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Is Incidence of Nausea Influenced by Brintellix in Patients Over the Age of 18 with Major Depressive Disorder?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Science- Physician Assistant

**Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania**

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ABSTRACT

OBJECTIVE: The Objective of this selective EBM review is to determine where or not, “Is Incidence of Nausea Influenced by Brintellix (Vortioxetine) in Patients over the Age of 18 with Major Depressive Disorder (MDD)?”

STUDY DESIGN: Review of three English language primary studies, published between 2011 and 2013

DATA SOURCES: Three double blind randomized controlled trials (RCTs). Sources were found on PubMed and Cochrane Library databases.

OUTCOMES MEASURED: To measure the incidence of nausea in patients over 18 who are diagnosed with major depressive disorder taking Brintellix compared to a placebo.

RESULTS: The randomized controlled studies results found that Brintellix was found to increase incidence of nausea when compared to placebo.

CONCLUSION: Brintellix treatment was well tolerated in patients 18 years and older with major depressive disorder; with nausea being the most common adverse event reported from patients.

KEY WORDS: Brintellix, nausea, major depressive disorder

Introduction

Major Depressive Disorders (MDD) is a serious condition that may manifest itself in a variety of ways. According to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), MDD is characterized by five or more symptoms that have been present for the same two week period and at least one of the symptoms has to be depressed mood or anhedonia.¹ The other presenting symptoms may be significant weight loss or weight gain (>5% of body weight per month), insomnia or hypersomnia, psychomotor agitation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, decreased concentration or indecisive, and recurrent thoughts of death or suicidal ideation.¹ These symptoms also have to cause impairment in social or occupational areas and cannot be attributed to drugs (medical or street), bereavement, or not better explained by other psychotic disorders.^{1,7,8,9}

Major depression is a common condition affects approximately 14.8 million or 6.7% of the American population.² An estimated 121 million people worldwide are currently affected by a form of depression and MDD is the 4th leading cause of disability worldwide.² In the United States, the annual cost related to MDD in 2010 was \$210.5 billion dollars.³ The latest statistics show in 2007-2010 there were 8 million visits per year for major depressive disorder.⁴ There is a higher incidence in women than men and MDD is a common comorbidity in patients with chronic medical conditions (arthritis, DM, heart disease, etc.).⁵ Major depression may affect all ages, races, and the incidence increases with age for both genders.⁵ The etiology for MDD is thought to be multifactorial, arising from genetic factors (neurotransmitter dysfunction), developmental (personality issues, childhood events), and psychosocial stress (divorce, unemployment, etc.).⁵ Some of the major neurotransmitter contributors to MDD are thought to be serotonin (5-HT), epinephrine, norepinephrine, and dopamine.^{5,7,8,9} This is why the

medications that are given to treat MDD attempt to achieve balance amongst the neurotransmitters that regulate our overall mood.

Psychotherapy is recommended for patients who suffer from major depressive disorder. This is a key component to treatment because it allows for a continuous assessment of suicide risk in this population.⁵ Psychotherapy is also aided with pharmacotherapy treatment. The drugs used pharmacotherapy treatment usually takes 3-6 week before the patient notices a positive affect from the medications.⁵ The first line treatment in patients with MDD are selective serotonin reuptake inhibitors (SSRIs), followed by selective norepinephrine reuptake inhibitors (SNRIs), or other drug classes that may alter brain neurotransmitter activity.⁵ If patients fail pharmacological therapy they may be candidates for electroconvulsive therapy or phototherapy.⁵

The pharmacological treatments listed above all play an important part in management for MDD however; these medications may not be tolerated or therapeutic to all patients. The U.S. Food and Drug Administration (FDA) approved Brintellix in 2013 for the management of major depressive disorder.⁶ Brintellix is a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and an inhibitor of the 5-HT transporters.^{7,8,9} The areas of the brain that Brintellix affects is designed to enhance neurotransmitter activity, which results in antidepressant activity. Since this drug works in the central nervous system (CNS) it is important to examine if patients are able to tolerate the CNS adverse effects associated with Brintellix. The RCT's demonstrated that there is increased CNS side effects, most common being nausea, but majority of patients are able to tolerate the medication and follow through with management.^{7,8,9}

Objective

The Incidence of nausea is influenced by Brintellix in patients over the age of 18 with Major Depressive Disorder (MDD).

