THE SAFETY PROFILE OF VILAZODONE – A STUDY ON POST-MARKETING SURVEILLANCE.

by

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Submitted as the dissertation component in fulfilment for the degree of Master of Pharmacy in the School of Health Sciences, University of KwaZulu-Natal.

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PREFACE

This dissertation is presented in an article format. The findings of the study are presented in chapter 3 and chapter 4, in manuscript format, as required by the regulations of the University of KwaZulu-Natal. The manuscript in chapter 3 has been submitted for publication to the Journal of Pharmacy Practice. The systematic review manuscript in chapter 4 will be submitted for publication to BMC Public Health. The references used in the manuscripts were cited according to the instructions/guidelines for authors as required by the journals.

The dissertation consists of five chapters as follows:

Chapter 1: Introduction highlights the background, problem statement and rationale of the study. It further describes the research questions, the aim and objectives of the study, a brief methodology and overview of the dissertation.

Chapter 2: Highlights the literature background to the study by providing an overview of adverse drug reactions, pharmacovigilance, ADR monitoring, post-marketing surveillance, and the efficacy and safety of vilazodone.

Chapter 3: Manuscript titled "The safety profile of vilazodone - a study on post-marketing surveillance" written according to the author guidelines and submitted for publication to the Journal of Pharmacy Practice.

Chapter 4: Manuscript titled "A systematic review based on the psychiatric adverse effects associated with the use of vilazodone" written according to the author guidelines to be submitted for publication to BMC Public Health.

Chapter 5: Provides the synthesis which includes general conclusions, significant findings, strengths and limitations of the study and recommendations are provided.

DECLARATION 1: DISSERTATION SUBMISSION

This is to certify that the contents of this dissertation are the original work of:

Student: Humraaz Kaja (214521556)

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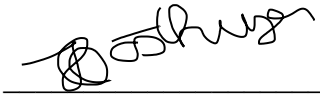
As the student's supervisor and co-supervisor, we have approved this dissertation for submission.

Supervisor: Dr Frasia Oosthuizen

Signed: 

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I, **Humraaz Kaja**, declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original work.

2. The work described in this dissertation has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

3. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers.

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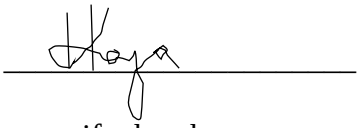
Signed  Date: 20/05/2020

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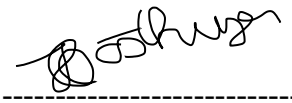

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2. **Name: Dr. Kofi Mensah** Date: 20/05/2020

DECLARATION 2 – ETHICS APPROVAL

The data accessed in this study is in the public domain readily accessible on the internet and does not contain any personal information that can be linked to real people. A waiver for ethical approval was obtained from the University of Kwa-Zulu-Natal School of Health Science (Annexure 1).

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. **My contribution to the project was as follows:**

   Humraaz Kaja: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of dissertation.

2. **The contributions of others to the project were as follows:**

   Dr Frasia Oosthuizen: Supervisor – supervision of the concept of the study and review of the dissertation and manuscripts. Assisted in obtaining data sets upon which the study was based.

   Dr Kofi Mensah: Co-Supervisor – guided the systematic review and review of the dissertation.

DEDICATION

Along with hard work, this dissertation would have not been possible without the blessings of Almighty God, who gave me the courage and strength to complete my studies. I dedicate this master's thesis to my family. To my father and my biggest fan, Yusuf Kaja for his continuous support, encouragement and always pushing me beyond my limits. To my mother, Yasmin Kaja who always consoled me when my spirits were low and for being my pillar of strength. Everything I am and everything I aspire to be is only because of you both. I will always strive to make you proud. To my siblings- Haaziq, Humaira and Haajirah Kaja for being my biggest support system. Without your encouragement and motivation, this dissertation would not have been possible. I am deeply grateful to you all. Thank you.

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And lastly, my gratitude goes to the University of KwaZulu-Natal, College of Health Sciences (CHS) for funding this study.

LIST OF ACRONYMS AND ABREVIATIONS

ADR	Adverse Drug Reaction
CDRS	Children's' Depression Rating Scale
CGI-I	Clinical Global Impression- Improvement Scale
CGI-S	Clinical Global Impression- Severity Scale
CNS	Central Nervous System
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
GIT	Gastro-Intestinal Tract
HAM-A	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
JBI	Joanna Briggs Institute
KZN	Kwa-Zulu Natal
MADRS	Montgomery-Asberg Depression Rating Scale
MedRA	Medical Dictionary for Regulatory Activities
MCC	Medicines Control Council
MDD	Major Depressive Disorder
NDoH	National Department of Health (South Africa)
PIDM	WHO Programme for International Drug Monitoring (PIDM)
PIL	Patient Information Leaflet
PMS	Post-Marketing Surveillance
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analysis
PV	Pharmacovigilance
RCT	Randomized Controlled Trials
SAHPRA	South African Health Products Regulatory Authority
SAMJ	South African Medical Journal
SSRI	Selective-Serotonin Reuptake Inhibitor
UKZN	University of KwaZulu-Natal
U.S.	United States
WHO	World Health Organisation

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ABSTRACT

Background and Aim

Vilazodone was approved in 2011 as an antidepressant to treat major depressive disorder. Like other antidepressants, vilazodone has adverse effects associated with the use of the drug. Being a relatively new drug, it is not clear if all adverse effects have been identified yet. The aim of this study was therefore to review the adverse effects reported to the WHO Programme for International Drug Monitoring (PIDM). This study then went on to explore the psychiatric adverse effects associated with the use of vilazodone and the factors that have been hypothesized as being responsible for these effects. This study aims to provide a critical summation of present findings to add to the knowledge about the safety profile and adverse effects caused by vilazodone.

Method

Data on adverse effects reported for vilazodone was obtained from the database VigiAccess managed by PIDM. Data was extracted from VigiAccess using Excel® and analysed using descriptive statistics. The data collected was compared to the patient information leaflet (PIL) of Viibryd® and the FDA documents to determine adverse drug reactions reported post marketing. In order to further explore the psychiatric adverse effects associated with vilazodone, a systematic review was conducted. Databases and reference lists for studies published between January 2000 to January 2020 were searched and a systematic review was conducted using the Cochrane Framework. Primary studies were screened for inclusion and a critical appraisal performed. Data was analysed and frequency tables were used to summarise the data followed by a narrative synthesis.

Results

A total of 9708 adverse events had been recorded on VigiAccess of which 6054 were not recorded on the PIL and the FDA approval document. Most of the reports were received from the Americas and were for adult women aged 45-64 years (24%, n=1059). The highest number of adverse events reported were for psychiatric events (19%; n=1889), followed by gastro-intestinal effects (18%; n=1839). Specific psychiatric disorders recorded included anxiety (316), depression (208), hallucination (168) and agitation (142). The systematic review confirmed several psychiatric adverse effects associated with the use of vilazodone. The findings of this study suggested that these common psychiatric adverse effects associated with

the use of vilazodone were not known during the time of FDA approval of the drug and is not currently recorded in the patient information leaflet (PIL).

Conclusions

In summary, this study found several adverse drug reactions not recorded in documents emanating from clinical trials pre-marketing. This highlights the importance of continued post-marketing surveillance of a drug, as well as the need for further studies on the psychiatric adverse events associated with vilazodone in order to improve the safety profile.

Keywords: Vilazodone, antidepressant, SSRI, major depressive disorder, pharmacovigilance, adverse drug reactions, post-marketing surveillance

CHAPTER 1

INTRODUCTION

This chapter provides the background of the study, problem statement and rationale of the study. It includes the research questions, aim and objectives and significance of the study. A general overview of the methodology has been included.

Background

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (World Health Organisation, 2004). It involves monitoring the effects of medicines after they have been approved for use to identify any previously unknown or unreported adverse drug reactions (ADRs). Before new medicines are registered, clinical trials are conducted to verify their efficacy and safety. Since the sample sizes used in clinical trials are much smaller than the populations that use the medicines, certain ADRs are only identified after the medicine has already been licensed for use (Selker et al., 2018) The purpose of pharmacovigilance is to detect, characterise, and mitigate these ADRs.

Post-marketing surveillance (PMS) is the process of identification, collection of information and practice of monitoring the safety of a pharmaceutical drug after it has been approved and released on to the market (Raj et al., 2019). This is an important part of pharmacovigilance. PMS evaluates pharmaceutical drugs taken by individuals under a wide range of circumstances and over an extended period (Raj et al., 2019).

Post-marketing pharmacovigilance is essential as adverse reactions to a drug often only becomes apparent after a drug enters clinical practice (Jeetu et al., 2010). Once marketed, the medicines are used by different patients' populations who have various diseases and who use several other drugs which may affect how they will react to the drug (Jeetu et al., 2010) Therefore, the adverse drug reactions need to be monitored amongst different populations. PMS studies can also provide valuable information on the use of drugs in special patient populations such as pregnant women, paediatrics and geriatrics, which is not obtained from pre-marketing studies due to ethical reasons. PMS further allows for the monitoring of populations not studied in clinical trials, such as patients with multiple comorbidities that may react differently to a drug (Suvarna, 2010).

The process of PMS can, therefore, refine, confirm or deny the safety of a drug (Raj et al., 2019). This process uses a number of approaches to monitor drug safety, including spontaneous reporting databases, prescription event monitoring, electronic health records and patient registries (Raj et al., 2019). The Food and Drug Administration (FDA) ensures the safety and efficacy of drugs available in the US (US Food and Drug Administration. 2011). In South Africa, the South African Health Products Regulatory Authority (SAHPRA), formerly known as the Medicines Control Council (MCC) are committed to improving drug safety through adverse drug reaction monitoring and reporting of adverse drug reactions.

Adverse drug reactions are presented on Patient Information Leaflets (PIL), specifically for patients and prescribers. A patient information leaflet is a document included in every medicine package to offer written information about the medication (Herber et al., 2014). The manufacturer provides PIL to inform patients about their medicines regarding its administration, precautions, and potential side effects.

Vilazodone is a drug used in the treatment of major depressive disorder (Hellerstein et al., 2015). It is relatively new drug that was released on to the market in 2011 and there is currently no therapeutically equivalent version of Viibryd® available. The aim of this study was to review current knowledge on the safety profile of vilazodone, the psychiatric adverse effects associated with the use of vilazodone and the need for continuous post-marketing surveillance.

1.1 Rationale for this study

Major depressive disorder (MDD) is a severe chronic and recurrent psychiatric illness and accounts for 10%–14% of all patients seen by primary care physicians (Yu et al., 2015). MDD is one of the major causes of disability globally (Gohil et al., 2015). The burden of the disease worldwide includes symptoms of decreased pleasure or interest in daily activities, changes in appetite or weight, sleep disorders, difficulty concentrating, fatigue, psychomotor agitation, sad mood, feelings of worthlessness, and even suicidal thoughts (Gohil et al., 2015).

Despite the availability of different types of antidepressants, many patients with depression do not achieve adequate results (Al-Harbi, 2012). Selective serotonin (5-HT)-reuptake inhibitors (SSRIs) are prescribed as first-line treatment options, but many patients do not adequately respond to an SSRI (Al-Harbi, 2012). Although all SSRIs modulate serotonin reuptake, they differ in their pharmacological properties and thus efficacy and safety in individual patients.

Despite numerous antidepressants being available, more than 30% of patients do not achieve adequate relief (Penn et al., 2012).

Vilazodone, sold under the brand name Viibryd®, is a medication used to treat MDD (Cruz, 2012). There are currently numerous effective antidepressants on the market that have been available for much longer than vilazodone. However, vilazodone has an advantage because it offers a dissimilar mechanism that produces remission of depressive symptoms (Singh et al., 2012). Thus, vilazodone provides a new alternative in the treatment of depressions. The unique mechanism of action of vilazodone lies in the fact that it simultaneously acts as an SSRI as well as a 5-HT_{1A}-receptor partial agonist and thus is speculated to be effective and well-tolerated for patients with MDD symptoms (Zhang et al., 2015). Vilazodone binds with high affinity to the serotonin reuptake site but not to the norepinephrine or dopamine reuptake site (Cruz, 2012).

In previous studies and reports, it is reported that vilazodone is effective and safe, with a low occurrence of side effects. It offers promise as an effective oral drug with a balance of efficacy and tolerability (Zhang et al., 2015). Over the years, several other adverse effects including diarrhoea, headache, nausea, vomiting and insomnia have been identified (Wang et al., 2016). However, being a new drug, it is not clear if all adverse effects have been identified. The purpose of the present study was to therefore review the adverse effects associated with vilazodone.

1.2 **Aims and objectives for this study**

The aim of this study was to explore the adverse effects associated with the use of vilazodone. To achieve this, the following specific objectives were outlined:

1.2.1 To quantify the adverse effects associated with vilazodone reported in VigiAccess, according to organ systems.

1.2.2 To compare the adverse effects reported in VigiAccess to the adverse effects indicated during the FDA approval process.

1.2.3 To compare the adverse effects reported in VigiAccess to adverse effects indicated on the PIL for Viibryd®.

1.2.4 To further explore associated psychiatric adverse effects.

1.3 **Significance of the study**

The study of the safety profile of any drug is a significant and relevant part of pharmacovigilance. Monitoring of the drug post-marketing is necessary as drugs are used amongst varied populations with several comorbidities and concomitant medication use. PMS provides valuable information on the use of medications in these special patient populations as well as allowing for the long-term monitoring of the effects of drugs.

As a relatively new drug, it is important to monitor vilazodone's adverse effects to improve and ensure the safety of the drug's use by patients. Studying the safety profile of vilazodone will give a greater insight into the safe use of this medicine.

1.4 **Research methodology**

1.4.1 ***Study design***

In order to determine the occurrence of ADRs not recorded at the time of FDA registration, data was obtained from VigiAccess (World Health Organisation, 2015) and subsequently compared to ADRs in the FDA approval document (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf) and PIL (https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/2018-05-8-Viibryd(vilazodone)-USPI-Clean.pdf). Further investigation on the psychiatric ADRs were done via a systematic review (to be discussed in chapter 4).

1.4.2 ***Data source***

VigiAccess allows access to information on side effects reported to the World Health Organization (WHO) Program for International Drug Monitoring (PIDM). VigiAccess was launched on 17 April 2015. It is the WHO international database of adverse drug reactions and has over 10 million reports dating back to 1968. It holds information from more than 120 countries participating in WHO PIDM.

This database presents ADRs in terms of body system, and provides demographics including, age, gender, and location (per continent). Specific patient information is not provided in the database, thus underlying medical conditions, mediation, and specific patient demographics are not available. Using the data available on this database, it was possible to quantify the adverse effects per body system, associated with the use of vilazodone.

For the systematic review conducted, a literature search using multiple databases, including Pubmed (Medline), Proquest Psychology Journals, Web of Science, Taylor & Francis Online Journals, PsychInfo, and Wiley Online Library. Additional searches were performed in Google Scholar. Studies were limited to publication date from January 2000 to April 2020 as the patent of vilazodone for registration was only received in 2011.

1.4.3 Data extraction

Data was extracted from VigiAccess using Excel® . Numeric data was extracted according to body system in the form of a table stating the number of previously unrecorded adverse drug incidents. Find below sample of data extraction sheet for blood and lymphatic system.:

Table 1: Data extraction tool for blood and lymphatic system from VigiAccess.

Blood and Lymphatic System	
Subgroup of Medical Conditions	**Number of Incidences Reported**
Anaemia	
Lymphadenopathy	
Blood Disorder	
Increased Tendency to bruise	
Splenic Vein Thrombosis	
Splenomegaly	

For the systematic review study, a predesigned data extraction form was employed and prepared in a Microsoft Excel® sheet. The following data were extracted: bibliographic information, study characteristics, participants' characteristics, treatment information, description of psychiatric adverse effects and outcome of interest.

1.4.4 Data analysis

Once the data was extracted from the database VigiAccess, the data was analysed using Excel®. Descriptive statistics was done, and data presented in the form of graphs and tables. The data collected was compared to adverse drug reactions of vilazodone listed on the PIL and FDA.

For the systematic review study, data was imported into SPSS Software for analysis. Frequency tables summarized categorical data, including sample characteristics, patient characteristics and psychiatric adverse effect outcomes. Psychiatric adverse effects found from selected articles were listed according to preferred terms based on the most commonly used coding

system, the Medical Dictionary for Regulatory Activities (MedDRA). A narrative synthesis was then done to describe and discuss the outcomes.

1.4.5 Data Management

The data extraction sheet was stored on a password protected computer and backed up on Google Drive®. Data will be removed upon completed dissemination of results. The bibliographic software (Endnote), 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.

1.5.**Ethical approval**

The data accessed in this study is in the public domain readily accessible on the internet and does not contain any personal information that can be linked to real people. A waiver of ethical approval was obtained from the School of Health Sciences, University of Kwa-Zulu-Natal (Annexure 1).

1.6 Chapter summary

This chapter provided background and rationale to the study, explaining pharmacovigilance, its importance, post-marketing surveillance, FDA approval, and the reasons why reporting of ADRs is important. The chapter gives a short overview of vilazodone. It also defines the aims, objectives, and a brief overview of the methodology.

REFERENCES

Al-Harbi K.S. (2012). Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Preference and Adherence*, *6*, 369–388.

Cruz M.P. (2012). Vilazodone HCl (Viibryd): A serotonin partial agonist and reuptake inhibitor for the treatment of major depressive disorder. *Pharmacy and Therapeutics*, 37(1): 28–31.

Gohil, K., & Shah, P. (2015). Major depressive disorder: new products are facing a saturated market. *Pharmacy and Therapeutics*, *40*(3), 215–217.

Hellerstein, D. J., & Flaxer, J. (2015). Vilazodone for the treatment of major depressive disorder: an evidence-based review of its place in therapy. *Core Evidence*, *10*, 49–62.

Herber O., Gies V., Schwappach D., Thürmann, P. & Wilm, S. (2014). Patient information leaflets: informing or frightening? A focus group study exploring patients' emotional reactions and subsequent behaviour towards package leaflets of commonly prescribed medications in family practices. *BMC Family Practice*, 15(1), 163.

Jeetu G. & Anusha, G. (2010). Pharmacovigilance: a worldwide master key for drug safety monitoring. *Journal of Young Pharmacists*, *2*(3), 315–320.

Penn, E. & Tracy, D.K. (2012). The drugs don't work.? Antidepressants and the current and future pharmacological management of depression. *Therapeutic Advances in Psychopharmacology*, *2*(5), 179–188.

Raj N., Fernandes S., Charyulu N.R., Dubey A. and Hebbar S. (2019). Post-market surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. *Therapeutic Advances in Drug Safety*, 10:1-13.

Selker H.P., Gorman S. & Kaitin, K.I. (2018). Efficacy-to-effectiveness clinical trials. *Transactions of the American Clinical and Climatological Association*, *129*, 279–300.

Singh M. & Schwartz, T.L. (2012). Clinical utility of vilazodone for the treatment of adults with major depressive disorder and theoretical implications for future clinical use. *Neuropsychiatric Disease & Treatment*. 8:123–30.

Suvarna, V. (2010). Phase IV of drug development. *Perspectives in Clinical Research*, *1*(2): 57–60

U.S. Food and Drug Administration. (2011). Highlights of prescribing information. Available at (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf) . Accessed on 26 August 2019.

Wang, S.M., Han C., Lee, S.J., Patkar, A.A., Masand, P.S., & Pae, C.U. (2016). Vilazodone for the treatment of depression: an update. *Chonnam Medical journal*, *52*(2):91–100.

World Health Organization (2004). Pharmacovigilance: ensuring the safe use of medicines – WHO Policy Perspectives on Medicines. http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf. Accessed on 26 August 2019.

