Drug Use Research & Management Program
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Class Update: Second Generation Antidepressant Medications

Month/Year of Review: May 2014
PDL Classes: Psychiatric: Antidepressants
New drug(s): vortioxetine (Brintellix®)
levomilnacipran extended-release (Fetzima®)

Last Oregon Review: April 2012
Source Document: OSU College of Pharmacy
Manufacturer: Takeda & Lundbeck/Forest
Dossier Received: Yes/Pending

Current Status of Voluntary PDL Class:

- **Preferred Agents:** BUPROPION HCL TABLET/TABLET ER, CITALOPRAM TABLET/SOLUTION, FLUOXETINE CAPSULE/SOLUTION/TABLET, FLUVOXAMINE, MIRTAZEPINE TAB RAPDIS/TABLET, PAROXETINE TABLET, SERTRALINE ORAL CONC/TABLET, VENLAFAXINE TABLET, VENLAFAXINE ER
- **Non-Preferred Agents:** BUPROPRION XL, DESVENLAFAXINE (PRISTIQ ER), DULOXETINE (CYMBALTA®), ESCITALOPRAM, FLUOXETINE DF (PROZAC® WEEKLY), NEFAZODONE, PAROXETINE HCL (PAXIL CR®), SELEGILINE PATCH (ENSAM®), VILAZODONE (VIIBRYD®), OLANZAPINE/FLUOXETINE (SYMBYAX®)

Status of the Voluntary Mental Health Preferred Drug List

Currently, all antidepressants are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. Second generation antidepressants have been reviewed for clinical efficacy and safety and specific agents were chosen as clinically preferred; this eliminates a copay. Oregon's Medicaid program currently charges no copayment for preferred PDL drugs.

Research Questions:

- Is there any new evidence of effectiveness or harms that will support changes to the voluntary PDL antidepressant class?
- Is there any evidence that vortioxetine is more effective or safer than currently available antidepressants for relapse or remission in the treatment of depression or in the treatment of anxiety?
- Is there any evidence that levomilnacipran is more effective or safer than currently available antidepressants for relapse or remission in the treatment of depression?
- Are there any subpopulations of patients with depression or anxiety for which vortioxetine or levomilnacipran is more effective or associated with less harm?

Conclusions:

- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder (MDD).

- There is moderate quality evidence that vortioxetine is safe and effective for the treatment of MDD based on short-term placebo-controlled trials. There is insufficient evidence to determine the most effective treatment dose.
- There is moderate quality evidence that vortioxetine is not superior to duloxetine 60 mg daily or venlafaxine XR 225 mg daily in efficacy.
- There is low quality evidence that levomilnacipran is safe and effective for the treatment of MDD based on short-term placebo-controlled trials.
- There is insufficient evidence to determine the effectiveness of either vortioxetine or levomilnacipran in the maintenance treatment of MDD, as well as in pediatric patients or patients with severe hepatic impairment.
- There is moderate quality evidence that fluoxetine, paroxetine, sertraline, topiramate and venlafaxine improve post-traumatic stress disorder (PTSD) symptoms. There is insufficient evidence to determine if there are any differences in effectiveness or whether any treatment approach was more effective for victims of particular trauma types.
- There is low quality evidence that there is no difference between treatment strategies in patients who fail to respond to SSRIs as first-line treatment in response and remission rates. These strategies include monotherapy (dose escalation, increased duration or switching drugs) or a combination of therapies.

Recommendations:
- Evidence does not support superiority of vortioxetine or levomilnacipran over other agents in this drug class. Recommend that both be listed as non-preferred agents.
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Previous P&T Conclusions and Recommendations (April 2012):
- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder (MDD). These findings pertain to patients in the acute, continuation, and maintenance phases; those with accompanying symptom clusters; and subgroups defined by age, sex, ethnicity, or comorbid conditions, although only sparse evidence for these findings exists for subgroups.
- Citalopram causes dose-dependent QT interval prolongation. The FDA recommends that citalopram should no longer be prescribed at doses greater than 40 mg per day
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.
- Include a dose limit of 40mg/day for citalopram.
- Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    - As an example, academic detailing can be used to promote appropriate utilization

Reason for Review: This class was last reviewed in April 2012. Since the last review, two antidepressants were approved. In addition, new guidelines, systematic reviews and head-to-head trials have been published.

