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Surveillance:
Newer Second-Generation Antidepressants

August 2021

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the 2020 individual topic request (ITR) on newer second-generation antidepressants for the treatment of major depressive disorder (MDD) or generalized anxiety disorder (GAD).[1] The literature search for this report focuses on new randomized controlled trials (RCTs), nonrandomized studies reporting harms outcomes, and actions taken by the US Food and Drug Administration (FDA) since the last report, including approval of new drugs, formulations, or indications and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of the ITR (August 2020). The search strategy for that ITR was through July 9, 2020. A full topic history appears in Table 1.

Table 1. Topic History and Search Dates

Document Type	Date Completed	Last Search Date
Individual Topic Request: Newer Second-Generation Antidepressants: Vortioxetine, Vilazodone, and Levomilnacipran[1]	August 2020	July 2020
Second Generation Antidepressants Targeted Update 6: Levomilnacipran, Vilazodone, and Vortioxetine Compared with Other Second-generation Antidepressants[2]	April 2017	September 2016
Second Generation Antidepressants Update 5[3]	March 2011	September 2010
Second Generation Antidepressants Update 4[4]	August 2008	April 2008
Second Generation Antidepressants Update 3[5]	May 2006	April 2006
Second Generation Antidepressants Update 2[6]	January 2006	November 2005
Second Generation Antidepressants Update 1[7]	May 2005	February 2005
Second Generation Antidepressants Original Report[8]	November 2004	January 2004

PICOS

Population

- Adult outpatient populations with MDD (as diagnosed by a validated instrument)
- Adult outpatient populations with GAD (as diagnosed by a validated instrument)

Interventions

- Newer second-generation antidepressants (Table 2)

Table 2. Included Interventions

Generic Name	Brand Name(s) or Model Number(s)	Indication	Date of FDA Approval
Serotonin Modulators			
Vortioxetine hydrobromide[9]	Trintellix Brintellix (outside US)	Adults with MDD	September 2013
Vilazodone hydrochloride[10]	Viibryd	Adults with MDD	January 2011
SNRI			
Levomilnacipran hydrochloride[11]	Fetzima	Adults with MDD	July 2013

Abbreviations. FDA: US Food and Drug Administration; MDD: major depression disorder; SNRI: serotonin norepinephrine reuptake inhibitor.

Comparators

- Older second-generation antidepressants (Table 3)

Table 3. Included Comparators

Generic Name	Brand Name(s)	Date of FDA Approval
SSRIs		
Escitalopram	Lexapro	August 2002
Citalopram	Celexa	July 1998
Fluvoxamine	Luvox	December 1994
Paroxetine	Paxil Paxil CR Pexeva	December 1992
Sertraline	Zoloft	December 1991
Fluoxetine	Prozac Sarafem	December 1987
SNRIs		
Desvenlafaxine	Pristiq	February 2008
Duloxetine	Cymbalta Drizalma Sprinkle	August 2004
Venlafaxine	Effexor XR	December 1993
NDRIs		
Bupropion hydrobromide	Aplenzin	April 2008
Bupropion hydrochloride	Forfivo XL	December 1985
Atypical Antidepressants		
Mirtazapine	Remeron Remeron SolTab	June 1996
Serotonin Modulators		
Nefazodone	None available	December 1994
Trazodone	None available	December 1981

Abbreviations. CR: controlled release; FDA: US Food and Drug Administration; NDRI; norepinephrine-dopamine reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SolTab: soluble tablet; SSRI: selective serotonin reuptake inhibitor; XR: extended release; XL: extended release.