Zhang, X. F., Wu, L., Wan, D. J., Liu, R. Z., Dong, Z., Chen, M., & Yu, S. Y. (2015). Evaluation of the efficacy and safety of vilazodone for treating major depressive disorder. *Neuropsychiatric disease and treatment*, *11*:1957–1965.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter provides a literature background to the study. The context of this literature review is set by first providing an overview of adverse drug reactions, pharmacovigilance, adverse drug reaction monitoring, pre-marketing clinical trials and post marketing ADR surveillance, approaches to improving pharmacovigilance, the safety profile of vilazodone and concludes with studies conducted to evaluate the safety and efficacy of vilazodone for the management of depression and anxiety disorders.

2.2 Adverse drug reactions (ADRs)

Over the years, drugs have changed how diseases are treated. However, the use of medicine has the possibility of unintended consequences. When harmful, these effects are referred to as adverse drug reactions (ADRs) (Vural et al., 2015). An ADR is defined as "any response to a drug which is noxious and unintended that occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease, or for the modification of physiologic function" (World Health Organization, 2004).

Adverse drug reactions (ADRs) can affect patients irrespective of age, gender, location or occupation, ultimately impacting on morbidity and mortality (Bogolubova et al., 2018). ADRs have become a major global health problem that needs to be addressed (Coleman et al, 2016). According to a study ADRs can be the 4th – 6th prime cause of death in the United States with the contribution of more than 100 000 deaths annually (Pirmohamed et al., 2004). In South Africa, it was estimated that 6.3% of hospitalised patients were admitted due to an ADR (Mehta et al., 2017).

Adverse drug reactions are categorised into events that occur seldomly and occur at an increased rate in the general population (Inácio et al., 2017). ADRs are further subdivided into categories according to the drugs' use: ADRs that occur with short-term use, ADRs that occur with long-term use, and those that occur after discontinuation of the drug (Coleman et al., 2016). Knowledge of the most common ADRs and population groups that are prone to experiencing ADRs will allow the National Department of Health (NDoH) to strengthen strategies to maximize patient safety and ensure the rational use of medicines (Jimmy et al., 2011).

2.3 Pharmacovigilance

Pharmacovigilance (PV) is defined as the "science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" (World Health Organization, 2004). Pharmacovigilance describes the processes for monitoring, evaluating and detecting ADRs that were previously unknown and is the main component for ensuring effective drug regulation systems (Jeetu et al., 2010).

In order to improve public health, pharmacovigilance mechanisms to evaluate and monitor the safety of medicines are necessary. Pharmacovigilance plays a vital role in ensuring that doctors and patients have enough information to decide on a drug of choice for treatment as well as the dangers and benefits involved with a drug (Jeetu et al., 2010).

When a new drug is released into the market, there is still some unknown information about its' safety (Berlin et al., 2008). Unexpected adverse events could arise at any time in the life cycle of a drug and could put the user at risk. During the pre-marketing phase, information regarding possible ADRs are incomplete as special groups such as children, pregnant women and the elderly are excluded from clinical trials (World Health Organization, 2012). Patients that are studied in the pre-marketing clinical trials of new medicines are usually limited to a small number and are studied for a short period (Duijnhoven et al., 2013). Therefore, pharmacovigilance initiatives after pre-marketing trials are required through post marketing surveillance to ensure the safety and efficacy of medicines throughout its' use.

Pharmacovigilance initiatives in South Africa are determined by three groups, the pharmaceutical industry, health care professionals, and public health programmes (Mehta et al., 2017). Adverse drug reaction reporting through these three initiatives aims at using ADR reports as a tool in clinical practice to increase the generation of ADR signals (Mehta et al., 2017). The WHO defines a signal as "Reported information on a possible causal relationship between an adverse event and a drug, of which the relationship is unknown or incompletely documented previously" (World Health Organisation, 2012). The process of detecting and assessing signals forms the most important aspect of pharmacovigilance. These signals can be generated by using sources such as spontaneous reporting, case control studies, cohort studies, pre-clinical and clinical trials (Talbot et al., 1998).

After a signal has been detected, reporting and analysis are carried out by a medical practitioner and sent to regional pharmacovigilance centres to be monitored (Inácio et al., 2017). After monitoring, laboratory tests and adherence counselling, the ADR report form is filled and

submitted to the National Department of Health to be filed in database records. This form indicates the patients' data, the ADR, current treatment and concomitant diseases (Mehta et al., 2017).

Spontaneous reporting is the most common method for ADR reporting used in pharmacovigilance practiced worldwide as part of the WHO Programme for International Drug Monitoring system (Nadew et al., 2020). The purpose of spontaneous reporting is the early detection of new and harmful ADRs signals during the process of diagnosis and treatment. Detecting unknown safety signals quickly from post-marketing data through spontaneous reporting is one of the main challenges of pharmacovigilance (Kumar et al., 2015). According to a study, it was observed that over 94% of all ADRs through spontaneous reporting are unreported (Kumar et al., 2015).

Health care professionals play a significant part in pharmacovigilance systems and are encouraged and obligated to report ADRs. The quantity of data collated and reported, is dependent on the level of awareness and determination of the health care professional (Bogolubova et al., 2018). Therefore, pharmacovigilance is required throughout the patient-practitioner relationship, when patients are being asked about their drug use and history and when diagnosing, prescribing, monitoring, and reassessing management of a condition (Mehta et al., 2017). In order to ensure safe medicine use, follow-ups are essential to the discovery of ADRs and are vital for as long as a medicine remains on the market. Failing to maintain consistent pharmacovigilance when using drugs in patients can have fatal consequences (Mehta et al., 2017).

2.4 ADR Monitoring

The early identification of patients at risk for ADRs can help health care professionals make better decisions regarding drug monitoring and management. Early detection or prevention of ADRs can help decrease the unnecessary cost burden associated with these effects (Sahu et al., 2014).

Underreporting of ADRs by medical professionals remains a global issue (Güner et al., 2019). When a patient experiences an ADR, the health care professional prescribing the drug is usually involved in treating the ADR and has the clinical expertise to estimate the probability that a drug has caused an ADR in the patient (Coleman et al., 2016). Unfortunately, health care professionals infrequently report suspected ADRs and it is commonly estimated that that only 1% to 10% of significant ADRs are reported (Klein et al., 2013).

The continued surveillance by health care professionals will enable the quick detection of any emerging signals, increase the reporting and awareness of ADRs and, reduce the ADR incidence rate (Shamim et al., 2016). Therefore, proper implementation of continued ADR monitoring will reduce detrimental effects and improve the rational use and selection of drugs (Coleman et al., 2016)

Pre-clinical or pre-marketing trials refer to the first step conducted in safety studies to determine a drugs' safety. This process involves in-vitro and in-vivo testing to determine the efficacy, toxicity and pharmacokinetic profiles of a drug (Andrade et al., 2016). Clinical trials involve multiple steps including laboratory investigations, clinical examination of patients and ADR monitoring.

Phase 0, also known as the first step of human trials is aimed at early decision making and includes giving subtherapeutic doses of a drug to a few volunteers (Karakunnel et al., 2018). Phase I is conducted to access and approve the tolerability and safety of a drug to be used in humans. This process usually takes 6-9 months and involves approximately 20 to 100 healthy volunteers who are given single doses of the drug (Karakunnel et al., 2018).

Phase II is used to assess the therapeutic activity and tolerance of a drug for long-term use to determine the most suitable dose to be used in humans. This process takes approximately six months to three years and can be conducted either as case series or randomized controlled trials involving a drug compared to a placebo. The drug is tested using 100- 500 patients to determine its' safety and effectiveness (Karakunnel et al., 2018).

Phase III involves determining the efficacy of a drug and includes larger groups of volunteer patients (1,000-5,000). Double blind randomized controlled trials are conducted to create substantial safety and efficacy data of a drug based on its risk and benefit relationship (Karakunnel et al., 2018). This phase determines the actual response of a drug and hence is a costly and time-consuming process that usually lasts approximately 1-4 years. As soon as the drug is deemed effective and safe for human use, data is compiled and sent for marketing approval to regulatory authorities (Karakunnel et al., 2018).

Post-marketing surveillance (PMS), also known as Phase IV of clinical trials, refers to the process of monitoring the safety of drugs after completion of clinical trials (Raj et al., 2019). The aim of ADR monitoring through post-marketing surveillance is to prevent untoward effects that could diminish a patient's quality of life, lead to death and have a negative impact on patient adherence (Raj et al., 2019). The prompt reporting of any adverse reaction to a drug can

lead to the early detection of unknown side effects and reactions (Klein et al., 2013). Post-marketing surveillance is important as it is the only means of obtaining information on the mutagenic and teratogenic effects of drugs in humans and allows for the long-term monitoring of the effects of drugs (Raj et al., 2019). The post-market surveillance for adverse events begins once the drug becomes available to the public and continues for as long as it is available on the market (Suvarna, 2010).

2.5 Vilazodone

In this study, vilazodone was used as a study example, as it is a relatively new drug used in the management of MDD. MDD is a severe, chronic and recurring mental disability, and the third leading cause of severe burden of disease in the world (World Health Organisation, 2012). The symptoms of MDD include changes in appetite and weight, sleeping difficulties, difficulties in concentration, fatigue, and suicidal thoughts (Kennedy, 2008). Despite the availability of several antidepressants, there are still over 30% of patients with MDD who do not achieve a satisfactory response (Al-Harbi, 2012). Some of the most significant issues affecting treatment discontinuation and non-adherence to antidepressants are limited efficacy, delayed onset of the drug, and the incidences of intolerable ADRs (Srimongkon et al., 2018).

In 2011, the US Food and Drug Administration (FDA) approved the use of vilazodone for the treatment of MDD in adults (Zhang et al., 2015). FDA approval of a drug means that data collected from clinical trials and testing on the drugs' effects have been reviewed with benefits that outweigh the potential risks of the drug (US Food and Drug Administration, 2019).

Vilazodone is a novel antidepressant with a unique mechanism of action by simultaneously acting as a selective serotonin reuptake inhibitor (SSRI) and a 5-HT_{1A}-receptor partial agonist (Zhang et al, 2015). Wang et al. speculated that vilazodone has three benefits compared to other antidepressants, owing to its combined serotonin reuptake inhibition and anxiolytic mechanism (Wang et al., 2016). These benefits of vilazodone include a faster onset of action, better efficacy, and improved tolerability (Wang et al., 2016). Vilazodone acts as a partial agonist at serotonin receptors, which results in faster desensitization of 5-HT_{1A} auto receptors without an excess activation of serotonin inhibition. Vilazodone binds to the serotonin reuptake site with a higher affinity for an extended period, which contributes to greater desensitization leading to a faster onset of action than conventional selective serotonin reuptake inhibitors (SSRIs) (Wang et al., 2016).

Vilazodone presents with various adverse effects significantly; diarrhoea, headache, nausea, vomiting, dizziness, and insomnia, which have been identified during the pre-marketing phase of the drug (Wang et al., 2016). As with long term exposure to other antidepressants, vilazodone is also associated with increased obesity (Carvalho et al., 2016). Vilazodone acts on the CNS and increases the risk of suicidal thoughts and behaviour in children and adults (Hellerstein et al., 2015), as is common is some other antidepressant drugs. Also, of note is the lower risk of sexual adverse effects possibly caused by the 5-HT_{1A} post-synaptic receptor actions (Wang et al., 2016).

2.5.1 *Safety and efficacy studies of vilazodone*

Several post-marketing studies have been conducted to elaborate on the safety and efficacy of vilazodone. A large, double-blind, randomised, placebo-controlled trial to test the effectiveness of the drug for the management of MDD in comparison to a placebo used found a significant improvement in depression scores associated with the use of vilazodone (Rickels et al., 2009) Patients in the age category of between 18-70 years old diagnosed with MDD were given 40mg/day of vilazodone or placebo once daily with food over two weeks. Four hundred thirty-six patients were given vilazodone, and 433 patients received the placebo drug for which the results received were compared after eight weeks (Rickels et al., 2009). In this study, vilazodone showed a significant advancement in the transformation from baseline to week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) and on the 17-item Hamilton Depression Rating Scale (HDRS-17) total scores in comparison to the placebo drug used. Differences between the use of vilazodone and the placebo on the MADRS and HAM-D-17 scales were seen after only one week of treatment (Rickels et al., 2009).

The adverse effects recorded in this study had an incident rate of more than 5% in patients who were treated with vilazodone (Rickels et al., 2009). 28% of patients experienced diarrhoea, dizziness occurred in 8.5% of patients, insomnia occurred in 6% of patients and 4.6% of patients experienced vomiting (Rickels et al., 2009). Further adverse effects included decreased libido, dry mouth, arthralgia, fatigue palpitations and abnormal dreams.

According to an open-label, multicentre study, it was shown that vilazodone given at 40 mg/day was well tolerated for the short- and long-term management of MDD (Wang et al., 2016).In a phase 3 randomised controlled trial by Khan et al. vilazodone at 40mg/day showed improvements in symptoms of depression on multiple measures of depression scales during

eight weeks of treatment. The use of vilazodone was also seen to show improvements in illness severity (Khan et al., 2011).

In a phase 4 randomised controlled trial over ten weeks, a 20 mg/day dose of vilazodone, a 40 mg/day dose vilazodone, a 40 mg/day dose of citalopram, and a placebo were compared (Mathews et al., 2015). The depression scale MADRS and symptom severity improvement scores were greater for vilazodone 20 mg/day compared to the other drugs used. The adverse drug reactions caused included diarrhoea, nausea, vomiting, and insomnia and occurred in more than 5% of the vilazodone group and 0.7% in the placebo group (Mathews et al., 2015). The majority of ADRs that occurred were mild or moderate in severity. Serious ADRs were reported in four patients treated with vilazodone and six patients treated with citalopram.

A phase 4 double-blind randomised placebo-controlled study was undertaken over eight weeks in which 253 patients were given vilazodone at 40mg/day, and 252 patients were given a placebo (Croft et al., 2013). The MADRS depression improvement score was much higher for vilazodone than the placebo. ADRs reported were diarrhoea, nausea, dizziness, and insomnia. Gastrointestinal effects such as nausea and diarrhoea occurred during the first week of treatment with vilazodone. The ADRs were recorded as diarrhoea (32.5%) and nausea (24.7%) in vilazodone-treated patients, compared to diarrhoea (10.3%) and nausea (8.3%) in placebo-treated patients (Croft et al., 2013).

From the above studies and literature, it can be concluded that vilazodone is a safe and effective drug for patients with MDD and GAD. It offers promise as a novel antidepressant due to its' tolerability in comparison to respective placebos and other antidepressants used in previous studies. Despite this, the long-term efficacy of vilazodone and a wider range of adverse effects should be established. Consistent pharmacovigilance and post-market surveillance are required for as long as vilazodone remains on the market.

Chapter summary

This chapter comprised of a literature review, highlighting the importance of pharmacovigilance for continued monitoring of drug safety. This chapter also focused on ADR monitoring through pre-marketing clinical trials and post-marketing surveillance.

REFERENCES

Al-Harbi K.S. (2012). Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Preference and Adherence, 6*:369–388.

Andrade E.L., Bento A.F., Cavalli J., Oliveira S.K., Schwanke R.C., Siqueira J.M., Freitas C.S., Marcon R. and Calixto J.B. (2016). Non-clinical studies in the process of new drug development - Part II: Good laboratory practice, metabolism, pharmacokinetics, safety and dose translation to clinical studies. *Brazilian Journal of Medical and Biological Research, 49*(12): e5646.

Berlin J.A., Glasser S.C. and Ellenberg S.S. (2008). Adverse event detection in drug development: recommendations and obligations beyond phase 3. *American Journal of Public Health, 98*(8):1366–1371.

Bogolubova S., Padayachee, N. and Schellack N. (2018). Knowledge, attitudes and practices of nurses and pharmacists towards adverse drug reaction reporting in the South African private hospital sector. *Health SA, 23*:1064.

Carvalho A.F., Sharma M.S., Brunoni A.R., Vieta E. and Fava G.A. (2016). The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychotherapy and Psychosomatics* 85 (5):270–288.

Coleman J.J. and Pontefract S.K. (2016). Adverse drug reactions. *Clinical Medicine 16*(5): 481–485.

Croft H.A., Pomara N., Gommoll C., Chen D., Nunez R. and Mathews M. (2014). Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*. 75(11): e1291–e1298.

Duijnhoven R.G., Straus S.M., Raine J.M., de Boer A., Hoes A.W. and De Bruin M.L. (2013). Number of patients studied prior to approval of new medicines: a database analysis. *PLoS Medicine, 10*(3): e1001407.

Güner M.D. and Ekmekci P.E. (2019). Healthcare professionals' pharmacovigilance knowledge and adverse drug reaction reporting behaviour and factors determining the reporting rates. *Journal of Drug Assessment, 8*(1):13–20.

Hellerstein D.J. and Flaxer J. (2015). Vilazodone for the treatment of major depressive disorder: an evidence-based review of its place in therapy. *Core Evidence*, *10*:49–62.

Inácio P., Cavaco A. and Airaksinen M. (2017). The value of patient reporting to the pharmacovigilance system: a systematic review. *British Journal of Clinical Pharmacology*, *83*(2):227–246.

Jeetu G. and Anusha G. (2010). Pharmacovigilance: a worldwide master key for drug safety monitoring. *Journal of Young Pharmacist*s, *2*(3): 315–320.

Jimmy B. and Jose J. (2011). Patient medication adherence: measures in daily practice. *Oman Medical Journal*, *26*(3):155–159.

Karakunnel J.J., Bui N., Palaniappan L., Schmidt K.T., Mahaffey K.W., Morrison B., Figg W.D. and Kummar S. (2018). Reviewing the role of healthy volunteer studies in drug development. *Journal of Translational Medicine*, *16*(1):336.

Kennedy S.H. (2008). Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues in Clinical Neuroscience*, *10*(3):271–277.

Khan A., Cutler A.J. and Kajdasz D.K. (2011) A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *Journal of Clinical Psychiatry*, 72(4):441–447.

Klein E. and Bourdette D. (2013). Post-marketing adverse drug reactions: A duty to report. *Neurology Clinical practice*, *3*(4):288–294.

Kumar A. and Khan H. (2015). Signal detection and their assessment in pharmacovigilance. *Open Pharmaceutical Sciences Journal*, 2. 66-73.

Mathews M., Gommoll C., Chen D., Nunez R. and Khan A. (2015) Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International Clinical Psychopharmacology*, 30:67–74.

Mehta U., Kalk E., Boulle A., Nkambule P., Gouws J., Rees H. and Cohen K. (2017). Pharmacovigilance: A public health priority for South Africa. *South African Health Review*, 2017, 125–133.

Nadew S.S., Beyene K.G. and Beza S.W. (2020). Adverse drug reaction reporting practice and associated factors among medical doctors in government hospitals in Addis Ababa, Ethiopia. *PloS One*, *15*(1): e0227712.

Pirmohamed M., James S., Meakin S., Green C., Scott A., Walley T. and Breckenridge A. (2004). Adverse Drug Reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *British Medical Journal, 329*(7456):15-19.

Raj N., Fernandes S., Charyulu N.R., Dubey A. and Hebbar S. (2019). Post-market surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. *Therapeutic Advances in Drug Safety*, 10:1-13.

Rickels K., Athanasiou M., Robinson D.S., Gibertini M., Whalen H. and Reed C.R. (2009) Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, 70:326-333.

Sahu R.K., Yadav R., Prasad P., Roy A. and Chandrakar S. (2014). Adverse drug reactions monitoring: prospects and impending challenges for pharmacovigilance. *SpringerPlus*, 2014;3:695.

Shamim S., Sharib S.M., Malhi S.M., Muntaha S.U., Raza H., Ata S., Farooq A.S. and Hussain M. (2016). Adverse drug reactions (ADRS) reporting: awareness and reasons of under-reporting among health care professionals, a challenge for pharmacists. *SpringerPlus*, *5*(1):1778.

Srimongkon P., Aslani P. and Chen T.F. (2018). Consumer-related factors influencing antidepressant adherence in unipolar depression: a qualitative study. *Patient Preference and Adherence, 12*, 1863–1873.

