11 (5.9)
Sleep paralysis	0 (0)	1 (0)	20 (5.1)	0 (0)
Suicidal ideation or attempt	18 (5.9)	62 (2.6)	20 (5.1)	8 (4.3)

Table 4: Summary of psychiatric-adverse effects of Vilazodone from reviewed articles

Psychiatric-adverse effects	Literature
Abnormal dreams	Khan A, *et al.*
	Gommoll C, *et al.*
	Robinson DS, *et al.*
	Hughes S, *et al.*
Aggravated depression, crying	Durgam S, *et al.*
	Hughes S, *et al.*
Aggression or increased anger	Hughes S, *et al.*
Agitation	Hughes S, *et al.*
Anxiety	Croft HA, *et al.*
	Robinson DS, *et al.*
	Durgam S, *et al.*
	Hughes S, *et al.*
Alterations in mental status	Durgam S, *et al.*
Confusion	Hughes S, *et al.*
Depersonalization	Hughes S, *et al.*
Emotional numbing	Hughes S, *et al.*
Irritability	Croft HA, *et al.*
	Durgam S, *et al.*
Nightmares	Durgam S, *et al.*
Sleep paralysis	Hughes S, *et al.*
Suicidal ideation or attempt	Croft HA, *et al.*
	Gommoll C, *et al.*
	Mathews M, *et al.*
	Robinson DS, *et al.*
	Durgam S, *et al.*
	Hughes S, *et al.*

DISCUSSION

Vilazodone was approved by the US Food and Drug Administration (FDA) for the treatment of MDD in adults in 2011 (Cruz MP, 2012). Thus, reviewed articles were mainly published over the period between 2012-2017, and clinical trials mostly in the Americans. According to statistics, antidepressants are one of the most commonly prescribed medications in the US population, mostly amongst older adults (Tamblyn R, *et al.*, 2019). Also, Vilazodone was released in the US before being marketed in Asia and Europe. This might have accounted for why the data was skewed to the US.

The main objective of all the included studies was to evaluate the safety and efficacy of Vilazodone for either the treatment of Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD). MDD is a serious, chronic, and debilitating psychiatric illness affecting approximately 120 million individuals worldwide with a lifetime prevalence of 10-15% (Lépine JP and Briley M, 2011). GAD is a condition of excessive and persistent worry about events in the future, with a distorted perception of risks and threats by patients (Allgulander C, 2012). GAD is associated with psychological symptoms including restlessness, difficulty concentrating, and disturbed sleep, often occurring comorbidly with MDD (Buoli M, *et al.*, 2013). The recommended dose for vilazodone is 20-40 mg/day (Song L, *et al.*, 2016), starting at 10 mg per day titrated upward to a target dose of 40 mg per day which is the dose level being evaluated for the treatment of GAD and MDD.

In terms of patient demographics, Vilazodone was mainly administered to adult (18-70 years) female patients. The mean age of participants for all the included studies was 38 years. Vilazodone is an antidepressant mostly used by adult patients and rarely used in children below the age of 12 (Cruz MP, 2012). The use of antidepressants in adults has increased due to several factors, including an increase in the adult population on antidepressant therapies, duration of therapy, which is mostly 180 days, and increase multiple chronic conditions within the adult population (Tamblyn R, *et al.*, 2019). According to a recent study, it was found that 50% of antidepressants were prescribed for unapproved indications including chronic pain, tiredness, and sleep disturbance, which are also more common in older adults (Tamblyn R, *et al.*, 2019). Due to the higher rate of use, most adverse events would be observed in adults.

The mean percentage for the race group, the Whites, which accounted for the highest population of users was 76%. Nationally, it was found that Black-Americans with depressive or anxiety disorders were one-third less likely than White-Americans to have used antidepressants, making the psychiatric need for antidepressants to be associated more with Whites (Gonzalez HM, *et al.*, 2008). The mean percentage of users in this study was highest for females (65%), compared to males. According to a study, females were about twice as likely as males to take antidepressants (Pratt LA, *et al.*, 2017). Women were found to be more likely to experience specific forms of depression-related illnesses, including postpartum depression, postmenopausal depression, and anxiety (Albert PR, 2015). Female hormonal fluctuations may be a trigger for depression, making young women at a higher risk for major depression and mental disorders globally (Albert PR, 2015).