Outcomes

- Response (e.g., Patient Health Questionnaire-9 [PHQ-9] score reduced by at least 50%)
- Remission (e.g., PHQ-9 score less ≤ 4)
- Time to onset of efficacy
- Prevention of relapse and recurrence
- Quality of life, measured using a validated instrument (e.g., Short Form 36 [SF-36], Quality of Life in Depression Scale)
- Functional capacity (e.g., Clinical Global Impression scales [CGI], Global Assessment of Functioning [GAF])
- Hospitalization
- Overall risk of adverse events (AEs)
- Overall discontinuation of treatment
- Discontinuation because of AEs
- Serious adverse events (SAEs), including:
  - Hyponatremia
  - Hepatotoxicity
  - Serotonin syndrome
  - Suicidal ideas or behaviors
  - Others
- Specific AEs, including:
  - Gastrointestinal symptoms
  - Nausea and vomiting
  - Sexual dysfunction
  - Weight gain
  - Others

Study Designs

- Double-blind, RCTs comparing newer second-generation antidepressants (Table 2) with one another or with another second-generation antidepressant (Table 3)
- For harms, nonrandomized controlled studies with a sample size of 100 participants or more
- Studies with a minimum treatment duration of 6 weeks, regardless of design

Key Questions

KQ1. For outpatients with MDD or GAD: do newer second-generation antidepressants differ in efficacy or effectiveness compared with older second-generation antidepressants?

KQ2. For outpatients with MDD or GAD: do newer second-generation antidepressants differ in harms compared with older second-generation antidepressants?

KQ3. Are there subgroups of patients based on demographics (age, racial groups, socio-demographic factors, and sex), other medications, or comorbidities for which a newer second-generation antidepressant is more effective or associated with fewer AEs than another?

Methods

Using the PICOS outlined above, the Center for Evidence-based Policy (Center) researchers searched for eligible RCTs and nonrandomized trials (for harms only) in ClinicalTrials.gov, the

ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE ALL from June 1, 2020, to July 12, 2021. We also searched Google Scholar to identify studies published since the implementation of the search strategy in the ITR (August 2020). We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used the Google search engine, IPD Analytics, and searched CenterWatch, a privately owned database of clinical trials information.

Findings

New Drugs or Formulations

Generic formulations of varying doses of vilazodone have been submitted to the FDA for approval by 3 manufacturers.[12-14] All 3 manufacturers have approval, or tentative approval, for one or more doses, but no dates were provided on the FDA or manufacturer websites. The current license of exclusivity expires in June 2022.

An investigational norepinephrine-dopamine reuptake inhibitor (NDRI) treatment for MDD that combines dextromethorphan and bupropion, named AXS-05, was identified with a Prescription Drug User Fee Act (PDUFA) date of August 22, 2021.[15]

An investigational serotonin-norepinephrine-dopamine triple reuptake inhibitor (SNDRI), ansofaxine hydrochloride (model number: LY03005), was identified with a pending PDUFA date.[16]

New Indications

No new indications were identified since the searches in the last surveillance document in June 2020.[17]

New Serious Harms or Warnings

Levomilnacipran (Fetzima)

A black box warning for increased suicidal thoughts and behavior in pediatric and young adult patients was issued in October 2019.[11] Additionally, 4 warnings and precautions were added to the FDA label in October 2019[11]:

- Serotonin syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRIs, SNRIs, triptans), or when taken alone
- Increased risk of bleeding: Concomitant use of NSAIDs, aspirin, or other antiplatelet or anticoagulant drugs may increase this risk
- Angle closure glaucoma: Has occurred in patients with untreated anatomically narrow angles treated with antidepressants
- Hyponatremia (low blood sodium levels): Can occur in association with syndrome of inappropriate antidiuretic hormone secretion

Vortioxetine (Trintellix)

A black box warning for increased suicidal thoughts and behavior in pediatric and young adult patients was issued in January 2021.[9] Additionally, 2 warnings and precautions were added to the FDA label in January 2021[9]:

- Increased risk of bleeding: Concomitant use of NSAIDs, aspirin, or other antiplatelet or anticoagulant drugs may increase this risk
- Discontinuation syndrome in doses of 15 mg/day or 20 mg/day

Randomized Controlled Trials

We identified 3 published head-to-head RCTs (Table 4; see Appendix A for the abstracts of the included studies).[18] A small 3-arm RCT (N = 60) from India compared vilazodone with amitriptyline or escitalopram over a period of 12 weeks in adults with MDD.[18] Two RCTs compared vortioxetine to sertraline in adults with MDD;[19,20] 1 RCT exclusively enrolled participants with type 2 diabetes.[20] Both trials ran for 8 weeks.[19,20] We did not identify any RCTs including adults with anxiety or any RCTs comparing levomilnacipran with older second-generation antidepressants published since the most recent ITR.