Suvarna V. (2010). Phase IV of drug development. *Perspectives in Clinical Research*, *1*(2), 57–60.

Talbot J.C. and Nilsson B.S. (1998). Pharmacovigilance in the pharmaceutical industry. *British journal of Clinical Pharmacology*, *45*(5), 427–431.

U.S. Food and Drug Administration. (2011). Highlights of prescribing information. Available at (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf). Accessed on 26 August 2019.

Vural F., Ciftci S. and Vural B. (2015). The knowledge, attitude and behaviours of nurses about pharmacovigilance, adverse drug reaction and adverse event reporting in a state hospital. *Northern Clinics of Istanbul*, *1*(3), 147–152.

Wang S.M., Han C., Lee S.J., Patkar A.A., Masand P.S. and Pae C.U. (2016). Vilazodone for the treatment of depression: an update. *Chonnam medical journal*, *52*(2), 91–100.

World Health Organization (2012). Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. Available from: http://www.ghwatch.org/who-watch/wha65/mental. Accessed on 19 December 2019.

World Health Organization (2004). Pharmacovigilance: ensuring the safe use of medicines – WHO Policy Perspectives on Medicines. http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf. Accessed on 19 December 2019.

Zhang, X.F., Wu L., Wan D.J., Liu R.Z., Dong Z., Chen M., and Yu S.Y. (2015). Evaluation of the efficacy and safety of vilazodone for treating major depressive disorder. *Neuropsychiatric Disease and Treatment*, *11*, 1957–1965.

CHAPTER 3

MANUSCRIPT 1

Introduction

This chapter describes the background, general findings and discussion of the results of the following objectives:

- To quantify the adverse effects associated with vilazodone reported in VigiAccess, according to organ systems.
- To compare the adverse effects reported in VigiAccess to the adverse effects indicated during the FDA approval process.
- To compare the adverse effects reported in VigiAccess to adverse effects indicated on the PIL for Viibryd®.

The chapter is in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submissions at the University of KwaZulu-Natal (UKZN). The chapter has been written according to the author guidelines and has been submitted for publication to the Journal of Pharmacy Practice (see Annexure 2). The reference list is cited according to the instructions for authors as required by the Journal of Pharmacy Practice.

The journal instructions to the author can be viewed in Annexure 3 or with the following link: https://us.sagepub.com/en-us/nam/journal-of-pharmacy-practice/journal201507#submission-guidelines

MANUSCRIPT

The safety profile of vilazodone - a study on post-marketing surveillance.

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Short Title: The safety profile of vilazodone

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Keywords: Vilazodone, antidepressant, SSRI, pharmacovigilance, adverse drug reactions, post-marketing surveillance

ABSTRACT

Background and Aim

Vilazodone is a novel antidepressant having a selective serotonin (5-HT) reuptake inhibitor and 5-HT_{1A}-receptor partial agonist profile. It was approved in 2011 by the U.S. Food and Drug Administration (FDA) for treating major depressive disorder in adults. The study aimed to review the adverse effects of vilazodone reported in the PIDM database, VigiAccess.

Method

Data on adverse effects reported for vilazodone was obtained from the database VigiAccess. VigiAccess provides an overview of adverse drug reactions reported according to body systems. Data was extracted from VigiAccess using Excel® and analysed using descriptive statistics. The data collected was compared to the patient information leaflet (PIL) of Viibryd® and the FDA approval documents to determine adverse drug reactions reported post-marketing.

Results

A total of 9708 adverse events had been recorded on VigiAccess, which 6054 were not mentioned on the PIL and the FDA approval document. Most of the reports were received from the Americas and were for adult women aged 45-64 years (24%, n=1059). The highest total number of adverse events reported were for psychiatric events (19%; n=1889). This was followed by gastro-intestinal effects (18%; n=1839). The highest number of previously unrecorded adverse events was observed under psychiatric disorders (19%; n=1181) for anxiety (n=316), depression (n=208), hallucinations (n=168) and agitation (n=142).

Conclusion

The safety profile of a drug may evolve over time due to appearance of previously unrecorded adverse drug reactions during post-marketing surveillance. This study found several adverse drug reactions not recorded in documents emanating from clinical trials pre-marketing. Therefore, it is imperative that post-marketing surveillance continues for the duration of a drug's use to ensure safety.

BACKGROUND

Vilazodone is a novel antidepressant with a unique mechanism of action - it simultaneously acts as a selective serotonin reuptake inhibitor (SSRI) and a 5-HT_{1A}-receptor partial agonist.[1]

The mechanism of action of vilazodone is related to its enhancement of serotonergic activity in the central nervous system (CNS) through selective inhibition of serotonin reuptake.[2] Vilazodone binds with high affinity to the serotonin reuptake site but not to the norepinephrine or dopamine reuptake site.[2] The combined serotonin reuptake inhibition and buspirone-like anxiolytic mechanism of vilazodone contributes to this drug's improved efficacy and tolerability compared to other antidepressants.[2]

Vilazodone was approved in 2011 by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder in adults.[1] Approval of a drug by the FDA implies that the perceived benefits outweigh its potential risks.[3] Vilazodone presents with a spectrum of known adverse effects including diarrhoea, headache, nausea, vomiting and insomnia.[4] Since drugs are approved based on clinical trial data, which involve relatively small numbers of controlled patients, post-marketing surveillance can further refine, confirm or deny the safety of a drug after it is used in the general population by large numbers of people who have a wide variety of medical conditions.[5]

Post-marketing drug surveillance, also known as Phase IV of clinical trials, takes place after a drug has been approved by the medicine regulatory authority and is being marketed.[5] The major part of post-marketing drug surveillance is related to the evaluation and monitoring of adverse drug reactions. Post-marketing surveillance provides valuable information on the use of drugs in special patient populations, which is not easily obtainable from pre-marketing studies.[6] The post-market surveillance for adverse events begins immediately after the drug is available to the public and continues for as long as the drug is available on the market.[6]

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[7] Post-marketing surveillance forms an important part of PV activities and the prompt reporting of any adverse reaction to a drug can lead to the early detection of side effects and reactions. The spontaneous reporting system for suspected ADRs represents the cornerstone of pharmacovigilance, because it allows for the rapid detection of potential alarm signals related to a drug's use.[8] However, spontaneous reporting shows several limitations, which are mainly related to under-reporting by health care professionals due to

a lack of time, quality of the reported data and the lack of information on drug exposure.[8] Healthcare professionals sometimes do not report ADRs because it is challenging to establish with certainty the causal relationship between the drug and adverse reaction.[8] Highlighting the need for continued monitoring and reporting of adverse effects due to the emergence of previously unknown ADRs will hopefully overcome these barriers to ADR reporting to enhance the post-marketing surveillance and the safety profile of medicines.

This study reviewed the adverse effects of vilazodone post-marketing, via reports on the database VigiAccess, to highlight the contribution of and need for post-marketing surveillance of a drug.

METHODOLOGY

For this descriptive study, data on adverse effects reported for vilazodone was obtained from VigiAccess (http://www.vigiaccess.org/). VigiAccess is a free-access database on side effects reported to the World Health Organization (WHO) Program for International Drug Monitoring (PIDM). This database presents ADRs in terms of body system, and provides demographics including, age, gender, and location per continent. Specific patient information is not provided in the database, thus underlying medical conditions, medication, and specific patient demographics are not available.

Data was extracted from VigiAccess using Excel®. The data was extracted according to body systems in the form of a table stating the number of previously unrecorded adverse drug incidents. Data was analysed using descriptive statistics. The data collected was compared to adverse drug reactions of vilazodone listed on the PIL (https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/2018-05-8-Viibryd(vilazodone)-USPI-Clean.pdf) and FDA approval documents (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf) to determine post-marketing ADRs.

RESULTS

At the time of the data extraction (25/08/19), a total of 9708 adverse events had been recorded on VigiAccess of which 6054 of these adverse events were not listed on the patient information leaflet (PIL) of Viibryd® and FDA approval document. Most of the reports were received from the Americas for adult patients aged 45-64 years (24%, n=1059). A high number of reports were also received for adult patients aged 18-44 years (20%, n=864). Sixty-eight percent of adverse events reported were observed in women. The highest number of ADR reports was seen in the year 2014, followed by 2012.

Table 1- Demographic data of ADR reports for vilazodone on Vigiaccess

GEOGRAPHICAL DISTRIBUTION		
Continent	**Count**	**Percentage**
America	4358	99
Asia	34	1
Europe	3	0,068
AGE GROUP DISTRIBUTION		
Age Group	**Count**	**Percentage**
0 - 27 days	1	0,02275
28 days to 23 months	6	0,1365
2 - 11 years	13	0,2956
12 - 17 years	51	1
18 - 44 years	864	20
45 - 64 years	1059	24
65 - 74 years	309	7
≥ 75 years	152	3
Unknown	1940	44
PATIENT SEX DISTRIBUTION		
Patient Sex	**Count**	**Percentage**
Female	3005	68
Male	1224	28
Unknown	166	4
ADR REPORTS PER YEAR		
Year	**Count**	**Percentage**
2019	398	9
2018	240	5
2017	387	9
2016	287	7
2015	209	5
2014	1814	41
2013	134	3
2012	926	21

Adverse events in VigiAccess were categorised according to 26 body systems. The highest percentage of adverse events reported were for psychiatric disorders (19%; n=1889) and specifically for insomnia (24%; n=455) and suicidal ideation (11%; n=205). This was followed by gastro-intestinal disorders (18%; n=1839), with the highest being diarrhoea (31%; n=582) and nausea (26%; n=477).

Several adverse events that were not recorded in the PIL or FDA approval report was reported in VigiAccess (Table 2). The highest frequency was observed under psychiatric disorders (19%; n=1181) and included anxiety (26%; n=316), depression (17%; n=208), hallucinations (14%; n=168) and agitation (12%, n=142).

Table 2- Adverse events reported for vilazodone, not recorded on the FDA and PIL

BODY SYSTEM	NUMBER OF previously unrecorded types of ADRS	MOST SIGNIFICANT PREVIOUSLY UNRECORDED ADRS
Blood and lymphatic system	7	Anaemia (6 reports) Lymphadenopathy (6 reports)
Cardiac Disorders	24	Tachycardia (16)
Ear and Labyrinth Disorders	9	Tinnitus (48) Vertigo (25)
Endocrine Disorders	6	Hyperthyroidism (2) Inappropriate ADHD secretion (2)
Eye Disorders	47	Blurry Vision (69)
Gastro-intestinal Disorders	359	Flatulence (38) Dyspepsia (33) Constipation (26)
Hepatobiliary disorders	7	Hepatitis (3)
Immune system disorders	56	Drug hypersensitivity (28)
Infections and infestations	60	Sinusitis (8) Influenza (6)
Investigations	421	Blood pressure increased (66) Heart rate increased (40)
Metabolism and Nutrition disorders	65	Hyponatremia (14)
Musculoskeletal and connective tissue disorders	343	Muscle twitching (73) Muscle spasms (58)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13	Neoplasm Malignant (2)
Nervous System	232	Serotonin syndrome (82) Seizures (72)
Pregnancy, puerperium and perinatal conditions	5	Abortion Spontaneous (2)
Psychiatric disorders	1181	Anxiety (316) Depression (208) Hallucination (168) Agitation (142)
Renal and urinary disorders	70	Pollakiuria (14)
Reproductive system and breast disorders	73	Vaginal Haemorrhage (10)
Respiratory, thoracic and mediastinal disorders	151	Dyspnoea (63)
Skin and subcutaneous tissue disorders	679	Pruritus (84) Alopecia (68) Rash (68)
Vascular disorders	93	Hypertension (26)
NUMBER OF PREVIOUSLY UNRECORDED ADR's- 6054		

DISCUSSION

Over a period of 8 years (2012 – 2019) a total of 9708 ADRs were reported for vilazodone to the WHO PIDM. According to geographical data, most ADR reports emanated from the Americas, followed by Asia and Europe. This relates to the availability of the drug - vilazodone was released in the US (Americas) in 2011 prior to being marketed in Asia and Europe. No reports were submitted from Africa the drug is not currently available in any African country.

In terms of patient demographics, reports were mostly submitted for ADRs experienced by adult (18 – 64 years) female patients. Vilazodone is an antidepressant mostly used by adult patients and rarely used in children below the age of 12.[2] Due to the higher rate of use in adults, most adverse events would be observed in adults.

In 2010 the global annual prevalence of depression was 5.5% in women and 3.2% in men, representing a 1.7-fold greater incidence in women.[9] Women are more likely to experience specific forms of depression-related illnesses, including postpartum depression, postmenopausal depression and anxiety.[9] Female hormonal fluctuations may be a trigger for depression making young women a greater risk for major depression and mental disorders globally.[9]

Most of the ADRs recorded in VigiAccess, including known as well as previously unrecorded ADRs, were psychiatric events. A series of studies have shown that antidepressants produce changes in the central nervous system by modifying the recognition of basic emotions.[10] While antidepressant effects occur as a result of excessive levels of serotonin and a downregulation of dopamine neurotransmission in neural circuits that regulate emotional processing, this may also contribute to emotional flattening and cognitive slowing resulting in anxiety, depression, hallucination and agitation in patients[11], all of which were represented in the VigiAccess data. While these effects may occur in the first 3 months of treatment, evidence suggests that these may persist even after the symptoms of depression have improved[11]. The chronic elevation of serotonin levels due to a down-regulation of dopamine turn-over in circuits is associated with emotional blunting that may continue.[10] For this reason, adverse effects such as anxiety and depression does not revert even after treatment with vilazodone.

A significant number of gastrointestinal adverse events were also reported on VigiAccess. It is well known that serotonin plays a major role in the motor and sensory regulation of the

gastrointestinal tract (GIT). Almost 95% of serotonin is found in the GIT, mainly in epithelial and glandular enterochromaffin cells.[12] As a gastrointestinal hormone, serotonin is responsible for the regulation of smooth muscle motor activity and glandular secretion.[13] It affects the gastrointestinal sensation of pain, nausea and vomiting by acting via specific receptors found in the GIT.[12] Conventional functions of 5-HT in the gut involving intrinsic reflexes include stimulation of propulsive and segmentation motility patterns, epithelial secretion, and vasodilation.[13] Drugs with effects on serotonin receptors such as vilazodone can therefore affect gastric motility.

The majority of ADRs reported for the GIT, such as nausea, vomiting and diarrhoea, may be ascribed to vilazodone's pharmacological mechanism of action.[2] Vilazodone blocks the serotonin reuptake pump, desensitizes serotonin receptors and therefore increases serotonergic neurotransmission.[14] Nausea, vomiting and diarrhoea results from stimulation of the central 5-HT_3 receptors and are one of the most common causes of treatment discontinuation associated with vilazodone.[4] Activation of extrinsic vagal and spinal afferent fibres results in slowed gastric emptying, pain as well as nausea and vomiting.[13]

The study found a significant number of ADRs reported in VigiAccess, not published in the PIL or the FDA approval document. It is therefore imperative that post-marketing surveillance continues for the duration the drug is being used by the public. Spontaneous reporting by healthcare professionals remain the mainstay of post-marketing surveillance. Post-marketing spontaneous reports of adverse drug reactions assist in detecting signals[15], ultimately resulting in confirmation or disclaiming of an adverse effect with resultant appropriate action to be taken.

Despite the importance of post-marketing surveillance and the need for spontaneous reporting to ensure efficient post-marketing surveillance, underreporting remains problematic.[16] Low rates of ADR reporting are a significant healthcare problem and can delay regulatory actions taken to remove medicines with unacceptable safety profiles from the market.[16] The most significant barrier to reporting ADRs as mentioned earlier is a lack of time by healthcare professionals.[15] This can be addressed by simplifying the current reporting procedures and ensuring the continued monitoring of drugs.[16] According to a key principle of pharmacovigilance, it is always better to report even a suspicion to generate an alarm in the interest of protecting public health.[8]

CONCLUSION

Global drug safety depends on strong systems that monitor the quality of medicines, report their adverse effects, and provides accurate information for their safe use. The safety profile of a drug may evolve, causing changes in its' clinical use and giving rise to previously unobserved adverse effects, necessitating post-marketing surveillance.

This study found several adverse drug reactions only being observed after clinical trials. More than half of the psychiatric adverse effects recorded on VigiAccess were not indicated on the PIL and FDA approval documentation, which clearly shows that continued monitoring of the safety of a drug is imperative. Health care professionals remain the primary source of ADR reporting by patients, and this problem can be addressed by ensuring the continuous monitoring and spontaneous reporting of drugs.

DECLARATIONS

Ethics approval: Ethical waiver for approval was obtained from the University of Kwa-Zulu-Natal (Annexure: 1)

Availability of data and materials: Most of the data used in this manuscript are publicly available.

Competing interests: The authors declare that they have no competing interests

Funding: The study was supported by the College of Health Sciences Scholarship, University of KwaZulu-Natal.

Acknowledgments

Not applicable

REFERENCES

1) Zhang X.F., Wu L., Wan D.J., et L. Evaluation of the efficacy and safety of vilazodone for treating major depressive disorder. *Neuropsychiatric Disease and Treatment.* 2015; 11: 1957–1965
2) Cruz M.P. Vilazodone HCl (Viibryd): A serotonin partial agonist and Reuptake inhibitor for the treatment of major depressive disorder. *Pharmacy and Therapeutics.* 2012;37(1): 28–31.
3) U.S. Food and Drug Administration. Drug development and approval process. Available at: https://www.fda.gov/drugs/development-approval-process-drugs. 2019. Accessed on 5 January 2020.
4) Wang SM., Han C., et al. Vilazodone for the treatment of depression: an update. *Chonnam Medical Journal.* 2016; *52*(2), 91–100.
5) Nautiyal N., Rastogi R. and Gamperl H.J. Drug safety assessment in clinical trials: concepts and issues. *International Journal of Pharmaceutical Sciences and Research.* 2015; 6(10): 4159-4167.
6) Suvarna V. Phase IV of drug development. *Perspectives in Clinical Research.* 2010;1(2): 57–60.
7) World Health Organization. Pharmacovigilance: ensuring the safe use of medicines – WHO Policy Perspectives on Medicines. http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf. 2004. Accessed on 19 December 2019.
8) Palleria C., Leporini C., Chimirri S., et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: two "challenging" case reports. *Journal of Pharmacology & Pharmacotherapeutics.* 2013;4 (Suppl 1), S66–S72.
9) Albert P.R. Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience.* 2015;40(4): 219–221.
10) Szmulewicz, A., Samamé C., Caravotta P., et al. Behavioural and emotional adverse events of drugs frequently used in the treatment of bipolar disorders: clinical and theoretical implications. *International Journal of Bipolar Disorders.* 2016;4. 10.

11) Belujon P., and Grace A.A. Dopamine system dysregulation in major depressive disorders. *The International Journal of Neuropsychopharmacology.* 2017;20(12): 1036–1046.

12) Penkova N.I. and Nikolova J.G. Serotonin and its functions as gastrointestinal hormone. *Journal of Gastrointestinal and Digestive System.* 2017;7: 537.

13) Mawe G.M. and Hoffman J.M.Serotonin signalling in the gut--functions, dysfunctions and therapeutic targets. *Nature reviews. Gastroenterology & Hepatology.* 2013;10(8), 473–486.

14) Singh M. and Schwartz T.L.Clinical utility of vilazodone for the treatment of adults with major depressive disorder and theoretical implications for future clinical use. *Neuropsychiatric Disease and Treatment*.2012; 8, 123–130.

15) Inácio P., Cavaco A., and Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. *British Journal of Clinical Pharmacology.* 2017;83(2): 227–246.

16) Li R., Curtain C. and Bereznicki L. Community pharmacists' knowledge and perspectives of reporting adverse drug reactions in Australia: a cross-sectional survey. *International Journal of Clinical Pharmacy.* 2018;40, 878–889.