In patients with depression, synaptic levels of serotonin are regulated by 5-HT1A auto-receptors. The activation of 5-HT1A auto-receptors, through the binding of serotonin, initially produces an increase of serotonin reuptake, and this mechanism makes the neurotransmitter more available to interact with these receptors (Yohn CN, *et al.*, 2017). Current theory predicts that sustained, long-term 5-HT1A receptor stimulation by Vilazodone leads to a down-regulation of the auto-receptors so that, over time, serotonin release is no longer inhibited causing psychiatric-adverse effects, resulting in altered mentation and instability (Pierz KA, *et al.*, 2014). Since some drugs take a shorter time to relapse after discontinuation than expected, the combination of long-term drug treatment followed by withdrawal of Vilazodone may be a causal factor in depression recurrence (Antonuccio D and Healy D, 2012).

A recent study also suggests that brain metabolism is reduced in the anterior cingulate which is responsible for emotional expression, in patients that suffer from depression. Therefore, leading to psychiatric-adverse effects such as emotional blunting, numbing and mental status changes (Kennedy SH, *et al.*, 2001). Kapur S, *et al.* proposed that prolonged and excessive serotonin in the synapse leads to a decrease in transmission of dopamine in the frontal lobe, causing a frontal lobe dysfunction, which is responsible for the apathy and emotional changes seen in patients (Kapur S and Mann JJ, 1992).

Discontinuation reactions have been reported after the withdrawal of prolonged Vilazodone treatment. According to studies by Durgam S, *et al.*, Khan A, *et al.*, and Croft HA, *et al.*, adverse effects such as nightmares, suicidal ideation, depression, anxiety, and abnormal dreams were all seen to have a higher incidence rate with the discontinuation of Vilazodone in comparison to placebo. Insomnia, nightmares, anxiety, agitation, depressive mood, sudden crying, increased suicidal thoughts, and confusion are psychiatric-adverse effects most frequently associated with the discontinuation of an antidepressant (Wang YQ, *et al.*, 2016). Clinical trials show that this discontinuation syndrome results from neurophysiologic readjustment in the central nervous system which may be one of the main reasons for adverse effects caused by Vilazodone (Citrome L, 2012). Intolerability to medication is one of the most common reasons patients discontinue antidepressant treatment (Hunkeler EM, *et al.*, 2004). Patients should be monitored for these symptoms and the Vilazodone dose should be tapered gradually when patients are discontinuing therapy (Goldenberg MM, 2011).

In the analysis of Internet postings of users' reviews of Vilazodone according to the study by Hughes S, *et al.*, it was seen that a greater range of behavioural and psychiatric-adverse effects from users' online postings appeared in comparison to published clinical trials (Hughes S, *et al.*, 2017). Vilazodone users reported the highest rates of abnormal dreams, aggression, and anger, aggravated depression and crying, sleep paralysis, agitation, and confusion in comparison to the other antidepressants. Psychiatric-adverse effects in this study were more often reported over the initial weeks of Vilazodone use. In this study, there were also meaningful differences in adverse effects amongst older and newer antidepressant agents. The more recently marketed drugs, such as Vilazodone, had higher reports of aggressive behaviour, agitation, aggravated depression, and abnormal dreams. These effects contribute to emotional instability and are associated with increased suicidality (Goldsmith L and Moncrieff J, 2011). The findings imply that important differences between antidepressants might be missed, due to poor adverse effect assessment in drug research and development (Hughes S, *et al.*, 2017).