Table 4. Eligible Published RCTs

Author, Year Trial Number Location	N Participant Characteristics Duration	Intervention	Comparator(s)	Outcomes
Vilazodone				
Kadam et al., 2020[18] India	• N = 60 • Adults with MDD • 12 weeks	• Vilazodone	• Amitriptyline • Escitalopram	• AEs • Remission • Response
Vortioxetine				
Levada et al., 2019[19] NCT03187093 Ukraine	• N = 66 • Adults with MDD • 8 weeks	• Vortioxetine	• Sertraline	• AEs • Functional capacity • Remission • Response
Tovilla-Zarate et al., 2019[20] NCT03978286 Mexico	• N = 50 • Adults with MDD and comorbid type 2 diabetes • 8 weeks	• Vortioxetine	• Sertraline	• BMI • Remission • Response

Abbreviations. AEs: adverse event; BMI: body mass index; MDD: major depressive disorder.

Ongoing Studies

We identified 6 eligible ongoing studies (Table 5). Expected enrollment ranges from 140 to 600 participants. A majority of the trials (4 of 6) have completion dates that passed but no publications were identified. The remaining 2 RCTs have completion dates in early 2022. We did not identify any ongoing RCTs comparing vilazodone with older second-generation antidepressants since the June 2020 surveillance document.[17]

Levomilnacipran

We identified 1 ongoing RCT comparing levomilnacipran with escitalopram or placebo (Table 5). An RCT, completed in June 2018, compared levomilnacipran to a participant's current SSRI

coupled with quetiapine (brand name: Seroquel; trial number NCT02720198), but no publications have been identified.

Vortioxetine

We identified 5 ongoing RCTs for vortioxetine with expected enrollments ranging from 129 to 600 participants (Table 5). Across 4 studies, vortioxetine monotherapy was compared with:

- Any older SSRI (e.g., sertraline, fluoxetine)
- Desvenlafaxine
- Escitalopram
- Escitalopram coupled with aripiprazole

One RCT enrolled adults (N = 128) with MDD and comorbid alcohol use disorder and treated participants with vortioxetine coupled with acamprosate or acamprosate coupled with placebo. A South Korean trial enrolled participants (N = 144) with MDD and comorbid anxiety.

Table 5. Eligible Ongoing Studies

Trial Number Trial Name (if provided) Location Study Design	Expected Enrollment Participant Characteristics Duration	Treatment Groups	Outcomes	Primary Completion Date
Levomilnacipran				
NCT03128021 NEMO USA RCT	• N = 140 • Aged ≥ 60 years with MDD • 12 weeks	• Levomilnacipran • Escitalopram • Placebo	• QoL • Remission • Response	April 2022
Vortioxetine				
NCT04448431 VIVRE Argentina, Russia, and 9 European countries (76 sites) RCT	• N = 600 • Aged 18 to 65 years with MDD • 8 weeks	• Vortioxetine • Desvenlafaxine	• Functional capacity • QoL • Remission • Response	May 2022
NCT04498897 South Korea RCT	• N = 128 • Aged 19 to 65 years with MDD with comorbid AUD • 8 weeks	• Vortioxetine + Acamprosate • Acamprosate + Placebo	• Remission • Response	April 2021
NCT03779789[21] VESPA Italy RCT	• N = 358 • Aged ≥ 65 years with MDD • 6 months	• Vortioxetine • Older SSRIs (e.g., sertraline, fluoxetine)	• Acceptability • AEs • Mortality • QoL • Remission • Response • Tolerability	July 2019