CHAPTER 4

MANUSCRIPT 2

Introduction

This chapter describes the background, general findings and discussion of the results pertaining to the psychiatric adverse effects associated with the use of vilazodone in the form of a systematic review.

The chapter is in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submissions at the University of KwaZulu-Natal (UKZN). The systematic review manuscript protocol is registered on Open Science Framework*:* OSF DOI-10.17605/OSF.IO/2M7HY. The protocol has been written according to author guidelines and submitted for publication to the British Medical Journal (BMJ) Open (see Annexure: 4)

The systematic review manuscript has been written according to author guidelines and will be submitted for publication to BMC Public Health. The reference list is cited according to the instructions for authors as required by BMC Public Health. The journal instructions to the author can be viewed in Annexure 5 or with the following link: https://bmcpublichealth.biomedcentral.com/submission-guidelines/preparing-your-manuscript/review

SYSTEMATIC REVIEW PROTOCOL

Title: Psychiatric adverse effects associated with the use of Vilazodone: a systematic review protocol

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Keywords: Vilazodone, psychiatric adverse effects, depression

ABSTRACT

Background

Vilazodone is a novel antidepressant that simultaneously acts as a selective serotonin reuptake inhibitor (SSRI) and a 5-HT_{1A}-receptor partial agonist. It is approved for the management of Major Depressive Disorder (MDD). While the long-term efficacy and safety of vilazodone has been established, there are no systematic reviews focusing on its psychiatric side effects. This systematic review aims to synthesize evidence from studies evaluating the psychiatric adverse effects of vilazodone.

Methods

We will conduct a systematic review of randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, cross-sectional studies, case series, and case reports that have evaluated the psychiatric adverse effects of vilazodone or comparative effects with other antidepressants. Two reviewers will independently search the following databases: Pubmed (Medline), Scopus, Web of Science, PsychInfo, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and ProQuest Dissertation and Theses. Additional studies will be identified from Google scholar and references of studies. Study eligibility, quality assessment, and data extraction will be conducted before the narrative synthesis of study findings. Two reviewers will screen the primary studies for inclusion and perform the critical appraisal. Data will be analysed using SPSS software. Frequency tables will be used to summarise the data followed by a narrative synthesis.

Ethics and dissemination

As this will be a systematic review, without patient involvement, there will be no requirement for ethical approval. Findings will be disseminated widely through peer-reviewed publications.

Protocol registration*:* OSF DOI- 10.17605/OSF.IO/2M7HY

Strengths and Limitations of the study

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines.
- This systematic review addresses a gap in the current evidence-base by providing a comprehensive assessment of the psychiatric adverse effects which may influence the effectiveness of vilazodone as an antidepressant.
- This review will include randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, cross-sectional studies, case series, and case reports that have evaluated the psychiatric adverse effects of vilazodone or comparative effects with other antidepressants.
- Non-English electronic databases will not be searched. This limitation may cause language bias.
- There is the potential for a low and inconsistent quality in the reporting of process evaluations and in the number of articles related to the topic that are published

BACKGROUND AND RATIONALE OF THE STUDY

A lot of information about the safety of a new drug is unknown when it is released onto the market. Unexpected adverse events or adverse drug reactions (ADRs) could arise at any time in the life cycle of a drug and could put the user at risk. ADRs have been reported as a significant clinical and public health problem causing nearly 5 to 35% hospitalization in both low-middle-income countries and high-income countries. [1 2 3] It is among the ten major causes of death in North American and Europe, as well as the rising cost of healthcare. [4 2 5]

Vilazodone is a novel antidepressant which simultaneously acts as a selective serotonin reuptake inhibitor (SSRI) and a 5-HT_{1A}-receptor partial agonist.[6] Vilazodone was approved in 2011 by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder in adults.[6] Vilazodone presents with various adverse effects that have mainly been identified during the pre-marketing phase trial of the drug.[7] An assessment of VigiAccess (vigiaccess.org) found that several adverse events caused by vilazodone were not recorded in the patient information leaflet (PIL) or FDA approval report. The highest frequency of ADRs observed in VigiAccess was observed for psychiatric disorders (19%) and included anxiety (26%), depression (17%), hallucinations (14%), and agitation (12%). These ADRs necessitate the need for post-marketing surveillance to ensure the safety and efficacy of vilazodone throughout its' use.

Current theory suggests that sustained, long-term 5-HT_{1A} receptor stimulation by vilazodone leads to a down-regulation of serotonin receptors so that, over time, serotonin release is no longer inhibited, thereby, causing psychiatric adverse effects.[8] Therefore, these effects do not revert even after vilazodone treatment.[9]

There are no systematic reviews that have gathered evidence of existing studies on the post-marketing surveillance of reported psychiatric adverse effects of vilazodone. Therefore, there is good reason for the present systematic review protocol to map up existing evidence of psychiatric adverse effects and central nervous system effects related to the drug.

Review Question

1. What are the psychiatric adverse effects associated with the use of Vilazodone?

Objective

The objective of this systematic review is to provide a synthesis of primary literature to:

- To evaluate the psychiatric adverse effects associated with the use of vilazodone
- To assess the risk factors of vilazodone psychiatric ADRs
- To evaluate the need for post-marketing surveillance of vilazodone

METHODS

The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines will be followed (see Appendix 7). The protocol is registered on the Open Science Framework (OSF) and is available at https://doi.org/10.17605/OSF.IO/2M7HY

Search strategy

The search strategy will be used to find published articles in a three-phase protocol (see Appendix: 2). First, a limited search of Medline and Pubmed will be carried out. The text words and index terms contained in the titles and abstract of the articles obtained will be analysed. Secondly, all related keywords and index terms identified will be used in all the included databases. Thirdly, the reference section of selected articles will be checked for additional related studies. This review and meta-analysis will use multiple literature databases, including Pubmed (Medline), Proquest Psychology Journals, Web of Science, Taylor & Francis Online Journals, PsychInfo, and Wiley Online Library. Additional searches will be performed in Google Scholar. Since the international patent filing of vilazodone was done in 1999,[10] our database search will be limited to publication dates from January 2000 to January 2020. Search limits will also be set to studies published in the English language because it is the only language of communication among the researchers and due to funding constraints. Our systematic search will be built on three concepts: 'vilazodone', 'adverse drug reaction' and 'psychiatric'. MeSH terms and free texts like the keywords will be used to optimize our search on PubMed before translating to other databases. All the results of the literature search will be imported into the bibliographic software 'Endnote X7', and duplicates will be identified and removed by the primary reviewer (HK).

The text words and index terms such as vilazodone, viibryd, depression, 5-HT1A, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion will be used in each database. The search terms will be combined using the Boolean operators 'AND' and 'OR' as indicated in Appendix 2.[11]

ELIGIBILITY CRITERIA

The Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework will be used to determine the eligibility of primary studies (see Appendix: 3).

Population

We will include studies with adolescents (12-18 years) and adults aged 18 years and older that report psychiatric adverse effects of vilazodone. Although we expect most studies to be on depression and anxiety disorders, we will not limit study choice to any medical indication provided.

Intervention

Vilazodone (irrespective of dose and duration).

Comparison

Placebo, no drug exposure or other antidepressants.

Outcome

The incidence and risk factors of psychiatric adverse effects associated with the use of vilazodone will be the outcomes of interest.

Study design

We will include all study designs, including randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, cross-sectional studies, case series, and case reports. Reviews, meta-analysis, editorials, conference abstracts, and presentations will be excluded. If multiple papers connected to a study have been published, we will either combine the results or select the paper with the largest sample size.

STUDY SELECTION

Two reviewers (HK and HM) will independently screen all titles and abstracts of the retrieved articles for inclusion/exclusion based on the eligibility criteria. The studies that meet the inclusion criteria will then undergo full-text screening. Where disagreements occur on inclusion/exclusion, a resolution will be by discussion, and a third reviewer (KM) if required.

Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. We may contact the authors of primary studies to seek clarification or to obtain additional data. Reasons for study exclusion will be noted and described in a PRISMA flowchart according to PRISMA guidelines.[12]

SCREENING AND DATA EXTRACTION

This systematic review will be carried out by three reviewers. All titles and abstracts of the retrieved articles will be independently screened by two reviewers independently to identify eligible studies for this systematic review, according to the inclusion criteria. Where disagreements occur on inclusion/exclusion, the third reviewer will resolve. The studies that do not meet the eligibility criteria will be excluded. Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. Inconsistencies in data collection will be solved by consensus. Concurrent and contradictory relationships between categories will be identified, and research findings will be discussed.

A standardized data extraction form will be used to extract data from the included studies. It will be developed considering the guide provided by the Cochrane Collaboration about content and structure.[11] This data extraction form will be piloted before use. The data extraction form will include authors, year, country, study title, study period, reference, method characteristics (study size, study design, study objective or research question, study participant characteristics, study setting, method of assessment, statistical analyses, the treatment used and associated psychiatric adverse effects caused) and key findings, conclusion, a summary of study strengths, and limitation. Any changes made during the data extraction process will be reported in the final manuscript. Detailed data extraction will be done using Microsoft Word tables or Microsoft Excel spreadsheets to summarise the data from the selected studies. Data will be extracted by the main reviewer (HK) and checked by the other reviewers, with disagreements resolved by consensus.

QUALITY ASSESSMENT

Two reviewers will independently examine each selected article to reduce bias. The quality of randomized controlled trials (RCTs), cross-sectional studies, case series, and case reports will be assessed using tailor-made tools from the Joanna Briggs Institute (JBI).[13] The results of this appraisal will be used to show the possibility of bias in the design, conduct, and analysis of

each study. Any conflicts over the assessment of quality will be resolved by consensus between reviewers.

DATA SYNTHESIS AND DESCRIPTIVE ANALYSIS

The data extracted will be imported into SPSS Software for analysis. This includes focusing on extracting insights from the data and sorting the findings into categories of thought. Data will be summarized using text and tables. Frequency tables will summarize categorical data, including sample characteristics, patient characteristics and psychiatric adverse effect outcomes. Psychiatric adverse effects found from selected articles will be listed according to preferred terms based on the most commonly used coding system, the Medical Dictionary for Regulatory Activities (MedDRA)[14] (see Appendix 5). Using these terms, the impact of psychiatric adverse effects on vilazodone will be described. A narrative synthesis will describe and discuss the outcomes.

ETHICS AND DISSEMINATION

This evidence-based systematic review will summarise the relevant information on the association of vilazodone use and psychiatric adverse effects. Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The results and findings of this study will be submitted and published in a scientific peer-reviewed journal. The findings from this study could be useful for assessing the psychiatric adverse effects with the use of vilazodone for prevention in the future.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not directly involved in the design of this study. As this is a protocol for a systematic review and no participant recruitment will take place, their involvement in the dissemination of findings to participants was not applicable.

AMENDMENTS

Any amendments to this protocol will be documented regarding saved searches and analysis methods, which will be recorded in bibliographic databases, EndNote for data collection and synthesis. Important protocol amendments post registration will be recorded and included in dissemination.

DEALING WITH MISSING DATA

Authors of primary studies will be contacted for additional information if relevant data is not reported in published manuscripts.

DISCUSSION

This systematic review will synthesize research evidence to establish the psychiatric adverse effects associated with the use of vilazodone. Psychiatric adverse effects caused by SSRI's have received little attention in clinical studies and are not listed in the literature as part of its' known or expected adverse effects.[15] The undetected ADRs of vilazodone assessed in the manuscript necessitate the need for post-marketing surveillance to ensure the safety and efficacy of the drug throughout its' use. Future research should more specifically and systematically examine these psychiatric adverse effects as they come into the market. Therefore, we will conduct a systematic review and meta-analysis, if possible, to show a general view of the current literature, as well as further improve research regarding the psychiatric adverse effects associated with vilazodone.

Potential limitations are inherent in conducting systematic reviews and meta-analyses: publication bias, information bias, weak statistical analyses, poor methodological quality, and inadequate reporting of methods and findings of the included studies. Another limitation might be the restriction of the analysis to studies published in English. Therefore, it is important to synthesise the information available in the manuscripts included adequately. This task will be conducted independently by two reviewers, and disagreements will be resolved by consensus. Likewise, the Cochrane Collaboration Handbook recommendations will be followed.

In summary, due to a lack of agreement and conclusions about the relationship between vilazodone and psychiatric adverse effects, it seems logical and important to carry out a systematic review and meta-analysis to make patients and health care professionals more aware of these effects that will contribute to the drug safety.

DECLARATIONS

Ethics approval: Not required

Availability of data and materials: Most of the data used in this systematic review protocol are publicly available.

Competing interests: The authors declare that they have no competing interests

Funding: The study was supported by the College of Health Sciences Scholarship, University of KwaZulu-Natal.

Authors contributions

Corresponding author: Humraaz Kaja
Supervisor: Dr Kofi Mensah
Co-author: Henry Michael
Co-supervisor: Dr Frasia Oosthuizen

HK conceived and designed the study. HK collected the data. HK and HM analysed and interpreted the data. HK drafted the manuscript with critical revisions from KM, FO and KM and FO supervised the study.

Acknowledgments: Not applicable

REFERENCES

1. Khalil, H. and Huang, C. Adverse drug reactions in primary care: a scoping review. *BMC Health Services Research.* 2020; 20, 5.
2. Avong Y.K., Jatau B., Gurumnaan R., Danat N., Okuma J. Addressing the under-reporting of adverse drug reactions in public health programs controlling HIV/AIDS, Tuberculosis and Malaria: A prospective cohort study. *PLOS ONE.* 2018; 13(8): e0200810.
3. Stausberg, J. International prevalence of adverse drug events in hospitals: an analysis of routine data from England, Germany, and the USA. *BMC Health Services Research.* 2014; 14, 125.
4. Kiguba R., Karamagi C. and Bird S.M. Incidence, risk factors and risk prediction of hospital-acquired suspected adverse drug reactions: a prospective cohort of Ugandan inpatients. *BMJ Open.* 2017;7: e010568.
5. Hadi M.A., Neoh, C.F., Zin R.M., Elrggal M.E. and Cheema, E. Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. *Integrated pharmacy research & practice.* 2017; 6, 91–98.
6. Zhang, X.F., Wu L., Wan D.J., Liu R.Z., Dong Z., Chen M., and Yu S.Y. Evaluation of the efficacy and safety of vilazodone for treating major depressive disorder. *Neuropsychiatric disease and treatment.* 2015; 11, 1957–1965.
7. Wang Y.Q., Li R., Zhang M.Q., Zhang Z., Qu W.M. and Huang Z.L. The neurobiological mechanisms and treatments of REM sleep disturbances in depression. *Current neuropharmacology*. 2015; 13(4), 543–553.
8. Pierz K.A. and Thase M.E. A review of vilazodone, serotonin, and major depressive disorder. *The primary care companion for CNS disorders*. 2014; 16(1), PCC.13r01554.
9. Belujon P. and Grace A.A. Dopamine system dysregulation in major depressive disorders. *The International Journal of Neuropsychopharmacology.* 2017; 20(12): 1036–1046.
10. Dawson L.A. The discovery and development of vilazodone for the treatment of depression: a novel antidepressant or simply another SSRI? *Expert Opinion on Drug Discovery.* 2013; 8:12, 1529-1539.

11. Higgins Julian P.T., Altman D.G., Gøtzsche P.C., Jüni P., Moher D. and Oxman A.D. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal.* 2011; 343: d5928
12. Moher D., Liberati A., Tetzlaff, J. and Altman, D.G. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Annals of Internal Medicine*. 2009; 151,4.
13. Moola S., Munn Z., Tufanaru C., Aromataris E., Sears K., Sfetcu R., Currie M., Qureshi R., Mattis P., Lisy K. and Mu P.F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. *The Joanna Briggs Institute.* 2017.
14. Le Noury, J., Nardo, J., Healy, D., Jureidini, J., Raven, M., Tufanaru, C., Abi-Jaoude, E. Restoring study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *British Medical Journal*. 2015; 351, h4320.
15. Sansone R.A. and Sansone L.A. SSRI-Induced Indifference. *Psychiatry. 2010;* 7(10), 14–18.

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SYSTEMATIC REVIEW

Psychiatric adverse effects associated with the use of vilazodone- a systematic review.

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Short Title: Psychiatric adverse effects associated with vilazodone

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Keywords: Vilazodone, psychiatric adverse effects, depression

Psychiatric adverse effects associated with the use of Vilazodone- a systematic review

ABSTRACT

Background: Vilazodone is a novel antidepressant used to treat Major Depressive Disorder (MDD). Available literature suggests that the efficacy and safety of vilazodone-associated psychiatric adverse effects have not yet been systematically assessed and described. To add to the knowledge about the psychiatric adverse effects caused by vilazodone, this study provides a systematic review of all available research literature and aims to provide a critical summation of present findings. The aim of this study is to provide a critical overview of the literature on the psychiatric adverse effects caused by vilazodone from January 2000 to January 2020, highlighting the effects, consistencies, knowledge gaps, current theories, and limitations of available understandings.

Method: We searched electronic databases and reference lists for studies published between January 2000 to January 2020. A systematic review of the literature on psychiatric adverse effects associated with vilazodone was conducted using the Cochrane Framework. Two reviewers screened the primary studies for inclusion and performed the critical appraisal. Data was analysed using SPSS software. Frequency tables were used to summarise the data followed by a narrative synthesis.

Findings: From an initial search of 124 articles, a total number of 7 full texts, that met the inclusion criteria, were included for 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 FDA registration document and patient information leaflet (PIL).

Conclusions: Vilazodone has a wide range of adverse psychiatric 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 researched articles shows that there is a lack of studies that can prove the safety of vilazodone associated with psychiatric adverse effects.

INTRODUCTION

Background

Adverse drug reactions (ADRs) can affect patients irrespective of age or gender, ultimately impacting on morbidity and mortality [1]. ADRs have become a major global health problem that needs to be addressed [2]. 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 [3].

Vilazodone is a relatively new drug that was released on to the market in 2011, sold under the brand name Viibryd, used to treat Major Depressive Disorder (MDD) [4]. 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 [5]. Vilazodone simultaneously acts as an SSRI and a 5-HT_{1A}-receptor partial agonist and enhances serotonergic activity in the CNS through selective inhibition of serotonin reuptake [4].

Over the years, several other adverse effects, including diarrhoea, headache, nausea, vomiting, and insomnia, have been identified with the use of vilazodone [6]. 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 [7]. More than half of the adverse effects recorded on the WHO site, VigiAccess, were not indicated on the patient information leaflet (PIL) and FDA approval documentation. The highest frequency of these undetected adverse effects was observed under psychiatric disorders, clearly indicating the need for continued monitoring of the safety aspects post-marketing.

Psychiatric adverse effects caused by SSRI's have received little attention in clinical studies and is not listed in the literature as part of the known or expected adverse effects [8]. Information about an antidepressants' adverse effects at the time of marketing is generated only from pre-marketing trials and studies [6]. This may be due to the failure of clinical studies to systematically assess psychiatric adverse effects [9]. 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. To add to the knowledge about the psychiatric adverse effects caused by vilazodone, this study provides a systematic review of all available research literature on the associations between the variables.

METHODS

Study Protocol

The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were followed in conducting and reporting this review [10]. (for PRISMA checklist see Appendix: 7).

Search strategy

The search strategy was used to find published articles in a three-phase approach (see Appendix 4). 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 analysed. 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 & Francis Online Journals, PsychInfo, and Wiley Online Library. Additional searches were performed in Google Scholar. Studies were limited to publication date from January 2000 to April 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 among the researchers. Filters were set to English, human studies and studies in adolescents (12 years and older) and adults (18yrs and older). Reference checking of included articles was also done to capture missing primary articles as a result of indexing errors [see supplementary material, table 2, for search details]. The bibliographic software (Endnote), 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 by the primary reviewer (HK).

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 ‘AND’ and ‘OR’ as indicated in Appendix 2.