Background:

Author: Amanda Meeker Date: May 2014

Before the late 1980s, the pharmacologic treatment of Axis I psychiatric disorders (such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders) was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[1] TCAs and MAOIs are often referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable. TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation and MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine.[1] Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters.[1] In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine.[1] Since then, five other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, and escitalopram.[1] The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine.[1] Other agents used for treatment of MDD include, nefazodone, mirtazapine, and bupropion.[1]

In randomized clinical trials (RCTs) of antidepressants, the FDA accepts a primary success criterion that is determined by measuring the difference between a baseline score and a post-treatment score for a primary effectiveness endpoint (measured via widely used scales). The most widely used observer-administered depression rating scales are the Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions (HAMD24 and HAMD17, respectively), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician Global Impressions-Severity of Illness (CGI-S) scale. The MADRS measures core symptoms of major depression on 10 items; each item is scored on a scale from 0 to 6. The HAMD assesses up to 24 items associated with major depression; each item is scored from 0 to 5. The CGI-S measures disease severity on a 7-point scale which scores the clinician's global assessment of the patient rather than individual aspects of the disease state. Limited information is available defining a clinically meaningful change in these scales.

Consensus definition of outcomes has been described.[2,3] Response refers to a clinically significant degree of depressive symptom reduction following treatment initiation.[2,3] Remission is the virtual absence of depressive symptoms.[2] The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).[2] The criteria for response and remission rates vary by trial, but the most widely accepted cutoffs for response is a ≥50% reduction from baseline (both MADRS and HAMD), and a specific threshold for remission. A score of ≤7 on the HAMD17 is widely accepted, with some suggesting a score of ≤5 be used, but there are differing recommendations for remission using MADRS.[3] A HAMD17 score of ≤7 corresponds to a MADRS score of ≤9, but others recommend a MADRS score of ≤5 to define remission, while most clinical trials use a score of ≤10.[3]

In PTSD, the most widely used measure is the Clinician-Administered PTSD Scale (CAPS).[4] This scale is often referred to as the "gold-standard" measure for PTSD.[4] CAPS is a semistructured interview that measures the 17 symptoms of PTSD and assesses each using two questions (34 total items) to measure symptom frequency of occurrence and symptom intensity. [4] The drawback of using this scale is the time of administration due to its large number of items; it can take 40-60 minutes to administer the scale. [4] A decrease of 15 points in this scale is considered clinically significant. [4]

An Agency for Healthcare Research & Quality (AHRQ) comparative effectiveness report on this class indicates that overall, 37% of patients with MDD do not achieve a treatment response and 53% do not achieve remission in short-term trials.[1] There is moderate quality evidence that all second-generation antidepressants have similar efficacy in MDD, and statistically significant differences for some head-to-head comparisons are not likely to be clinically relevant.[1] There was moderate quality evidence of no difference in health-related quality of life, although this is rarely measured as a primary outcome measure.[1] There is moderate quality evidence that mirtazapine may have statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine and sertraline (NNT to yield one additional responder after 1 or 2 weeks of treatment is 7).[1] There is moderate quality evidence that active treatment is favored over placebo in relapse prevention

Author: Amanda Meeker Date: May 2014

and recurrence prevention trials and moderate quality evidence of no difference in efficacy of maintaining remission between antidepressants.[1] There is insufficient evidence available to evaluate whether switching from one medication to another increases the number of patients who remain in remission.[1]

Recently, two antidepressants were approved for use in MDD. The first to be approved, levomilnacipran, is the active enantiomer of milnacipran (Savella®), an SNRI approved for use in fibromyalgia.[5] Vortioxetine (Brintellix®) is a multimodal antidepressant believed to work through a unique mix of serotonin (5-HT) subtype 5-HT_3 and 5-HT_7 receptor antagonism, 5-HT_{1B} receptor partial agonism, 5-HT_{1A} receptor agonism and inhibition of the 5-HT transporter.[6] The FDA approved vortioxetine with a target dose of 20 mg daily due to a lack of efficacy in smaller doses in the US population despite trials showing benefit in other populations.[6] The FDA-accepted primary endpoint of trials evaluating both drugs for efficacy was change in baseline in either MADRS or HAMD total score.[5,6]

Methods:
A Medline literature search ending March 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, bupropion, and mirtazapine. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, two systematic reviews[7,8], one guideline[9], three head-to-head trials[10–12], and two new drugs were identified[5,6].