Trial Number Trial Name (if provided) Location Study Design	Expected Enrollment Participant Characteristics Duration	Treatment Groups	Outcomes	Primary Completion Date
KCT0002173 South Korea (5 sites) RCT	• N = 129 • Aged 18 to 65 years with MDD without comorbid psychosis • 6 weeks	• Vortioxetine • Escitalopram • Desvenlafaxine	• AEs • Functional capacity • QoL • Remission • Response	October 2018
KCT0002173 South Korea (5 sites) RCT	• N = 144 • Aged 18 to 65 years with MDD with comorbid anxiety • 6 weeks	• Vortioxetine • Escitalopram • Escitalopram + aripiprazole • Desvenlafaxine	• AEs • Functional capacity • QoL • Remission • Response	October 2018

Abbreviations. AEs: adverse event; AUD: alcohol use disorder; MDD: major depressive disorder; QoL: quality of life; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Summary

Since the completion of the DERP ITR in August 2020, we identified:

- 3 new RCTs
  - 3 head-to-head studies comparing vilazodone or vortioxetine with older second-generation antidepressants
- 6 ongoing studies
  - 6 head-to-head studies comparing levomilnacipran or vortioxetine with older second-generation antidepressants
- No new indications
- 2 new serious harms or warnings for levomilnacipran and vortioxetine
- New generic formulations of vilazodone
  - License of exclusivity expires in June 2022

We did not identify any new or ongoing studies in adults with GAD.

Using the Is There a There There Scale (ITS) (Table 6), we rated this topic as *No* (see Appendix B for ratings and definitions).

Table 6. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial	☑ 1 vilazodone RCT 2 vortioxetine RCTs	
New Meaningful[a] Study		☒

Clinical Evidence	Yes How many?	No
Ongoing Study Likely to be Published in the Next Year	☑ 4 RCTs	
FDA Actions	**Yes** **Description**	**No**
New Drug or Formulation	☑ Generic formulations of vilazodone	
New Indication		☒
New Serious Harm or Warning	☑	
ITS Rating: *No*		

Abbreviations. ITS: Is There a There There Scale; RCT: randomized controlled trial. Note.[a] *Large studies (≥ 100 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*

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multicentre, open-label, parallel-group, superiority, randomized trial. *Trials*. 2020;21(1):695. doi: 10.1186/s13063-020-04460-6.

Appendix A. Abstracts of New Eligible Studies

Vilazodone

Kadam RL, Sontakke SD, Tiple P, Motghare VM, Bajait CS, Kalikar MV. Comparative evaluation of efficacy and tolerability of vilazodone, escitalopram, and amitriptyline in patients of major depressive disorder: a randomized, parallel, open-label clinical study. *Indian J Pharmacol.* 2020;52(2):79-85. doi: 10.4103/ijp.IJP_441_18.

OBJECTIVES: To evaluate and compare efficacy and tolerability of Vilazodone with Escitalopram and Amitriptyline in patients of major depressive disorder (MDD). METHODS: This was a randomized, prospective, parallel-group, open label clinical study in which newly diagnosed patients of MDD were randomized to receive Tab Vilazodone 20 mg daily or Tab Escitalopram 20mg daily or Tab Amitriptyline 75mg daily for 12 weeks. Antidepressant activity was assessed by change in score from baseline to week 12 on HAMD-17 and MADRS scales while change in score on HAM-A scale was used to assess antianxiety effect. Change in scores on the three scales was also compared between the three treatment groups. Severity and causality of adverse events were assessed by the modified Hartwig & Siegel scale and Naranjo scale respectively. Data was analyzed in accordance with per protocol analysis. RESULTS: Reduction in HAMD-17 and MADRS scores was significantly more in vilazodone group compared to the other two drugs indicating that vilazodone is more efficacious antidepressant. Number of remitters were also significantly more in the vilazodone group (n = 11) compared to escitalopram (n = 4) ($p < 0.05$) and amitriptyline (n = 0) ($p < 0.001$) at 12 weeks. Similar results were also obtained with HAM-A score. Number of patients showing MADRS sustained response at 12 weeks was statistically significantly more in vilazodone (n = 12) and escitalopram (n = 12) groups compared to amitriptyline (n = 01) ($p < 0.001$). Reported adverse events were constipation and sedation (amitriptyline group); nausea and headache (escitalopram and vilazodone groups). These adverse events were of mild severity. Most adverse events belonged to probable category. CONCLUSION: Vilazodone is more efficacious and well tolerated antidepressant compared to escitalopram and amitriptyline.