Study Eligibility

The PICOS framework was used to set criteria to identify potential studies (7). The inclusion criteria were study population (adolescents aged >12 and adults aged >18 years who reported psychiatric adverse effects with the use of vilazodone), intervention (vilazodone irrespective of dose and duration), comparator (may include studies comparing psychiatric adverse effects and outcomes with vilazodone and other antidepressants), outcomes (psychiatric adverse effects caused with the use of vilazodone), and study design (randomized controlled trials (RCTs), case reports of vilazodone, cross-sectional studies and cohort studies). We excluded studies if they were not published in English, published before 2000, were not primary studies, and if they did not report any psychiatric effects and outcomes.

Study Selection

All articles were retrieved independently from the search of the electronic databases by HK and HM and then exported to EndNote. The articles were reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [10]. Duplicates were identified and removed using EndNote. HK and HM independently reviewed all titles and abstracts to determine eligibility based on set criteria. With this, HK and HM then evaluated full texts of the articles identified for their final eligibility for data extraction. All disagreements were resolved by discussion or consultation with a third reviewer KM.

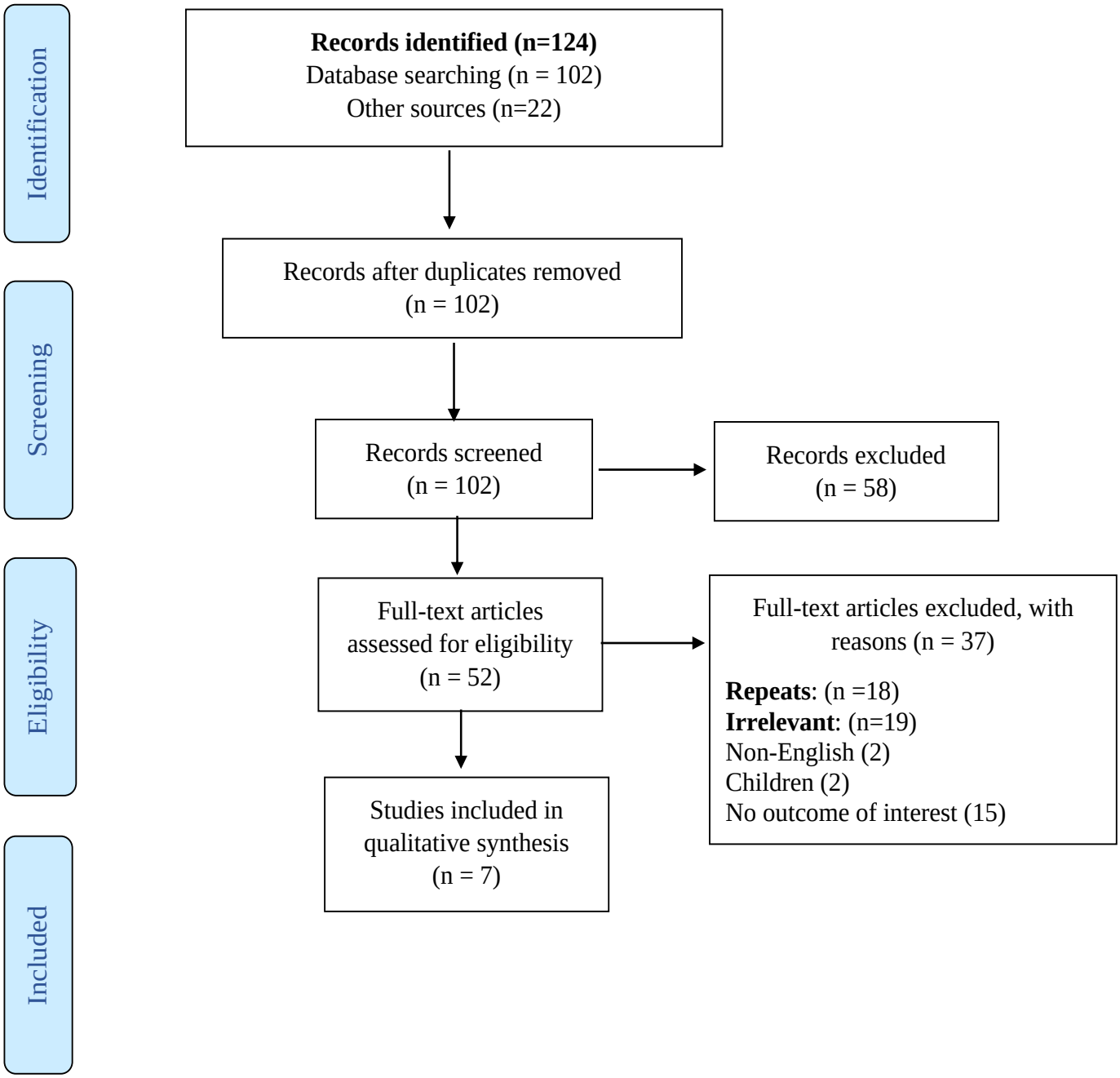
Quality Assessment and Data Extraction

HK and HM critically evaluated the quality of selected articles by employing the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies, JBI critical appraisal checklist for cohort studies, the JBI critical appraisal tool for case series/reports and JBI critical appraisal tool for randomized controlled trials [11]. The articles were then ranked based on their quality scores as less than 50% (low-quality), 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. HK and KM piloted the data extraction form 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.

Data Synthesis

Data was imported into SPSS Software for analysis. Frequency tables summarized categorical data, including sample characteristics, patient characteristics and psychiatric adverse effect outcomes. Psychiatric adverse effects found from selected articles were listed according to preferred terms based on the most commonly used coding system, the Medical Dictionary for Regulatory Activities (MedDRA) [12] (see Appendix: 5). Using these terms, the impact of psychiatric adverse effects on vilazodone were then described. A narrative synthesis was then done to describe and discuss the outcomes.

Figure: 1 PRISMA FLOW DIAGRAM (Moher, Liberati, Tetzlaff & Altman, 2009)



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 that yielded a total of 124 articles. As shown in the PRISMA flow chart (see Figure: 1), upon the removal of any duplicates, the articles available were then reduced to n=102. The abstracts of each article were screened according to the abovementioned search criteria, following which n=58 texts were excluded. This left a total of 52 potentially eligible full texts to be assessed. A total of 37 articles were excluded from the reviewed full-texts due to the repetition of articles or article irrelevance. Thus, the final number of full-text articles included in this review was n=7.

Quality assessment/risk of bias

Using the JBI levels of evidence, one study [9] in this review is a cross-sectional study. One study [13] is a cohort study. Five studies in this review are RCTs [14-18]. Appraisal of individual studies using the JBI critical appraisal method is shown in the supplementary information (see Appendix: 6, Table 6A-C). To summarize, the cross-sectional studies were of high quality (100%). The prospective cohort studies were of moderate quality studies (50-75%). All RCTs were of high quality (>75%).

ANALYSIS OF FINDINGS

Study Characteristics

The articles that were selected were all published in the years between 2009-2017, with majority of the studies conducted only after vilazodone was released on to the market in 2011 (n=6). All included studies were published articles including randomized controlled trials cohort studies (RCTs) (n=5), open-label cohort studies (n=1), and cross-sectional studies (n=1) that were selected and included in this review. Of the RCTs (n=5), there were (n=3) phase IV trials and phase III trials conducted (n=2). Most of the studies took place over 8-10 weeks (n=6). The dose range for all studies included vilazodone 40mg- 10mg taken once daily for seven days, 20mg for the next seven days, then increased to 40mg for the duration of the study.

Demographic and patient characteristics

All studies took place in the USA, also being the country with the highest rate of use of vilazodone. The main objective of all the included studies was completed to evaluate the safety and efficacy of vilazodone for either the treatment 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 users were white (76%). The mean percentage of users was highest for females (65%), followed by males (35%).

Table 1- Study characteristics of included studies

Studies	Design	Groups (n)	Duration	Functional Tests	Dose range	Summary of main objective	Inclusion Population	Summary of findings (psychiatric adverse effects)
Croft et al., 2014	RCT Double blind Phase IV	n = 797 Vilazodone 40mg = 253 Vilazodone 20mg =292 Placebo= 252	8 weeks	C-SSRS MADRS CGI-S HAM-A	Vilazodone 10mg once daily for seven days, 20mg for the next seven days and 40mg 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 an MADRS total score ≥26	Anxiety, irritability, depression and suicidal ideation
Mathews et al., 2015	RCT Double blind Phase: IV	n= 1133 Vilazodone 40mg= 291 Citalopram 40mg= 289 Placebo= 290	10 weeks	C-SSRS MADRS HAM-A CGI-I CGI-S	Vilazodone 10mg once daily for seven days, 20mg for the next seven days and 40mg for the duration of the study	To evaluate the safety and efficacy of vilazodone 20-40mg in patients with MDD	Adults with MDD who had an ongoing major depressive episode lasting ≥8 weeks and up to 12 months, and had an MADRS total score ≥26	Suicidal ideation
Robinson et al., 2015	Open Label multicentre safety trial cohort study	n = 599	52 weeks	MADRS CGI C-SSRS	Vilazodone titrated from 10-40mg 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
Gommoll et al., 2015	RCT Double blind Phase: 3	n= 673 Vilazodone 40mg= 225 Vilazodone 20mg= 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

Durgam et al., 2016	RCT Double blind	n= 529 Vilazodone 15mg= 175 Vilazodone 30mg= 180 Placebo= 174	10 weeks	C-SSRS CDRS-R CGI-S	Vilazodone 15-30mg	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
Khan et al., 2009	RCT Double blind Phase: III	n= 481 Vilazodone 40mg= 235 Placebo= 233	8 weeks	HAM-A MADRS CGI-I CGI-S HDRS 17 HDRS 21 HARS	Vilazodone 10mg once daily for seven days, 20mg for the next seven days and 40mg 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
Hughes et al., 2017	Cross Sectional Study	n= 3243 Escitalopram = 2359 Vilazodone= 394 Duloxetine= 305 Vortioxetine = 185		N/A	Vilazodone 10mg	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 AskAPatient.	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	Publication	Country	Age	Mean Age	Race	Gender
Croft et al., 2014	2015	Article	USA	18-70 years	39 years	80% white	68% female 32% male
Mathews et al., 2015	2015	Article	USA	18-70 years	41 years	71% white	57% female 43% male
Robinson et al., 2015	2015	Article	USA	18-70 years	42 years	80% white	68% female 32% male
Gommoll et al., 2015	2015	Article	USA and Mexico	18-70 years	40 years	81% white	69% female 31% male
Durgam et al., 2016	2016	Article	USA	12-17 years	15 years	67% white	59% female 41% male
Khan et al., 2009	2009	Article	USA	18-70 years	41 years	77% white	59% female 41% male
Hughes et al., 2017	2017	Article	USA	19-75 years	47 years		77% female 23% male

Table 3- Psychiatric adverse effect outcomes of vilazodone from reviewed studies

PSYCHIATRIC ADVERSE EFFECT	GROUPS (n)		
Croft et al., 2014			
	Vilazodone 40mg n = 255 (%)		Placebo 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%
Durgam et al., 2016			
	Vilazodone 15mg n=175 (%)	Vilazodone 30mg n=180 (%)	Placebo 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%	31.1%	33%
Suicidal behaviour based on C-SSRS scale	1.1%	1.1%	1.8%
Gommoll et al., 2015			
	Vilazodone 20-40mg n=200 (%)		Placebo N=198 (%)
Abnormal dreams	10 (5)		3 (1.5)
Suicidal ideation based on C-SSRS scale	6%		8%

Hughes et al., 2017				
	Duloxetine n=305 (%)	Escitalopram n=2,359 (%)	Vilazodone n=394 (%)	Vortioxetine n=185 (%)
	119 (39.0)	930 (39.4)	225 (57.1)	76 (41.1)
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)

Khan et al., 2009		
	Vilazodone 40mg (235)	Placebo (233)
Abnormal dreams	14 (6.0)	4 (1.7)

Mathews et al., 2015				
	Vilazodone 20mg n=288 (%)	Vilazodone 40mg n=284 (%)	Citalopram 40mg n=280 (%)	Placebo n=281 (%)
Suicidal ideation based on C-SSRS scale	17.4%	18.1%	16.3%	24.2%

Robinson et al., 2015	
	Vilazodone 40mg n=599 (%)
Abnormal dreams	62 (10.4)
Anxiety	36 (6.0)
Suicidal Ideation	5 (0.8)

Table 4- Summary of psychiatric adverse effects from reviewed articles

Psychiatric Adverse Effects	Literature
Abnormal dreams	Hughes et al., 2017 Gommoll et al., 2015 Khan et al., 2009 Robinson et al., 2015
Agitation	Hughes et al., 2017
Aggression or increased anger	Hughes et al., 2017
Aggravated depression, crying	Hughes et al., 2017 Durgam et al., 2016
Irritability	Croft et al., 2014 Durgam et al., 2016
Anxiety	Hughes et al., 2017 Croft et al., 2014 Durgam et al., 2016 Robinson et al., 2015
Confusion	Hughes et al., 2017
Depersonalization	Hughes et al., 2017
Emotional numbing	Hughes et al., 2017
Sleep paralysis	Hughes et al., 2017
Suicidal ideation or attempt	Hughes et al., 2017 Robinson et al., 2015 Mathews et al., 2015 Gommoll et al., 2015 Croft et al., 2014 Durgam et al., 2016
Alterations in mental status	Durgam et al., 2016
Nightmares	Durgam et al., 2016

Psychiatric adverse effect outcomes

A double-blind placebo-controlled study was conducted over ten weeks by Durgam 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, n = 2; placebo, n = 0), suicidal ideation (vilazodone, n = 4; placebo, n = 1), and depression (vilazodone, n = 4; placebo, n = 0). In the study by Croft et al., anxiety (0.8%) was recorded with vilazodone use, higher than the placebo (0.4%). Irritability was also recorded but was lower than the placebo (vilazodone= 0.4%, placebo=0.8%).

Khan et al. reported that abnormal dreams recorded with the use of vilazodone (6%) were much higher than with the use of the placebo (1.7%). In the article by Gommoll et al., abnormal dreams (5%) were reported higher with the use of vilazodone (5%) in comparison to the use of the placebo (1.5%). In the open- label cohort study by Robinson et al., psychiatric adverse effects such as abnormal dreams (10.4%), anxiety (6%), and suicidal ideation (0.8%) were also recorded with the use of vilazodone.

According to the article by Hughes 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 effect profiles [9]. 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%); vortioxetine, n=185 (5.7%) from three popular health websites [9]. Patients reported 57% of psychiatric adverse effects with the use of vilazodone, followed by 41.4% of gastrointestinal and 28.4% of sleep effects [9]. Psychiatric adverse effects demonstrated moderate to substantial relationships with patients' satisfaction for vilazodone, whereas gastrointestinal, metabolic, or sexual adverse effects were minimally related [9]. Vilazodone was reported by 6-20% of users to cause insomnia. Vilazodone users reported the highest rates of abnormal dreams (25.6%), aggression and 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. Patients described symptoms of feeling irritable with anger spells, crying, anger, and sleep paralysis that occurred with the use of vilazodone [9]. Worsened anxiety was a highly reported psychiatric adverse effect among the users of vilazodone. Patients reported 57% of psychiatric adverse effects with the use of vilazodone, followed by 41.4% of gastrointestinal and 28.4% of sleep effects. Psychiatric adverse effects demonstrated moderate to substantial for vilazodone.

Based on C-SSRS findings, in the article by Durgam et al., reports of 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 15mg, was recorded as the highest in comparison to the placebo. The incidence of suicidal ideation during double-blind treatment in the article by Mathews et al., was also determined by the C-SSRS scale. The results showed suicidal ideation as being 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 the article by Gommoll et al., C-SSRS-rated suicidal ideation was also reported more often among patients in the placebo group (8%) compared with the vilazodone group (6%). Suicidal ideation, according to the C-SSRS scale in the study by Croft et al., was recorded as 19% with the use of vilazodone and 21% with placebo use.

DISCUSSION OF RESULTS

Vilazodone was approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in adults in 2011 [4]. 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 among older adults [19]. Also, vilazodone was released in the US before being marketed in Asia and Europe. This might have accounted for the data been skewed to the US.

The main objective of all the included studies were completed 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% [20]. GAD is a condition of excessive and persistent worry about events in the future, with a distorted perception of risks and threats by patients [21]. GAD is associated with psychological symptoms including restlessness, difficulty concentrating, and disturbed sleep, often occurring comorbidly with MDD [22]. The recommended dose for vilazodone is 20–40 mg/day [23], starting at 10mg per day titrated upward to a target dose of 40mg per day which is the dose level being evaluated for the treatment of GAD and MDD.

In terms of patient demographics, vilazodone was mainly used by adult (18 – 70 years) female patients. The mean age for all included studies was 38 years. Vilazodone is an antidepressant mostly used by adult patients and rarely used in children below the age of 12 [4]. The use of antidepressants in adults has increased due to several factors, including an increase in the adult population on antidepressants therapies, duration of therapy, which is mostly 180days, and increase multiple chronic conditions within the adult population [19]. 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 [19]. Due to the higher rate of use, most adverse events would be observed in adults.

The mean percentage for the race group, which accounted for the highest population of users were white (76%). Nationally, it was found that black Americans with depressive or anxiety disorders were one-third less likely as white Americans to have used antidepressants, making the psychiatric need for antidepressants to be associated more with whites [24]. The mean percentage of users in this study were highest for females (65%), followed by males (35%). According to a study, females were about twice as likely as males to take antidepressant

medication [25]. Women are more likely to experience specific forms of depression-related illnesses, including postpartum depression, postmenopausal depression, and anxiety [26]. Female hormonal fluctuations may be a trigger for depression, making young women a higher risk for major depression and mental disorders globally [26].

In patients with depression, synaptic levels of serotonin are regulated by 5-HT_{1A} auto-receptors. The activation of 5-HT_{1A} auto-receptors, through the binding of serotonin, initially produces an increase of serotonin reuptake, thereby more of the neurotransmitter is available to interact with these receptors [27]. Current theory predicts that sustained, long-term 5-HT_{1A} receptor stimulation by vilazodone leads to a down-regulation of the auto-receptors so that, over time, serotonin release is no longer inhibited thereby causing psychiatric adverse effects, resulting in altered mentation and instability [28]. 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 [29].

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 [30]. Kapur 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 [31].

Discontinuation reactions have been reported after withdrawal of prolonged vilazodone treatment. According to studies by Durgam et al., Khan et al., and Croft 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 than in comparison to the placebo drug used in respective studies. 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 [6]. 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 [32]. Intolerability to medication is one of the most common reasons patients discontinue antidepressant treatment [33]. Patients should be monitored for these symptoms vilazodone dose should be tapered gradually when patients are discontinuing therapy [7].

In the analysis of Internet postings of users' reviews of vilazodone according to the study by Hughes 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 [9]. 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 among 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 [34]. The findings imply that important differences between antidepressants might be missed, due to poor adverse effect assessment in drug research [9].

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 [7]. In a study, SSRI use was associated with a nearly five-fold higher risk of completed suicide and suicidal thoughts in comparison to other antidepressants [35]. 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 [35].

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 [36]. According to the C-SSRS findings in all pooled studies, the rates of suicidal ideation was more common in placebo treated patients than in vilazodone-treated patients in the included studies. 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 [36].

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 [37], this analysis and review suggest that psychiatric 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 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- analytical approach. 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.

CONCLUSION

The findings of this systematic review hypothesize that vilazodone has a greater range of psychiatric adverse effects than appears 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.

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 user initiating vilazodone, and more considerable attention in research should be given to a broader range of effects that could affect 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 efficacy in treating MDD and is being investigated for other possible indications, further detailed clinical trials are required to establish their psychiatric safety profile. Future research should more specifically and systematically examine these psychiatric adverse effects as they come into the market.

Declarations

Competing interests: The authors declare that they have no competing interests

Ethics approval: Not required

Availability of data and materials: Most of the data used in this systematic review are publicly available.