Method

The criteria used for the 3 RCT studies included patients over 18, diagnosed with MDD, who met the baseline total score on Montgomery-Asberg Depression Rating Scale (MADRS) on the first visit. Patients who were eligible for the study were randomized equally to one of the treatment groups and were instructed to take their medication at the same time each day. The placebo capsule was identical to Brintellix capsule. Some variations did exist between the three studies. In the study by Alvarez et al. 5mg Brintellix was compared to placebo for six weeks.⁷ In the study by Boulenger et al. 5mg Brintellix was compared to placebo for eight weeks.⁸ In the trial by Mahableshwarkar et al. 15mg Brintellix was compared to placebo for eight weeks.⁹ The outcomes measured in the three studies included the incidence of nausea in patients who are taking Brintellix for MDD.

Clinical experts who received rater training and received their rating training certificated were allowed to rate patients.^{7,8,9} These experts followed up with the eligible patients to examine the efficacy and tolerability of the medication. When patients reported to the clinical experts, the patients were asked non-leading questions, such as, “how do you feel”? All adverse events were either observed by the clinical expert or reported directly by the patient.

A detailed search using Cochrane Systematic Reviews and PubMed databases were completed by using the keywords “Vortioxetine”, Major Depression, “Brintellix” with English language being used in all studies. The three RCTs were published between 2011 -2013 and located in PubMed database. Articles were selected based on their relevance to clinical practice and importance to patient-oriented outcomes. Inclusion criteria consisted of articles that were either RCTs or Primary studies which were up to date with no other systematic review, meta-analysis, or review article found on the Cochrane database answering the same questions. Studies excluded were those with patients treated with other antidepressant drugs, current psychiatric disorder other than MDD, current or past history of manic or

hypomanic episodes, schizophrenia, or any other psychotic features, or received electroconvulsive therapy within the last six months. A summary of statistics reported or used were CEA, EER, RRI, ARI, NNH, and P-values. Table 1 displays the demographics and characteristics of these articles.

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Alvarez ⁷ (2011)	RCT	213	18-65	Patients with MDD presenting with current major depressive episodes according to DSM-IV-TR criteria were included if there were an outpatient of either sex, MADRS total score >30	Current psychiatric disorder other than MDD, Current or past history of manic or hypomanic episodes, schizophrenia, or any other psychotic features	28	Brintellix 5 mg VS. Placebo assessing adverse reactions at each visit for 6 weeks, starting at baseline. During visits patients were asked non-leading questions.
Boulenger ⁸ (2013)	RCT	151	18-75	Primary diagnosis of MDD according to DSM-IV-TR criteria, a current major depressive episode (MDE) of greater than 3 month's duration with a MADRS score of ≥ 26 .	Current psychiatric disorder other than MDD as defined by DSM-IV-TR or a current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic features	34	Brintellix 15 mg VS. Placebo assessing adverse reactions at each visit for 8 weeks, starting at baseline. During visits patients were asked non-leading questions.
Mahables-hwarkar ⁹ (2013)	RCT	153	18-75	Primary diagnosis of major depressive disorder (according to DSM-IV-TR for at least 3 months who scores ≥ 22 on MADRS.	History of psychosis, substance abuse, neurological disorders, on a medication, risk of suicide, resistant to 2 adequate anti-depressant	31	Brintellix 5mg VS placebo assessing adverse reactions at the end of 8 week trial, comparing to baseline.

					treatments for at least 6 weeks or received electro-convulsive therapy within 6 months		
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Outcome Measured

The outcomes measured were patient oriented evidence that matters (POEMs), relating to increased incidence of nausea in patients taking Brintellix for MDD. The patients in the study had to meet with the clinical expert as scheduled times. During this time the clinical expert asked non-leading questions such as, how do you feel?^{7,8,9} Nausea was reported by the patient or observed by the clinical expert then added to adverse events and analyzed by using the Fischer exact test.