The most important safety issue concerning depression is the reported link between suicidality and antidepressants. Antidepressants increase the risk of suicidal thinking and behaviour in adolescents, and adults with MDD and other psychiatric disorders (Goldenberg MM, 2011). In a study, SSRI use was associated with a nearly five-fold higher risk of completed suicide and suicidal thoughts in comparison to other classes of antidepressants (Nischal A, *et al.*, 2012). Antidepressant therapy involves a substantial delay before clinical improvements can occur, causing suicidal impulses. The psychopharmacological effects of SSRIs suggest that patients experience a worsening of mood with SSRI treatment and may cause agitation and impulsivity, resulting in an increased risk of suicide (Nischal A, *et al.*, 2012).

The Columbia-Suicide Severity Rating Scale (C-SSRS) measures suicidal ideation and behaviour and gauges the severity over specified periods. This measure is considered essential in depressive patients for assessing suicide-related phenomena (Posner K, *et al.*, 2011). According to the C-SSRS findings in all pooled studies, except the study by Durgam S, *et al.*, the rates of suicidal ideation were more common in the Placebo-treated patients than in the Vilazodone-treated patients. Despite this, the rates of suicidal ideation and behaviour in some studies were still relatively high with the use of Vilazodone. Although clinical trial reports usually provide suicide-related results, such information may be limited as suicidal events are uncommon and most trials specifically exclude patients with a current risk of suicide. A higher risk of suicidal ideation should encourage clinicians to be more cautious in their management, with intensive monitoring during the early phase of treatment (Nischal A, *et al.*, 2012).

While cardiac (e.g., dizziness) and gastrointestinal (e.g., nausea, vomiting) effects have been cited in published clinical trial research as adverse effects, most often leading to treatment discontinuation (Crawford AA, *et al.*, 2014), this analysis and review suggest that psychiatric-adverse effects might have a more significant role in treatment decision-making than previously recognized.

LIMITATIONS AND RECOMMENDATIONS

This systematic review was limited in its selection of databases and its restriction to English publications. Although an extensive review was covered, not all the literature obtained was relevant. This resulted in a very small sample size and may not be representative of all the available research between January 2000 and January 2020. Also due to the heterogeneity in the data, it was not possible to undertake a meta-analysis. Vilazodone was only approved by the FDA and put onto the market in 2011, thus a considerably new drug with limited research. There are very few articles published that discuss the psychiatric-adverse effects caused by Vilazodone, which is why there is a need for post-marketing surveillance. Recommendations for future research will include an increase in studies conducted specifically on the psychiatric-adverse effects caused by Vilazodone.

CONCLUSIONS

The findings of this systematic review hypothesize that Vilazodone has a wider range of psychiatric-adverse effects than documented in published clinical trials. The analysis of reviews of Vilazodone provides information about critical adverse effects yet to emerge in testing and surveillance. The present findings thus imply that significant adverse effects might be missed, due to the long-standing problem of poor assessment in drug research.

The emotional and behavioural effects of antidepressants should be central to the process of monitoring and evaluating treatment benefits and harms. The most commonly used checklists in short-term clinical studies neglect psychiatric-adverse effects, resulting in incomplete information about expected benefits and harms of the drug to patients and health care professionals. More intensive monitoring for psychiatric-adverse effects may be appropriate for any Vilazodone-naïve patient, and more considerable attention in research should be given to a broader range of effects that could impact treatment. Health care professionals should adopt tools to regularly monitor psychiatric-adverse effects upon the initiation and withdrawal of Vilazodone. Patients should be warned that Vilazodone may induce altered emotions and prescribers should also be more aware of its' mental effects to help make prescribing decisions more rational and effective.

Although Vilazodone has proven efficacious in the management of MDD and is being investigated for other possible indications, detailed clinical trials are required to establish their psychiatric safety profile. Future research should more specifically and systematically examine these psychiatric-adverse effects as the drug is released onto the market.

DECLARATIONS

Authors' contribution statement

All the listed authors contributed significantly to the design, implementation, and development of the manuscript for publication, with approval.

Data availability

Most of the data used in this systematic review are publicly available.

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