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Authors' contribution

HK conceived and designed the study. HK collected the data. HK and HM analysed and interpreted the data. HK drafted the manuscript with critical revisions from KM, FO and KM and FO supervised the study.

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Not applicable

REFERENCES

1. Bogolubova S., Padayachee, N. and Schellack N. Knowledge, attitudes and practices of nurses and pharmacists towards adverse drug reaction reporting in the South African private hospital sector. *Health SA.* 2018*; 23*, 1064.
2. Coleman J.J. and Pontefract S.K. Adverse drug reactions. *Clinical Medicine.* 2016*;* 16(5), 481–485.
3. Pirmohamed M., James S., Meakin S., Green C., Scott A., Walley T. and Breckenridge A. Adverse Drug Reactions as cause of admission to hospital: Prospective Analysis Of 18 820 Patients. *British Medical Journal*. 2004; 329(7456), 15-19.
4. Cruz M.P. Vilazodone HCl (Viibryd): A serotonin partial agonist and Reuptake inhibitor for the treatment of major depressive disorder. *Pharmacy and Therapeutics.* 2012*;* 37(1): 28–31.
5. Singh M. and Schwartz T.L. Clinical utility of vilazodone for the treatment of adults with major depressive disorder and theoretical implications for future clinical use. *Neuropsychiatric Disease Treatment*. 2012; 8:123–30.
6. Wang Y.Q., Li R., Zhang M.Q., Zhang Z., Qu W.M. and Huang Z.L. The neurobiological mechanisms and treatments of REM sleep disturbances in depression. *Current neuropharmacology*. 2015; 13(4), 543–553.
7. Goldenberg M.M. Pharmaceutical approval update. *Pharmacy and Therapeutics: a peer-reviewed journal for formulary management*. 2011; 36(3), 162–164.
8. Sansone R.A. and Sansone L.A. (2010). SSRI-Induced Indifference. *Psychiatry, 7*(10), 14–18.
9. Hughes S., Lacasse J., Fuller R.R., et al. Adverse effects and treatment satisfaction among online users of four antidepressants. *Psychiatry Research*. 2017; 255: 78–86.
10. Moher D., Liberati A., Tetzlaff, J. and Altman, D.G. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Annals of Internal Medicine*. 2009; 151,4.
11. Aromataris E. and Munn Z. (2017). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute. Available from https://reviewersmanual.joannabriggs.org/. Accessed on 2 March 2020.

12. Le Noury, J., Nardo, J., Healy, D., Jureidini, J., Raven, M., Tufanaru, C., Abi-Jaoude, E. Restoring study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *British Medical Journal*. 2015; 351, h4320.
13. Robinson D.S., Kajdasz D.K., Gallipoli S., Whalen H., Wamil A., Reed CR. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. *Journal of Clinical Psychopharmacology*. 2011; 31(5):643- 646.
14. Croft H.A., Pomara N., Gommoll C., Chen D., Nunez R., Mathews M. Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*. 2014; 75(11): e1291–e1298.
15. Durgam S., Chen C., Migliore R., Prakash C., Edwards J. and Findling R.L. A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Vilazodone in Adolescents with Major Depressive Disorder. *Paediatric drugs*. 2018; 20(4), 353–363.
16. Gommoll C., Forero G., Mathews M., Nunez R., Tang X., Durgam S., and Sambunaris A. Vilazodone in patients with generalized anxiety disorder: a double-blind, randomized, placebo-controlled, flexible-dose study. *International clinical psychopharmacology*. 2015; 30(6), 297–306.
17. Khan A., Cutler A.J., Kajdasz D.K. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *Journal of Clinical Psychiatry*. 2011; 72(4):441–447.
18. Mathews M., Gommoll C., Chen D., Nunez R., Khan A. Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International Clinical Psychopharmacology*. 2014; 30:67–74.
19. Tamblyn, R., Bates, D. W., Buckeridge, D. L., Dixon, W., Forster, A. J., Girard, N., Haas, J., Habib, B., Kurteva, S., Li, J., & Sheppard, T. Multinational comparison of new antidepressant uses in older adults: a cohort study. *British Medical Journal open*. 2019; 9(5), e027663.
20. Lépine, J. P., & Briley, M. The increasing burden of depression. *Neuropsychiatric disease and treatment* 2011; 7(Suppl 1), 3–7.
21. Allgulander C. Generalized anxiety disorder: a review of recent findings. *Journal of Experimental and Clinical Medicine*. 2012; 4:88–91.

22. Buoli M., Caldiroli A., Caletti E., Paoli R.A. andAltamura A.C. New approaches to the pharmacological management of generalized anxiety disorder. *Expert Opinion on Pharmacotherapy*. 2013; 14:175–184.
23. Song L., Liu Y., Liu F., Zhang R., Ji H., and Jia Y. Vilazodone for major depressive disorder in adults. *The Cochrane Database of Systematic Reviews*. 2016; (9), CD012350.
24. González, H. M., Croghan, T., West, B., Williams, D., Nesse, R., Tarraf, W., Taylor, R., Hinton, L., Neighbors, H., & Jackson, J. Antidepressant use in black and white populations in the United States. *Psychiatric services (Washington, D.C.)*. 2008; 59(10), 1131–1138.
25. Pratt, L. A., Brody, D. J., & Gu, Q. Antidepressant use in persons aged 12 and over: United States, 2005-2008. *National Centre for Health Statistics data brief*. 2011; (76), 1–8.
26. Albert P.R. Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience*. 2015; 40(4): 219–221.
27. Yohn C.N., Gergues M.M. and Samuels B.A. The role of 5-HT receptors in depression. *Molecular brain*. 2017; 10(1): 28.
28. Pierz K.A. and Thase M.E. A review of vilazodone, serotonin, and major depressive disorder. *The primary care companion for CNS disorders*. 2014; 16(1), PCC.13r01554.
29. Antonuccio D. and Healy D. Relabelling the medications, we call antidepressants. *Scientifica*. 2012; 965908.
30. Kennedy S.H. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues in clinical neuroscience*. 2008; 10(3), 271–277.
31. Kapur S. and Mann J.J. Role of the dopaminergic system in depression. *Biological Psychiatry*. 1992; 32:1-17
32. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practitioner*s. 2012 ;66(4):356–368.
33. Hu XH., Bull SA., Hunkeler EM., et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for

depression: patient report versus physician estimate. *Journal of Clinical Psychiatry*. 2004; 65:959–965

34. Goldsmith, L., Moncrieff, J. The psychoactive effects of antidepressants and their association with suicidality. *Current Drug Safety*. 2011; 6, 115-121.
35. Nischal A., Tripathi A., Nischal A., and Trivedi J.K. Suicide and antidepressants: what current evidence indicates. *Mens sana monographs*. 2012; 10(1), 33–44.
36. Posner K., Brown G.K., Stanley B., Brent D.A., Yershova K.V., Oquendo M.A., Currier G.W., Melvin G.A., Greenhill L., Shen S., and Mann J.J. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *The American journal of psychiatry*. 2011; 168(12), 1266–1277.
37. Crawford, A., Lewis, S., Nutt, D., Peters, T., Cowen, P., O'Donovan, M., Wiles, N. and Lewis, G. Adverse effects from antidepressant treatment: randomised controlled trial of 601 depressed individuals. *Psychopharmacology*. 2014; 231, 2921-2931.

CHAPTER 5

CONCLUSION

Introduction

This chapter highlights the significant findings of the study; it gives a general conclusion drawn from the study, states the strengths and limitations and provides recommendations for future studies.

Vilazodone has several adverse effects, as listed in the PIL and known at the time of registration of the drug. However, being a relatively new drug, it is not clear if all adverse effects have been identified. It is therefore important to monitor for new or unknown adverse effects to improve and ensure the safety profile of the drug. This study was carried out to review the adverse effects of vilazodone using data of adverse events recorded on the PIDM site, VigiAccess. The study then went on to explore, in more detail the psychiatric adverse effects associated with vilazodone via a systematic review.

In order to achieve this, the following specific objectives were outlined:

- To identify and quantify the adverse effects associated with vilazodone reported in VigiAccess, according to organ systems.
- To compare the adverse effects reported in VigiAccess to the adverse effects indicated during the FDA approval process.
- To compare the adverse effects reported in VigiAccess to adverse effects indicated on the patient information leaflet for Viibryd®.
- To describe the psychiatric adverse effects associated with the use of vilazodone.

Conclusions drawn from the study findings based on each of the objectives

At the time of the data extraction, a total of 9708 adverse events had been recorded on VigiAccess of which 6054 of these adverse events were not listed on the patient information leaflet (PIL) of Viibryd® and FDA approval document. The highest percentage of adverse events not recorded in the PIL or FDA but reported in VigiAccess were for psychiatric disorders (19%; n=1181). This included anxiety (26%; n=316), depression (17%; n=208), hallucinations (14%; n=168) and agitation (12%, n=142).

Upon further exploration of psychiatric adverse effects associated with vilazodone, abnormal dreams, agitation, aggression or increased anger, aggravated depression, crying, anxiety, confusion, depersonalization, emotional numbing, sleep paralysis, suicidal ideation or attempt, irritability and mental status changes were found to be associated with the drug. Of these, the adverse drug reactions with the highest occurrence included abnormal dreams, depression and suicidal ideation.

Significance of the study

The study of the safety profile of any drug is a significant part of pharmacovigilance. Monitoring of the drug post-marketing is necessary as the safety of a drug may evolve over time as it is used by different populations. This study found several adverse drug reactions only being observed after clinical trials. More than half of the psychiatric adverse effects recorded on VigiAccess were not indicated on the PIL and FDA approval documentation, clearly indicating the need for continued monitoring of the safety aspects post-marketing. Post-marketing surveillance provides valuable information on the use of drugs in special patient populations as well as allows for the long-term monitoring of the effects of drugs. As a relatively new drug, it is important to monitor vilazodone's adverse effects in order to improve and ensure the safe prescribing of the drug.

Strengths

This study addresses a gap in the current knowledge by providing a comprehensive assessment of the psychiatric adverse effects which may influence the safe use of vilazodone as an antidepressant. The findings of this study can aid prescribers and other healthcare professionals to be aware of certain risks associated with the drug.

Data collection for this study was cost-effective as the data sets used in the study were obtained from research articles and the free database VigiAccess.

Limitations

This study was limited in its selection of databases and its restriction to English publications as this may cause a language bias. Differences among the study designs and sample characteristics restricted comparison of selected studies. Although an extensive review was covered, not all the literature obtained was relevant. Vilazodone was only approved by the FDA and put onto the market in 2011, therefore, not many clinical trials have been able to study its long-term efficacy and adverse effects. At present, there are very few articles published that

discuss the psychiatric adverse effects caused by vilazodone, that is why there is a need for post-marketing surveillance.

Recommendations

Prescribers and other healthcare professionals should take cognisance of psychiatric adverse effects associated with vilazodone that could affect treatment. This study highlights the need for continuous post-marketing surveillance of all, and specifically newer medicines. Continued surveillance improves the proper and safe use of medicines.

Chapter summary

The final chapter highlighted the conclusions drawn from the findings of the study, described the strengths and limitations of the study, as well as provided further recommendations.

ANNEXURES

ANNEXURE: 1

Waiver of ethical approval obtained from the School of Health Sciences, University of Kwa-Zulu-Natal

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

Dr Frasia Oosthuizen (11735)
School Of Health Sciences
Westville

Dear Dr Frasia Oosthuizen,

Protocol reference number: 00002022
Project title: Evaluating safety profiles of medication making use of VigiAccess

Exemption from Ethics Review

In response to your application received on 5 June 2019, your school has indicated that the protocol has been granted **EXEMPTION FROM ETHICS REVIEW.**

Any alteration/s to the exempted research protocol, e.g., Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through an amendment/modification prior to its implementation. The original exemption number must be cited.

For any changes that could result in potential risk, an ethics application including the proposed amendments must be submitted to the relevant UKZN Research Ethics Committee. The original exemption number must be cited.

In case you have further queries, please quote the above reference number.

PLEASE NOTE:
Research data should be securely stored in the discipline/department for a period of 5 years.

I take this opportunity of wishing you everything of the best with your study.

Yours sincerely,

Prof Pragashnie Govender
Academic Leader Research
School Of Health Sciences

ANNEXURE: 2

Cover page and confirmation for submission of manuscript: 1 to the Journal of Pharmacy Practice

Journal of Pharmacy Practice

The safety profile of vilazodone - a study on post-marketing surveillance.

Journal:	*Journal of Pharmacy Practice*
Manuscript ID	JPP-20-0211
Manuscript Type:	Original Manuscript
Keywords:	Drug Information, Internal Medicine, Medication Safety, Pharmacy Education
Abstract:	Background and Aim Vilazodone is a novel antidepressant having a selective serotonin (5-HT) reuptake inhibitor and 5-HT1A-receptor partial agonist profile. It was approved in 2011 by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder in adults. The aim of this study was to review the adverse effects of vilazodone reported post-marketing, in the database VigiAccess. Method Data on adverse effects reported for vilazodone was obtained from the database VigiAccess. VigiAccess provides an overview of international adverse drug reaction reports according to body systems. Data was extracted from VigiAccess using Excel□ and analysed using descriptive statistics. The data collected was compared to the patient information leaflet (PIL) of Viibryd® and the FDA documents to determine adverse drug reactions reported after marketing. Results A total of 9708 adverse events was recorded on VigiAccess of which 6054 were not recorded on the PIL and FDA approval document. Reports were received mainly from the Americas and adult women aged 45-64 years (24%, n=1059). The highest number of adverse events reported were for psychiatric events (19%; n=1889), followed by gastro-intestinal effects (18%; n=1839). The highest frequency of previously unrecorded adverse events was observed under psychiatric disorders (19%; n=1181) namely: anxiety (316), depression (208), hallucination (168) and agitation (142). Conclusion This study found several adverse drug reactions not recorded in documents emanating from clinical trials pre-marketing. It is therefore imperative that post-marketing surveillance continues for the duration of a drug's use to ensure safety.

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You have listed the following individuals as authors of this manuscript:
Kaja, Humraaz; Oosthuizen, Frasia; Mensah, Kofi

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ANNEXURE: 3

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  d. References (150 limit)
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  c. References (50 limit)

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- **Case Reports or Case Studies**
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  b. Keywords (5 keywords limit)
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7. Further information
Any correspondence, queries or additional requests for information on the manuscript submission process should be sent to the *JPP* editorial office as follows:

Henry Cohen, MS, PharmD, BCPP, BCGP
Editor in Chief, *JPP*
Tel: (718) 604-5373
Email: HCohenLIU@aol.com

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If an author believes the decision regarding their manuscript was affected by a publication ethics breach, the author may contact the publisher with a detailed written description of their concern, and information supporting the concern, at publication_ethics@sagepub.com

ANNEXURE: 4

Cover page and confirmation for submission of Systematic Review protocol submitted to BMJ Open.

BMJ Open

Psychiatric adverse effects associated with the use of Vilazodone: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039677
Article Type:	Protocol
Date Submitted by the Author:	23-Apr-2020
Complete List of Authors:	Kaja, Humraaz; University of KwaZulu-Natal College of Health Sciences, Pharmacy Mensah, Kofi; University of KwaZulu-Natal College of Health Sciences Michael, Henry; University of KwaZulu-Natal College of Health Sciences Oosthuizen, Frasia; University of KwaZulu-Natal College of Health Sciences, Discipline of Pharmaceutical Sciences
Keywords:	CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Depression & mood disorders < PSYCHIATRY, PSYCHIATRY

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to me, kofimensah227, 219060765, Oosthuizenf

COVID-19: A message from BMJ: https://authors.bmj.com/policies/covid-19

23-Apr-2020

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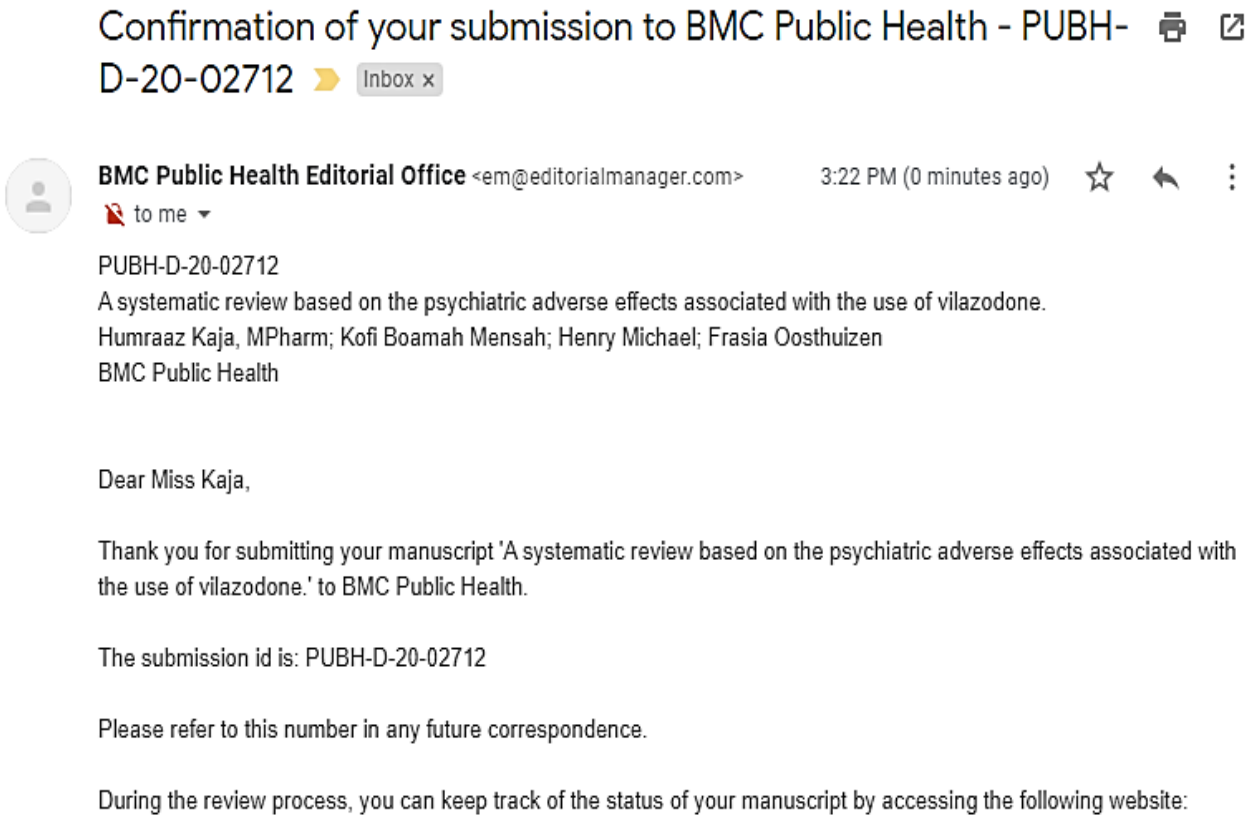
Your manuscript entitled "Psychiatric adverse effects associated with the use of Vilazodone: a systematic review protocol" has been successfully submitted online and is presently being given full consideration for publication in BMJ Open.

Your manuscript ID is bmjopen-2020-039677.

ANNEXURE: 5

Confirmation for submission of Systematic Review manuscript 4 submitted to BMC Public Health.



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PUBH-D-20-02712
A systematic review based on the psychiatric adverse effects associated with the use of vilazodone.
Humraaz Kaja, MPharm; Kofi Boamah Mensah; Henry Michael; Frasia Oosthuizen
BMC Public Health

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ANNEXURE: 6

Submission guidelines for BMC Public Health

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies: a description of what the article reports
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the article, its aims, a summary of a search of the existing literature and the issue under discussion.

Main text

This should contain the body of the article, and may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions and include an explanation of their relevance or importance to the field.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

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All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

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2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

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Acknowledgements

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Smith JJ. The world of science. Am J Sci. 1999; 36:234-5.