Results

The three studies chosen evaluated for the incidence of nausea in patients 18 and older taking Brintellix for MDD.^{7,8,9} All patients included in each study were assessed prior to eligibility and assessed through the study at prescribed intervals. All the studies compared Brintellix to a placebo group, but varied in duration of study or dosage of Brintellix given. During the duration of the study adverse events were recorded, with nausea being the most common adverse event.^{7,8,9}

In the study conducted by Alvarez et al.⁷ (2011) analyzed if the incidence of nausea is increased in patients taking 5mg of Brintellix (n=108; 38 male 70 female) compared to the placebo (n=105; 36 male 69 female). The study design was a randomized, double blind, placebo controlled trial for a six week duration. In the experimental and control there were male/female 18 years and older with a diagnosis of MDD. Refer to Table 1 for inclusion and exclusion criteria. Incidence of nausea was assessed after the completion of each week until the study was

finished. After the completion of the study patients were tapered off for two weeks. The experimental and control group both received the placebo for two weeks and then reported for a safety follow-up 4 weeks after the completion of the study. It was reported that 18 (4 to adverse events) patients withdrew from the control group and 10 (3 to adverse events) patients withdrew from the experimental group. Patient withdrawal in either group due to nausea was 0.10 (9.5%) patients in the control group and 32 (29.6%) patients in the experiential group reported nausea. Patients taking 5mg of Brintellix had a 2.12 times higher risk of experiencing nausea as those taking control. Patients taking 5mg of Brintellix had a 20.1% absolute increase in experiencing nausea. For every 4 MDD patients taking 5mg Brintellix, 1 patient would also experience nausea, compared to control. At the end of the study there was a significant ($p < 0.001$) increase in nausea in experimental group compared to control group (Table 2).

In the study conducted by Boulenger et al⁸ (2013) analyzed if the incidence of nausea is increased in patients taking 15mg of Brintellix (n=151; 54 male 97 female) compared to the placebo (n=158; 48 male 110 female). The study design was a randomized, double blind, placebo controlled trial for 8 weeks. In the experimental and control group there were male/female 18 years and older with a diagnosis of MDD. Refer to Table 1 for inclusion and exclusion criteria. Incidence of nausea was assessed weekly for the first 2 weeks and then every 2 weeks till the end of the study. After the completion of the study, experimental and control were tapered off for 2 weeks with placebo and followed up on 4th week for safety measures. It was reported that 25 (7 to adverse events) patients withdrew from control group and 34 (10 to adverse events) patients withdrew from experimental group. The leading adverse event that leads for withdrawal was nausea in the experimental group. The study did not specify the leading cause of withdrawal in control group. 16 (10.1%) patients in the control group and 40

(26.5%) in the experimental group reported nausea. Patients taking 15mg of Brintellix had a 2.15 higher risk of experiencing nausea as those taking control. Patients taking 15 mg of Brintellix had a 21.7% absolute increase in experiencing nausea. For every 4 MDD patients taking 15mg Brintellix, 1 additional patient would also experience nausea, compared to control. At the end of the study there was a significant ($p<0.001$) increase in nausea in experimental group compared to control group (Table 2).

In the study conducted by Mahableshwarkar et al.⁹ (2011) analyzed if the incidence of nausea is increased in patients taking 5mg of Brintellix (n=122; 60 male/93 female) compared to the placebo group (n=120; 47 male/106 female). The study design was a randomized, double blind, placebo controlled trial for 8 weeks. In the experimental and control group there were male and female 18 years and older with a diagnosis of MDD. Refer to Table 1 for inclusion and exclusion criteria. Incidence of nausea was assessed at weeks 1,2,4,6, and 8. Control and experimental group were both given a placebo taper for 1 week following the study. Safety follow up was done over the phone, 4 weeks after the study. It was reported that 33 (7 to adverse events) participants withdrew from the placebo group and 31 (12 to adverse events) withdrew from experiential group. The study did not specify if adverse events relating to nausea was a cause of withdraw. 16 (10.6%) patients in the control group and 44 patients in the experimental group reported nausea. Patients taking 5mg of Brintellix had a 1.72 higher risk of experiencing nausea as those taking control. Patients taking 5mg of Brintellix had an 18.2% absolute increase in experiencing nausea. For every 5 MDD patients 18 years and older taking 5mg Brintellix, 1 additional patient would also experience nausea, compared to control. At the end of the study there was a significant ($p<0.05$) increase in nausea in experimental group compared to control group (Table 2).