Vortioxetine

Levada OA, Troyan AS. Cognitive-functional relationships in major depressive disorder: crucial data from a Ukrainian open-label study of vortioxetine versus escitalopram. *J Affect Disord.* 2019;250:114-122. doi: 10.1016/j.jad.2019.03.040.

Background Major depressive disorder (MDD) is one of the most prevalent mental illnesses associated with impairments in different spheres of functioning. Cognitive deficits are currently investigated as a possible factor of functional decline. We aimed: 1) to assess the influence of cognitive domains among other MDD symptoms on functional impairment; 2) to compare effects of eight weeks` vortioxetine versus escitalopram treatments on cognitions and consequent influence on various domains of functioning. Methods At baseline, 119 MDD (according to DSM-5, MADRS ≥ 7) patients and 71 healthy controls completed neurocognitive tests (RAVLT, TMT-B, DSST) and Sheehan Disability Scale. After 8 weeks of vortioxetine/escitalopram treatment, 56 patients had repeated clinical and neuropsychological evaluations. Linear regression analyses were performed to find significant predictors of impairment (at baseline) and improvement (after treatment) of functioning. Differences between groups after treatment were

analyzed using mixed models for repeated measurements. Results Cognitive impairments predominantly affected social functioning and were crucial for working productivity and total functioning along with anhedonia, hypothymia. Working memory disturbances impaired all aspects of functioning. Executive dysfunction made an additional contribution to workplace performance disturbances. At week 8, vortioxetine compared with escitalopram greater improved all impaired cognitive parameters and aspects of functioning and had higher remission rates. Cognitive improvement was the most significant factor for total functioning recovery and among crucial contributors to workplace performance recovery. Limitations No placebo group. Conclusion Cognitions play a key role in social, working, overall functioning in Ukrainian MDD patients. Compared to escitalopram, vortioxetine treatment greater improves all cognitive and functioning domains, which leads to higher remission rates.

Tovilla-Zarate CA, Perez-Mandujano A, Ramirez-Gonzalez IR, et al. Vortioxetine versus sertraline in metabolic control, distress and depression in Mexican patients with type 2 diabetes. *Ann Transl Med*. 2019;7(22):656. doi: 10.21037/atm.2019.10.56.

Background: Depression in patients with type 2 diabetes (T2D) is often undiagnosed and remains untreated, leading to poor therapy adherence and ill health-related outcomes. We evaluated the effect of vortioxetine versus sertraline in the treatment of depression, distress and metabolic control in subjects with T2D and depression. Methods: Participants were selected from the Clinic for Diabetes, diagnosed with depression when the score was ≥ 14 in the Hamilton Depression Rating Scale, and verified by a psychiatrist in agreement with the DSM-5 instrument (Diagnostic and Statistical Manual of Mental Disorders, fifth edition). The criteria for recruitment also included glycosylated hemoglobin ≥ 7.5%, 18 to 60 years of age, and written informed consent. Pharmacological treatment for depression was assigned randomly: vortioxetine (10 mg/day) or sertraline (75 mg/day) for 8 weeks. Biochemical parameters, anthropometric measures and depression symptoms were evaluated after antidepressant treatment. This was a randomized singled-blind study. Results: Subjects that met the inclusion criteria were 50, of which only 21 patients with T2D and depression finished the treatment. Vortioxetine and sertraline showed partial remission of depression. Vortioxetine showed a major effect size in glycosylated hemoglobin and a moderate effect size on weight loss, fasting plasma glucose (FPG), cholesterol and triacylglycerol levels. On the other hand, patients treated with sertraline presented a slight increase in body weight, body mass index (BMI), and in all biochemical markers. Conclusions: Vortioxetine may ameliorate depressive symptoms and metabolic control in patients with T2D and depression. Trial registration number: NCT03978286.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.