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Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Medicine. 2013; 11:63.

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Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database.
2011. http://dx.doi.org/10.5524/100012.

APPENDICES

APPENDIX: 1

NEW ADVERSE DRUG REACTIONS OF VILAZODONE NOT PRESENT IN THE FDA AND PIL

BODY SYSTEM	
Blood and lymphatic system disorders	**Number of incidences reported (17)**
Anaemia	6
Lymphadenopathy	6
Blood disorder	1
Increased tendency to bruise	1
Splenic vein thrombosis	1
Splenomegaly	1
Thrombocytopenia	1
Number of previously unreported ADRs – 7 Most common unreported ADR's- Anaemia and Lymphadenopathy	

Cardiac disorders	**Number of incidences reported (168)**
Palpitations #	115
Tachycardia	16
Atrial fibrillation	7
Myocardial infarction	7
Ventricular extrasystoles #	5
Arrhythmia	4
Cardiac disorder	4
Supraventricular tachycardia	4
Cardio-respiratory arrest	3
Angina pectoris	2
Atrial flutter	2
Cardiac failure congestive	2
Atrioventricular block	1
Cardiac arrest	1
Cardiac discomfort	1
Cardiomegaly	1
Cor pulmonale	1
Coronary artery occlusion	1

Cyanosis	1
Extrasystoles	1
Foetal heart rate deceleration abnormality	1
Long QT syndrome	1
Sinus bradycardia	1
Stress cardiomyopathy	1
Supraventricular extrasystoles	1
Wolff-Parkinson-White syndrome	1

Number of previously unreported ADRs – 24

Most common unreported ADR's- Tachycardia

Ear and labyrinth disorders	**Number of incidences reported (84)**
Tinnitus	48
Vertigo	25
Ear discomfort	4
Auditory disorder	2
Deafness	2
Ear pain	1
Hyperacusis	1
Hypoacusis	1
Meniere's disease	1
Number of previously unreported ADRs – 9 Most common unreported ADR's- Tinnitus and Vertigo	
Endocrine disorders	**Number of incidences reported (8)**
Hyperthyroidism	2
Inappropriate antidiuretic hormone secretion	2
Adrenocortical insufficiency acute	1
Autoimmune thyroiditis	1
Hyperprolactinaemia	1
Hypothyroidism	1
Number previously unreported ADRs – 6 Most common unreported ADR's- Hyperthyroidism	

Eye disorders	Number of incidences reported (164)
Vision blurred	69
Visual impairment	19
Dry eye	13
Eye swelling	9
Lacrimation increased	8
Eye pain	7
Ocular hyperaemia	7
Eye pruritus	6
Asthenopia	5
Blindness transient	5
Eye movement disorder	5
Mydriasis	5
Abnormal sensation in eye	4
Blepharospasm	4
Eye irritation	4
Photopsia	4
Eye disorder	3
Photophobia	3
Visual acuity reduced	3
Cataract	2
Diplopia	2
Dyschromatopsia	2
Eyelid oedema	2
Ocular discomfort	2
Vitreous detachment	2
Altered visual depth perception	1
Angle closure glaucoma	1
Blepharitis	1
Blindness	1
Blindness unilateral	1

Chromatopsia	1
Conjunctival haemorrhage	1
Contact lens intolerance	1
Dark circles under eyes	1
Episcleritis	1
Exophthalmos	1
Eye discharge	1
Foreign body sensation in eyes	1
Halo vision	1
Lid sulcus deepened	1
Miosis	1
Night blindness	1
Periorbital oedema	1
Strabismus	1
Swelling of eyelid	1
Visual brightness	1
Vitreous floaters	1
Number of previously unreported ADRs – 47 Most common unreported ADR's- Vision blurred	
Gastrointestinal disorders	**Number of incidences reported (1839)**
Diarrhoea #*	582
Nausea #*	477
Vomiting #*	140
Abdominal pain upper #	75
Abdominal discomfort #	74
Abdominal pain #	47
Dry mouth #	47
Abdominal distension #	38
Flatulence	33
Dyspepsia	28
Constipation	26

Gastrointestinal disorder	20
Gastrooesophageal reflux disease	17
Haematochezia	11
Rectal haemorrhage	11
Frequent bowel movements	10
Swollen tongue	10
Pancreatitis	8
Gastritis	7
Lip swelling	6
Anal incontinence	5
Irritable bowel syndrome	5
Stomatitis	5
Tongue disorder	5
Diarrhoea haemorrhagic	4
Eructation	4
Gastric disorder	4
Gastrointestinal sounds abnormal	4
Haemorrhoids	4
Hypoaesthesia oral	4
Pancreatitis acute	4
Abdominal pain lower	3
Haematemesis	3
Retching	3
Abnormal faeces	2
Colitis	2
Defaecation urgency	2
Dysphagia	2
Faeces discoloured	2
Gastrointestinal haemorrhage	2
Malabsorption	2
Oedema mouth	2
Oral disorder	2

Paraesthesia oral	2
Proctitis ulcerative	2
Salivary hypersecretion	2
Tooth loss	2
Toothache	2
Anal sphincter atony	1
Anorectal disorder	1
Aptyalism	1
Change of bowel habit	1
Coating in mouth	1
Colitis ulcerative	1
Crohn's disease	1
Dental discomfort	1
Duodenitis	1
Epigastric discomfort	1
Erosive duodenitis	1
Faeces soft	1
Food poisoning	1
Gastric ulcer	1
Gastrointestinal hypomotility	1
Gastrointestinal motility disorder	1
Gastrointestinal pain	1
Gastrointestinal tract irritation	1
Gingival bleeding	1
Gingival pain	1
Glossodynia	1
Hiatus hernia	1
Impaired gastric emptying	1
Inflammatory bowel disease	1
Infrequent bowel movements	1
Lip disorder	1
Lip exfoliation	1

Lip pain	1
Lip ulceration	1
Melaena	1
Mouth ulceration	1
Mucous stools	1
Noninfective gingivitis	1
Oesophagitis	1
Oral discomfort	1
Oral mucosal eruption	1
Pancreatic pseudocyst	1
Peptic ulcer	1
Plicated tongue	1
Small intestinal haemorrhage	1
Tongue oedema	1
Tongue spasm	1
Tooth deposit	1
Tooth discolouration	1
Aptyalism	1
Change of bowel habit	1
Coating in mouth	1
Colitis ulcerative	1
Crohn's disease	1
Dental discomfort	1
Duodenitis	1
Epigastric discomfort	1
Erosive duodenitis	1
Faeces soft	1
Food poisoning	1
Gastric ulcer	1
Gastrointestinal hypomotility	1
Gastrointestinal motility disorder	1
Gastrointestinal pain	1

Gastrointestinal tract irritation	1
Gingival bleeding	1
Gingival pain	1
Glossodynia	1
Hiatus hernia	1
Impaired gastric emptying	1
Inflammatory bowel disease	1
Infrequent bowel movements	1
Lip disorder	1
Lip exfoliation	1
Lip pain	1
Lip ulceration	1
Melaena	1
Mouth ulceration	1
Mucous stools	1
Noninfective gingivitis	1
Oesophagitis	1
Oral discomfort	1
Oral mucosal eruption	1
Pancreatic pseudocyst	1
Peptic ulcer	1
Plicated tongue	1
Small intestinal haemorrhage	1
Tongue oedema	1
Tongue spasm	1
Tooth deposit	1
Tooth discolouration	1
Vomiting projectile	1
Number of previously unreported ADR's- 359 Most common unreported ADR's- Flatulence and Dyspepsia	

General disorders and administration site conditions	Number of incidences reported (1134)
Feeling abnormal	239
Drug ineffective	199
Fatigue #	157
Crying	102
Asthenia	72
Malaise	71
Feeling jittery	53
Pain	52
Unevaluable event	42
Drug interaction	37
Gait disturbance	33
Chest pain	32
Withdrawal syndrome	32
Condition aggravated	26
Oedema peripheral	26
Chest discomfort	24
Pyrexia	24
Death	21
Feeling hot	21
Drug withdrawal syndrome	20
Influenza like illness	19
Chills	18
Therapeutic response unexpected	18
Energy increased	14
Oedema	13
Screaming	12
Therapeutic product effect increased	12
Feeling cold	10
Swelling	10
Therapeutic product effect decreased	10

Adverse event	9
Therapeutic response decreased	8
Adverse drug reaction	7
Peripheral swelling	7
Sluggishness	7
Discomfort	6
Drug intolerance	6
Gait inability	6
Drug ineffective for unapproved indication	5
No adverse event	5
Feeling drunk	4
Hunger	4
Thirst	4
Inflammation	3
Nonspecific reaction	3
Temperature intolerance	3
Therapeutic product effect incomplete	3
Therapy non-responder	3
Adverse reaction	2
Disease recurrence	2
Face oedema	2
Hangover	2
Ill-defined disorder	2
Mucosal dryness	2
Potentiating drug interaction	2
Pre-existing condition improved	2
Apparent death	1
Axillary pain	1
Chronic disease	1
Cyst	1
Drug resistance	1
Exercise tolerance decreased	1

Impaired self-care	1
Inflammatory pain	1
Injection site pain	1
Localised oedema	1
Loss of control of legs	1
Multiple organ dysfunction syndrome	1
Polyp	1
Secretion discharge	1
Sensation of foreign body	1
Therapeutic product effective for unapproved indication	1
Therapeutic response changed	1
Thirst decreased	1
Treatment noncompliance	1
Ulcer	1
Number of previously unreported ADR's-977 Most common unreported ADR's- Feeling abnormal, ineffective drug and crying	

Hepatobiliary disorders	**Number of incidences reported (17)**
Hepatitis	3
Gallbladder disorder	2
Jaundice	2
Liver disorder	2
Acute hepatic failure	1
Autoimmune hepatitis	1
Cholecystitis	1
Cholecystitis acute	1
Cholelithiasis	1
Drug-induced liver injury	1
Hepatic failure	1
Hepatic steatosis	1

Number of previously unreported ADR's – 17 Most common unreported ADR's- Hepatitis	
Immune system disorders	**Number of incidences reported (56)**
Drug hypersensitivity	28
Hypersensitivity	21
Anaphylactic reaction	3
Anaphylactic shock	2
Allergy to plants	1
Mycotic allergy	1
Number of previously unreported ADR's – 56 Most common unreported ADR's- Drug hypersensitivity	
Infections and infestations	**Number of incidences reported (60)**
Sinusitis	8
Influenza	6
Urinary tract infection	5
Bronchitis	4
Nasopharyngitis	4
Pneumonia	4
Herpes zoster	3
Kidney infection	3
Viral infection	3
Vulvovaginal mycotic infection	3
Cystitis	2
Gastroenteritis	2
Infection	2
Abdominal abscess	1
Abscess	1
Abscess limb	1
Ear infection	1
Eye infection	1

Fungal infection	1
Fungal skin infection	1
Gastroenteritis viral	1
Gingivitis	1
Hepatitis B	1
Herpes virus infection	1
Mastitis	1
Mastoiditis	1
Oral candidiasis	1
Oral herpes	1
Pyuria	1
Rash pustular	1
Staphylococcal infection	1
Streptococcal infection	1
Subcutaneous abscess	1
Tooth abscess	1
Tooth infection	1
Upper respiratory tract infection	1
Urethritis	1
Number of previously unreported ADR's – 60 Most common unreported ADR's- Sinusitis and Influenza	
Injury, poisoning and procedural complications	**Number of incidences reported (862)**
Off label use	438
Product dose omission	74
Intentional product misuse	54
Wrong technique in product usage process	51
Contusion	39
Fall	31
Intentional overdose	30
Overdose	24
Expired product administered	22

Incorrect dose administered	19
Medication error	18
Inappropriate schedule of product administration	14
Toxicity to various agents	14
Product prescribing error	13
Accidental overdose	12
Product use issue	10
Road traffic accident	10
Accidental exposure to product	9
Prescribed overdose	9
Gun shot wound	6
Head injury	6
Intentional dose omission	6
Drug titration error	5
Accidental exposure to product by child	4
Concussion	4
Exposure during pregnancy	4
Intentional product use issue	4
Skin laceration	4
Ankle fracture	3
Joint injury	3
Product dispensing error	3
Scar	3
Scratch	3
Wrong product administered	3
Accident	2
Discontinued product administered	2
Electric shock	2
Incorrect dosage administered	2
Ligament sprain	2
Maternal exposure during breast feeding	2
Product administration error	2

Product use in unapproved indication	2
Rib fracture	2
Sunburn	2
Tooth fracture	2
Arthropod bite	1
Back injury	1
Bite	1
Chemical poisoning	1
Contraindicated product administered	1
Contraindicated product prescribed	1
Corneal abrasion	1
Craniocerebral injury	1
Depression postoperative	1
Drug dose titration not performed	1
Extra dose administered	1
Fibula fracture	1
Foot fracture	1
Heat exhaustion	1
Hip fracture	1
Hypobarism	1
Incorrect product administration duration	1
Incorrect route of product administration	1
Injury	1
Intercepted product prescribing error	1
Labelled drug-drug interaction medication error	1
Maternal exposure during pregnancy	1
Multiple fractures	1
Nerve injury	1
Poisoning	1
Procedural complication	1
Product name confusion	1
Product preparation error	1

Skin abrasion	1
Skin wound	1
Thermal burn	1
Underdose	1
Upper limb fracture	1
Wrong patient received product	1
Number of previously unreported ADR's – 862 Most common unreported ADR's- Off label use and product dose omission	
Investigations	**Number of incidences reported (421)**
Weight increased #	141
Blood pressure increased	66
Heart rate increased	40
Blood glucose increased	38
Weight decreased	38
Blood pressure decreased	9
Blood glucose decreased	8
Drug screen positive	8
Heart rate irregular	7
Hepatic enzyme increased	7
Blood cholesterol increased	6
Drug screen false positive	6
Alanine aminotransferase increased	5
Body temperature increased	5
International normalised ratio increased	5
Blood triglycerides increased	4
Haemoglobin decreased	4
Heart rate decreased	4
Aspartate aminotransferase increased	3
Blood creatine phosphokinase increased	3
Blood creatinine increased	3
Blood potassium decreased	3

Blood sodium decreased	3
Electrocardiogram abnormal	3
Glycosylated haemoglobin increased	3
Platelet count decreased	3
Blood glucose fluctuation	2
Blood urea increased	2
Blood urine present	2
C-reactive protein increased	2
Electrocardiogram QT prolonged	2
Hepatic enzyme abnormal	2
Liver function test abnormal	2
Oxygen saturation decreased	2
Prostatic specific antigen increased	2
Respiratory rate increased	2
Urine output decreased	2
White blood cell count decreased	2
Vitamin B12 decreased	2
Vitamin D decreased	2
Amphetamines positive	1
Bleeding time prolonged	1
Blood alkaline phosphatase abnormal	1
Blood alkaline phosphatase increased	1
Blood bilirubin abnormal	1
Blood bilirubin increased	1
Blood calcium abnormal	1
Blood calcium decreased	1
Blood chloride decreased	1
Blood count abnormal	1
Blood electrolytes decreased	1
Blood iron decreased	1
Blood magnesium	1
Blood oestrogen increased	1

Blood potassium increased	1
Blood pressure abnormal	1
Blood pressure measurement	1
Blood pressure systolic increased	1
Blood testosterone increased	1
Blood thyroid stimulating hormone decreased	1
Body temperature abnormal	1
Cortisol decreased	1
CSF pressure increased	1
Electrocardiogram	1
Electrocardiogram change	1
Electrocardiogram T wave amplitude decreased	1
Glomerular filtration rate decreased	1
Haematocrit increased	1
Hepatic enzyme	1
Intraocular pressure increased	1
JC polyomavirus test positive	1
Laboratory test abnormal	1
Liver function test increased	1
pH urine increased	1
Pulse abnormal	1
Quality of life decreased	1
Red blood cell count decreased	1
Red blood cell sedimentation rate increased	1
Respiratory rate decreased	1
Toxicologic test abnormal	1
Ultrasound antenatal screen abnormal	1
Urine amphetamine positive	1
Number of previously unreported ADR's – 421 Most common unreported ADR's- Blood pressure and heart rate increased	
Metabolism and nutrition disorders	**Number of incidences reported (157)**

Decreased appetite #	58
Increased appetite #	38
Hyponatraemia	14
Dehydration	9
Food craving	6
Fluid retention	4
Hyperglycaemia	4
Diabetes mellitus	3
Hypokalaemia	3
Hypophagia	3
Appetite disorder	2
Cardiometabolic syndrome	2
Diabetes mellitus inadequate control	2
Diabetic ketoacidosis	2
Feeding disorder	2
Hypoglycaemia	2
Lactose intolerance	2
Abnormal loss of weight	1
Abnormal weight gain	1
Fluid overload	1
Glucose tolerance impaired	1
Gout	1
Hyperkalaemia	1
Hyperphagia	1
Malnutrition	1
Metabolic acidosis	1
Obesity	1
Weight fluctuation	1
Weight loss poor	1
Vitamin D deficiency	1
Number of previously unreported ADR's – 61 Most common unreported ADR's- Hyponatremia	

Musculoskeletal and connective tissue disorders	Number of incidences reported (343)
Muscle spasms	73
Arthralgia #	64
Muscle twitching	58
Myalgia	50
Pain in extremity	44
Musculoskeletal stiffness	36
Back pain	17
Muscular weakness	15
Joint swelling	14
Muscle tightness	13
Musculoskeletal pain	8
Joint stiffness	7
Neck pain	6
Fibromyalgia	5
Muscle rigidity	5
Musculoskeletal discomfort	5
Pain in jaw	5
Arthritis	3
Mobility decreased	3
Tendon pain	3
Extremity contracture	2
Flank pain	2
Intervertebral disc protrusion	2
Joint noise	2
Rhabdomyolysis	2
Rheumatoid arthritis	2
Spinal stenosis	2
Arthritis enteropathic	1
Arthropathy	1
Bone disorder	1

Bone pain	1
Finger deformity	1
Foot deformity	1
Groin pain	1
Jaw disorder	1
Joint range of motion decreased	1
Limb discomfort	1
Muscle atrophy	1
Muscle disorder	1
Muscle fatigue	1
Musculoskeletal chest pain	1
Musculoskeletal disorder	1
Myositis	1
Polyarthritis	1
Scoliosis	1
Spinal disorder	1
Systemic lupus erythematosus	1
Temporomandibular joint syndrome	1
Tendonitis	1
Number of previously unreported ADR's-343 Most common unreported ADR's- Muscle twitching and muscle spasms	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Number of incidences reported (13)**
Neoplasm malignant	2
Renal cancer	2
Thyroid cancer	2
Bladder cancer	1
Breast cancer stage IV	1
Hepatic neoplasm	1
Juvenile melanoma benign	1
Lung neoplasm malignant	1

Melanocytic naevus	1
Neoplasm skin	1
Number of previously unreported ADR's – 13	

Nervous system disorders	**Number of incidences reported (1433)**
Dizziness #	298
Headache #	288
Paraesthesia #	246
Tremor #	144
Somnolence #	136
Serotonin syndrome	82
Seizure	72
Amnesia	53
Memory impairment	51
Hypoaesthesia	48
Sleep paralysis #*	47
Loss of consciousness	44
Migraine #	42
Lethargy	38
Disturbance in attention	35
Restless legs syndrome	33
Balance disorder	24
Speech disorder	24
Dyskinesia	23
Syncope	21
Generalised tonic-clonic seizure	18
Burning sensation	17
Dysgeusia	15
Hypersomnia	13
Movement disorder	13
Psychomotor hyperactivity	13