Table 2 - Incidence of Nausea is Influenced by Brintellix (Vortioxetine) in Patients Over the Age of 18 with Major Depressive Disorder (MDD)

Study	Control event rate (CER)	Experimental event rate (EER) Dosage/ EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)	P-value	Statistically Significant
Alvarez et al. ⁷	9.5%	5mg/29.6%	212%	20.1%	4	P<0.001	Yes
Boulenger et al. ⁸	10.1%	15mg/31.8%	215%	21.7%	4	P<0.001	Yes
Mahableshwarkar et al. ⁹	10.6%	5mg/28.8%	172%	18.2%	5	P<0.05	Yes

Discussion

Major Depressive Disorder is a serious condition that may manifest itself in a variety of ways. Treatment for MDD is difficult due to the fact that a variety of variables contribute to this condition. Using pharmacological therapy to attempt to balance the CNS neurotransmitters has been shown to be an effective treatment for MDD. When choosing a medication for any condition it is important to weigh the advantages vs the disadvantages of a medication. For example, a medication may be effective for desired outcome but the adverse effect(s) of the medication may also be harmful. Therefore it is important for a patient to pick a medication that is effective and tolerable than a medication that will treat a symptom but replace it with another. These decisions are even more important for patients who have to take a medication for the rest of their life.

Brintellix is a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and an inhibitor of the 5-HT transporters.^{7,8,9} Brintellix was approved for the treatment of MDD on September 30, 2013 and is considered a multimodal antidepressant because it works in multiple ways in the CNS.⁶ Brintellix is available in 5mg, 10 mg, 15mg, and 20mg tablets and cost for 1 month supply ranges from \$300-350\$.¹⁰ However,

with the availability of cost reduction cards and insurance, many patients pay \$50-\$100 per month.¹¹ This medication is used to treat major depressive disorder and has a black box warning with increased suicide in children, young adults, and adults > 65 years old. The only indication for the use of Brintellix is major depressive disorder.^{6,10}

Patients with MDD are known to have a high relapse rate and often are found taking antidepressants for the duration of their life.⁵ The three RCTs found that Brintellix was an effective treatment for MDD in patients over 18 years old but the focus of this study was to analyze the impact of nausea due to Brintellix therapy.^{7,8,9} Nausea was reported as the most common adverse event during the trials.^{7,8,9} Even though nausea was the number one adverse event the studies reported that they were mild cases.^{7,8,9} So the severity of nausea was low. Therefore, even though Brintellix was significant for increasing incidence of nausea, due to the low severity of nausea, Brintellix was well tolerated by the patients.

Similar limitations existed in all the following studies. In the three RCTs nausea was reported by participant or observed by the clinical expert during follow up. Nausea is a symptom that may arise from a variety of reasons such as, diet, exercise, emotional stress, motion sickness, etc. Therefore it may be difficult to decipher if nausea was contributed by lifestyle factors or primarily from the experimental arm. The study did not include this variable as a possibility which would result in false positives. Due to this limitation, there needs to be a more valid procedure in recording the influence of nausea due to Brintellix.

Conclusion

The systematic review of three randomized controlled trials comparing Brintellix to a control group concluded that Brintellix was influential in increasing the incidence of nausea in patients over 18 with major depressive disorder. Variability of major depressive disorder

medications is important because these mediations affect the CNS which may contribute to undesirable adverse reactions. With more pharmacological options available helps increases the opportunity for management of MDD. Future studies should include extra guideline with reporting incidence of nausea, allowing for clinical reporters to decipher if nausea is due to lifestyle factors or Brintellix.

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