Cognitive disorder	12
Coordination abnormal	12
Sensory disturbance	12
Paralysis	11
Dysarthria	10
Mental impairment	10
Sedation	10
Ageusia	9
Formication	8
Head discomfort	8
Poor quality sleep	8
Aphasia	7
Nervous system disorder	7
Akathisia	6
Cerebrovascular accident	6
Anosmia	5
Dystonia	5
Hyperreflexia	5
Cerebral disorder	4
Cerebral haemorrhage	4
Clumsiness	4
Neuroleptic malignant syndrome	4
Partial seizures	4
Petit mal epilepsy	4
Altered state of consciousness	3
Dysstasia	3
Encephalopathy	3
Hypokinesia	3
Judgement impaired	3
Neuralgia	3
Parkinsonism	3
Parosmia	3

Presyncope	3
Slow speech	3
Tension headache	3
Tunnel vision	3
Aura	2
Cerebral infarction	2
Cold-stimulus headache	2
Depressed level of consciousness	2
Drooling	2
Epilepsy	2
Extrapyramidal disorder	2
Facial paralysis	2
Hyposmia	2
Incoherent	2
Motor dysfunction	2
Muscle spasticity	2
Myoclonus	2
Parkinsonian rest tremor	2
Seizure like phenomena	2
Tardive dyskinesia	2
Visual field defect	2
Ataxia	1
Brain injury	1
Burning feet syndrome	1
Carpal tunnel syndrome	1
Cataplexy	1
Chronic inflammatory demyelinating polyradiculoneuropathy	1
Clonus	1
Coma	1
Cranial nerve disorder	1
Dementia	1

Dizziness postural	1
Dreamy state	1
Dysgraphia	1
Epileptic aura	1
Guillain-Barre syndrome	1
Haemorrhage intracranial	1
Head titubation	1
Hemiparesis	1
Hypertonia	1
Hypogeusia	1
Language disorder	1
Migraine with aura	1
Monoplegia	1
Multiple sclerosis	1
Muscle contractions involuntary	1
Neuritis	1
Neuropathy peripheral	1
Nystagmus	1
Olfactory nerve disorder	1
Paraparesis	1
Paraplegia	1
Parkinson's disease	1
Resting tremor	1
Sciatica	1
Sinus headache	1
Slow response to stimuli	1
Status epilepticus	1
Stupor	1
Subarachnoid haemorrhage	1
Tongue biting	1
Transient ischaemic attack	1
Unresponsive to stimuli	1

Number of previously unreported ADR's – 232 Most common unreported ADR's- Serotonin syndrome and Seizures	
Pregnancy, puerperium and perinatal conditions	**Number of incidences reported (5)**
Abortion spontaneous	2
Foetal death	2
Pregnancy	1
Number of previously unreported ADR's – 5	
Product issues	**Number of incidences reported (13)**
Product substitution issue	4
Product quality issue	3
Failure of child resistant mechanism for pharmaceutical product	1
Product formulation issue	1
Product label issue	1
Product lot number issue	1
Product physical issue	1
Product taste abnormal	1
Number of previously unreported ADR's – 13	
Psychiatric disorders	**Number of incidences reported (1889)**
Insomnia #*	455
Anxiety	316
Depression	208
Suicidal ideation	205
Hallucination	168
Agitation	142
Abnormal dreams #	126
Nightmare	121
Irritability	107
Confusional state	96
Panic attack #	85

Anger	77
Mania	70
Aggression	61
Suicide attempt	57
Nervousness	55
Completed suicide	52
Restlessness #	42
Paranoia	39
Disorientation	33
Hallucination, auditory	33
Sleep terror	31
Hallucination, visual	29
Abnormal behaviour	26
Depressed mood	26
Mood swings	26
Psychotic disorder	24
Thinking abnormal	24
Sleep disorder	23
Libido decreased	22
Tachyphrenia	21
Fear	19
Mood altered	19
Stress	19
Emotional disorder	17
Mental status changes	14
Middle insomnia	13
Hypomania	12
Mental disorder	12
Anorgasmia	11
Apathy	11
Intentional self-injury	10
Tearfulness	10

Initial insomnia	9
Bruxism	8
Hallucinations, mixed	8
Hypnagogic hallucination	8
Impulsive behaviour	8
Terminal insomnia	8
Violence-related symptom	8
Affect lability	7
Decreased interest	7
Delirium	7
Euphoric mood	7
Hostility	7
Personality change	7
Suicidal behaviour	7
Emotional distress	6
Logorrhoea	6
Morbid thoughts	6
Obsessive-compulsive disorder	6
Somnambulism	6
Affective disorder	5
Drug dependence	5
Loss of libido	5
Panic reaction	5
Bradyphrenia	4
Delusion	4
Dissociation	4
Dysphemia	4
Feeling of despair	4
Homicidal ideation	4
Libido increased	4
Obsessive thoughts	4
Panic disorder	4

Rapid eye movements sleep abnormal	4
Tension	4
Bipolar disorder	3
Derealisation	3
Impulse-control disorder	3
Negative thoughts	3
Social avoidant behaviour	3
Tic	3
Abnormal sleep-related event	2
Anxiety disorder	2
Communication disorder	2
Confabulation	2
Conversion disorder	2
Daydreaming	2
Dependence	2
Disturbance in sexual arousal	2
Eating disorder	2
Fear of death	2
Female orgasmic disorder	2
Flashback	2
Head banging	2
Hypervigilance	2
Impatience	2
Listless	2
Major depression	2
Male orgasmic disorder	2
Obsessive-compulsive symptom	2
Orgasm abnormal	2
Self esteem decreased	2
Staring	2
Acute stress disorder	1
Agoraphobia	1

Alcoholism	1
Arachnophobia	1
Autoscopy	1
Binge drinking	1
Change in sustained attention	1
Compulsive cheek biting	1
Delusional disorder, unspecified type	1
Depressive symptom	1
Dermatillomania	1
Disinhibition	1
Dissociative amnesia	1
Dissociative disorder	1
Dysphoria	1
Enuresis	1
Excessive sexual fantasies	1
Fear of disease	1
Flat affect	1
Frustration tolerance decreased	1
Grandiosity	1
Hallucination, gustatory	1
Hallucination, tactile	1
Helplessness	1
Illusion	1
Loss of dreaming	1
Merycism	1
Onychophagia	1
Orgasmic sensation decreased	1
Parasomnia	1
Performance fear	1
Phobia of driving	1
Premature ejaculation	1
Psychogenic seizure	1

Psychomotor retardation	1
Psychotic behaviour	1
Self-injurious ideation	1
Sexually inappropriate behaviour	1
Sleep talking	1
Substance-induced psychotic disorder	1
Number of previously unreported ADR's – 1181 Most common unreported ADR's- Anxiety, Depression, Suicidal ideation, Hallucination and Agitation	
Renal and urinary disorders	**Number of incidences reported (70)**
Pollakiuria	14
Urinary retention	7
Dysuria	6
Urinary hesitation	6
Incontinence	5
Urinary incontinence	5
Acute kidney injury	2
Bladder discomfort	2
Bladder irritation	2
Chromaturia	2
Haematuria	2
Nephrolithiasis	2
Nocturia	2
Renal disorder	2
Renal failure	2
Bladder spasm	1
Glomerulonephritis	1
Micturition disorder	1
Micturition frequency decreased	1
Micturition urgency	1
Renal pain	1
Urinary bladder haemorrhage	1

Urine flow decreased	1
Urine odour abnormal	1
Number of previously unreported ADR's – 70 Most common unreported ADR's- Pollakiuria	
Reproductive system and breast disorders	**Number of incidences reported (125)**
Sexual dysfunction #	34
Erectile dysfunction #	14
Vaginal haemorrhage	10
Priapism	6
Menorrhagia	5
Metrorrhagia	5
Ejaculation failure #	4
Menstruation irregular	4
Breast tenderness	3
Ejaculation delayed	2
Menopausal symptoms	2
Penile haemorrhage	2
Polymenorrhoea	2
Premenstrual syndrome	2
Spontaneous penile erection	2
Vulvovaginal dryness	2
Amenorrhoea	1
Breast atrophy	1
Breast discharge	1
Breast enlargement	1
Breast swelling	1
Dysmenorrhoea	1
Ejaculation disorder	1
Endometriosis	1
Infertility	1
Menometrorrhagia	1

Menstrual disorder	1
Menstruation delayed	1
Ovarian enlargement	1
Ovulation disorder	1
Pelvic pain	1
Penile size reduced	1
Penis disorder	1
Peyronie's disease	1
Prostatomegaly	1
Semen discolouration	1
Testicular pain	1
Uterine pain	1
Vaginal discharge	1
Vulvovaginal burning sensation	1
Vulvovaginal pain	1
Number of previously unreported ADR's – 73	
Respiratory, thoracic and mediastinal disorders	**Number of incidences reported (151)**
Dyspnoea	63
Cough	15
Pulmonary embolism	7
Epistaxis	6
Oropharyngeal pain	6
Asthma	5
Respiratory disorder	5
Sleep apnoea syndrome	5
Throat tightness	5
Aspiration	4
Dysphonia	4
Nasal congestion	4
Asphyxia	3
Haemoptysis	3

Lung disorder	3
Pharyngeal oedema	3
Rhinorrhoea	3
Sneezing	3
Choking sensation	2
Dry throat	2
Hyperventilation	2
Nasal pruritus	2
Pulmonary hypertension	2
Respiratory tract congestion	2
Acute respiratory failure	1
Apnoea	1
Apparent life threatening event	1
Bronchospasm	1
Choking	1
Dyspnoea exertional	1
Hiccups	1
Hypopnoea	1
Hypoxia	1
Laryngospasm	1
Nasal dryness	1
Oropharyngeal discomfort	1
Pharyngeal disorder	1
Pneumonia aspiration	1
Productive cough	1
Pulmonary mass	1
Pulmonary oedema	1
Reflux laryngitis	1
Respiratory failure	1
Sinus congestion	1
Throat irritation	1
Yawning	1

Number of previously unreported ADR's – 151 Most common unreported ADR's- Dyspnoea	
Skin and subcutaneous tissue disorders	**Number of incidences reported (552)**
Hyperhidrosis #	96
Pruritus	84
Alopecia	68
Rash	68
Night sweats #	31
Urticaria	25
Pruritus generalised	19
Swelling face	18
Acne	15
Cold sweat	11
Erythema	9
Rash pruritic	8
Psoriasis	7
Rash generalised	6
Skin exfoliation	6
Angioedema	4
Blister	4
Eczema	4
Photosensitivity reaction	4
Rash erythematous	4
Skin burning sensation	4
Madarosis	3
Petechiae	3
Rash macular	3
Rash maculo-papular	3
Skin discolouration	3
Dermatitis contact	2
Dry skin	2

Mechanical urticaria	2
Onychoclasis	2
Scab	2
Seborrhoea	2
Skin reaction	2
Skin tightness	2
Stevens-Johnson syndrome	2
Sweat gland disorder	2
Acne cystic	1
Dilated pores	1
Drug eruption	1
Hair colour changes	1
Hair disorder	1
Hair texture abnormal	1
Nail discolouration	1
Nail disorder	1
Onychomadesis	1
Pigmentation disorder	1
Piloerection	1
Rash papular	1
Sebaceous glands overactivity	1
Skin depigmentation	1
Skin disorder	1
Skin odour abnormal	1
Skin texture abnormal	1
Skin ulcer	1
Skin warm	1
Telangiectasia	1
Trichorrhexis	1
Number of previously unreported ADR's – 679 Most common unreported ADR's- Pruritus, Alopecia and Rash	
Social circumstances	Number of incidences reported (46)

Loss of personal independence in daily activities	11
Impaired driving ability	8
Impaired work ability	8
Alcohol use	2
Economic problem	2
Homicide	2
Child abuse	1
Disability	1
Drug abuser	1
Impaired quality of life	1
Imprisonment	1
Job dissatisfaction	1
Legal problem	1
Loss of employment	1
Marital problem	1
Physical assault	1
Refusal of treatment by patient	1
Theft	1
Unemployment	1
Walking aid user	1
Walking disability	1
Number of previously unreported ADR's – 46	
Surgical and medical procedures	**Number of incidences reported (21)**
Therapy cessation	5
Surgery	4
Therapy change	3
Brain operation	2
Gastric bypass	1
Hospitalisation	1
Knee arthroplasty	1
Knee operation	1
Spinal operation	1

Steroid therapy	1
Vasodilation procedure	1
Number of previously unreported ADR's – 21	
Vascular disorders	**Number of incidences reported (93)**
Hypertension	26
Hot flush	18
Flushing	15
Hypotension	12
Haemorrhage	6
Shock	4
Thrombosis	3
Deep vein thrombosis	2
Hypertensive crisis	2
Peripheral coldness	2
Angiopathy	1
Arterial occlusive disease	1
Blood pressure fluctuation	1
Circulatory collapse	1
Iliac artery rupture	1
Pallor	1
Phlebitis	1
Shock symptom	1
Varicose vein	1
Number of previously unreported ADR's – 93 Most common unreported ADR's- Hypertension	

Total number previously unreported ADR's - 6054

KEY:

#- Adverse drug reaction listed in the FDA only

*- Adverse drug reaction listed in the PIL only

APPENDIX: 2

Search Record Tool

ELECTRONIC SEARCH RECORD			
DATE	KEYWORD SEARCHED	SEARCH ENGINE USED	NO OF PUBLICATIONS RETRIEVED

APPENDIX 3

The PICOS framework will be used for the determination of eligible studies for the primary research question.

P - Participant/ Population:	Adolescents aged >12 and adults aged >18 years who reported psychiatric adverse effects with the use of Vilazodone
I – Intervention(s), exposure(s):	Vilazodone irrespective of dose and duration
C- Comparator(s)/Control:	There may be studies comparing psychiatric adverse effects and outcomes with vilazodone and other antidepressants
O- Outcome(s):	Psychiatric adverse effects caused with the use of vilazodone
S – Study design:	Randomized and controlled trials (RCTs), prospective and retrospective cohort studies, cross-sectional, case series, case reports of vilazodone, and comparisons of psychiatric side effects of vilazodone with other antidepressants and its effect on mental health.

APPENDIX: 4

Search strategy

ELECTRONIC SEARCH RECORD			
Date	**Keyword searched**	**Search engine used**	**Number of publications received**
26/03/20	[(Vilazodone OR Viibryd) AND (5HT1A partial agonists OR antidepressants or SSRIs) AND (Depression, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion)	Pubmed (Medline)	**41**
27/03/20	[(Vilazodone OR Viibryd) AND (5HT1A partial agonists OR antidepressants or SSRIs) AND (Depression, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion)	Wiley Online Library	**35**
27/03/20	[(Vilazodone OR Viibryd) AND (5HT1A partial agonists OR antidepressants or SSRIs) AND (Depression, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion)	Taylor and Francis Online	**21**

27/03/20	[(Vilazodone OR Viibryd) AND (5HT1A partial agonists OR antidepressants or SSRIs) AND (Depression, psychiatric disturbances, mental disorders, anxiety, depression, crying, sleep paralysis, and confusion)	Pysch Info	**5**

APPENDIX: 5

Psychiatric adverse effects listed according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) (Le Noury, et al., 2015).

Psychiatric adverse effect	Description
Abnormal dreams	vivid, unusual, unpleasant, strange, or bad dreams; nightmares or night terrors
Aggression	increased anger
Anger or easily angered	rage, violence, bad temper, hostile, aggressive
Aggravated depression and crying	new, worsened, or deepened depression, sadness, crying spells, uncontrollable crying or tearfulness
Agitation	irritable, tense, agitated, on edge, little patience or tolerance for others
Akathisia	restlessness, akathisia, can't stop moving, feel like jumping out of my skin
Anxiety	new, worsened anxiety, panic attacks
Low concentration	inability to concentrate or focus, difficulty completing tasks
Confusion	disoriented, fog, brain fog, fuzziness, cloudy, feeling lost or confused, disoriented, lacking ability to think or process
Depersonalization	feeling spacy or dazed, "out of it," "not like myself," stoned or drugged, zombie-like, separated from reality, detached from my body, unreal disinhibition
Impulsivity	risk-taking, poor judgment, irrational decisions, reduced self-control, and impulsive, out of character behaviour
Emotional instability	emotional rollercoaster, feeling "bipolar," moody or mood swings, meltdowns, "spazzy," highly unstable emotions
Emotional numbing	mentally or emotionally numb, unable to feel emotional highs or lows, lack of interest in people or activities, apathetic, "don't care" attitude, "I feel nothing," emotionally dead or flat, socially withdrawn
Hopelessness	feeling of hopelessness, despair, worthlessness, impending doom
Mania	hypomania, increased energy, talkative, hyper, feeling overcaffeinated or on cocaine, euphoric
Nervousness	nervous, jittery, jumpy, paranoia, feeling paranoid or having strange thoughts
Psychosis	auditory or visual hallucinations, strange (delusional) thinking, psychotic
Sleep paralysis	sleep paralysis, feeling held down or unable to move while sleeping
Suicidal ideation or attempt	new or increased thoughts of suicide or self-harm, suicide attempt

APPENDIX: 6

Table 6A- Summary of Risk Bias for Cross-sectional studies examining impact of psychiatric adverse effects associated with the use of vilazodone

JBI Critical Appraisal checklist for analytical cross-sectional studies	
	Hughes et al
1. Were the criteria for inclusion in the sample clearly defined?	+
2. Were the study subjects and the setting described in detail?	+
3. Was the exposure measured in a valid and reliable way?	+
4. Were objective, standard criteria used for measurement of the condition?	+
5. Were confounding factors identified?	+
6. Were strategies to deal with confounding factors stated?	+
7. Were the outcomes measured in a valid and reliable way?	+
8. Was appropriate statistical analysis used?	+
Comments	**100%**

KEY: - High Risk

\+ Low Risk

? Unclear Risk

Table 6B- Summary of Risk Bias for Cohort studies examining impact of psychiatric adverse effects associated with the use of Vilazodone

JBI Critical Appraisal Checklist for Cohort Studies	
	Robinson et al
1. Were the two groups similar and recruited from the same population?	+
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	+
3. Was the exposure measured in a valid and reliable way?	+
4. Were confounding factors identified?	?
5. Were strategies to deal with confounding factors stated?	?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	+
7. Were the outcomes measured in a valid and reliable way?	+
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	+
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	+
10. Were strategies to address incomplete follow up utilized?	?
11. Was appropriate statistical analysis used?	+
Comment	**73%**

KEY: - High Risk

\+ Low Risk

? Unclear Risk

Table 6C- Summary of Risk Bias for Cohort studies (Randomized controlled trials) examining the impact of psychiatric adverse effects associated with the use of vilazodone

JBI Critical Appraisal checklist for Randomized Controlled Trials					
	Croft	**Durgam**	**Gommoll**	**Khan**	**Mathews**
1. Was true randomization used for assignment of participants to treatment groups?	+	+	+	+	+
2. Was allocation to treatment groups concealed?	+	?	?	?	+
3. Were treatment groups similar at the baseline?	+	+	+	+	+
4. Were participants blind to treatment assignment?	+	+	+	+	+
5. Were those delivering treatment blind to treatment assignment?	+	+	+	+	+
6. Were outcomes assessors blind to treatment assignment?	?	?	?	?	?
7. Were treatment groups treated identically other than the intervention of interest?	+	+	+	+	+
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	+	+	+	+	+
9. Were participants analysed in the groups to which they were randomized?	+	+	+	+	+
10. Were outcomes measured in the same way for treatment groups	+	+	+	+	+
11. Were outcomes measured in a reliable way?	+	+	+	+	+
12. Was appropriate statistical analysis used?	+	+	+	+	+
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial	+	+	+	+	+
	92%	**85%**	**85%**	**85%**	**92%**

KEY:
- \- High Risk
- \+ Low Risk
- ? Unclear Risk

Appendix: 7- PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**47**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**48**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**49**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**49**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**50**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**51**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**50**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**50**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**51**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**51 and 52**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**51**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**51 and 52**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**-**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**52**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**51 and 52**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**-**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**53**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**54**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**54**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**55-60**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**61-62**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix: 6 137-139**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**-**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**64-67**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**67**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**67-68**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**68**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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