Systematic Reviews:

Agency for Healthcare Research and Quality:

An AHRQ comparative effectiveness review by Jonas et al.[7] evaluated the efficacy, effectiveness and harms of psychological and pharmacological treatments for adults with PTSD with a literature search through May 2012. After review, 92 RCTs were included in the analysis. There is moderate strength of evidence (SOE) supporting the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms; effect sizes were small or medium (e.g., 4.9- to 15.5-point reduction in CAPS compared with placebo), and low SOE for risperidone in reducing PTSD symptoms. Evidence was insufficient evidence to determine if other medications improve symptoms. There is moderate SOE for paroxetine (NNT 8) and venlafaxine (NNT 9) supporting their efficacy for inducing remission and insufficient evidence for other medications. Evidence supports paroxetine's efficacy for improving depression symptoms and functional impairment (moderate SOE) and venlafaxine's efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). There was little direct comparative evidence to determine if there are any differences in treatments in effectiveness or whether any treatment approached were more effective for victims of particular trauma types.. Network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective than most medications for reducing PTSD symptoms, but analysis was based largely on indirect evidence and limited to one outcome measure (low SOE). Overall, evidence was insufficient to compare adverse events for various interventions or to draw conclusions about withdrawals due to adverse events, mortality, suicide, suicidal ideation, or self-harmful behaviors. .

A second AHRQ comparative effectiveness review by Santaguida et al. was undertaken to evaluate treatment strategies in patients who failed to respond to SSRIs as first-line treatment.[8] The efficacy (benefits and harms) of monotherapy approaches (dose escalation, increased duration, or switch) or combined therapies were

evaluated. From a literature search through April 2011, 44 studies and 27 clinical practice guidelines (CPGs) were identified. There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. Based on 12 studies comparing monotherapy interventions relative to other monotherapies, there is no certainty of any advantage between different monotherapies for either response to treatment or remission. The exception was one single study that demonstrated that low-dose sertraline had small improvement in response. There is also insufficient evidence to conclude that a dose escalation or a switch to another antidepressant is equivalent or superior to any comparator treatment in patients with inadequate response to initial SSRI.. Thirty three studies evaluated monotherapy compared to combined therapies, in which the majority showed no clear difference for any monotherapy, relative to combined therapy, in response and remission. The exception was with atypical antipsychotics. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit compared to combined therapy. The majority of studies were not designed to assess superiority of the strategies.

Authors also evaluated the range of recommendations following the failure of a SSRI based on CPGs published between 2004 and 2011. There were significant differences between the CPGs and variability in quality. For adults, increasing the dose or duration was frequently recommended, but the interval or change in dose was not specific. The majority did not recommend any specific type of antidepressant when switching.

New Guidelines:

National Institute for Health and Care Excellence (NICE)
NICE issued a new guideline regarding social anxiety disorder in May 2013 based on a review of the evidence.[9] These guidelines recommend that if drug treatment is needed, an SSRI should be offered.[9] Specifically, escitalopram or sertraline are recommended first line.[9] If the first SSRI is not effective, recommendations include using an alternative SSRI (fluvoxamine or paroxetine) or SNRI (venlafaxine), taking into account the efficacy, side effect profile, risk of early activation symptoms and tendency of drugs to produce a withdrawal syndrome.[9] Patients should be carefully monitored for side effects, including suicidal thinking and self-harm and follow up visits should be conducted every 2-4 weeks during the first 3 months of treatment and every month thereafter; patients under 30 who are prescribed an SSRI or SNRI should be monitored every week for the first month of use for suicidal thinking and self-harm.[9] For adults whose symptoms have not responded to an alternative SSRI or an SNRI, a monoamine oxidase inhibitor is recommended.

Randomized Controlled Trials: After the literature review, a total of 3 head to head RCTs were identified. Other studies were excluded because they had the wrong outcome, were placebo-controlled, or were not randomized. The abstracts of these can be found in Appendix 3.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Bose et al. (2012).[10] Parallel group, double-blind randomized	Escitalopram vs duloxetine	Patients with severe depression (n=571)	Time to all cause premature study discontinuation	There was no difference in time to all-cause discontinuation between groups (hazard ratio escitalopram/duloxetine = 0.95 [95% CI 0.64, 1.41]; p = 0.727). Treatment with escitalopram compared with duloxetine resulted in significant improvement in MADRS total score at the end of week 8 (least squares mean difference = -1.87 [95% CI -3.60, -0.14]; p = 0.034

				Significantly more escitalopram (54%) than duloxetine (42%) patients achieved remission (MADRS ≤10) by week 8 (p = 0.013). Adverse events were similar between the two treatment groups.
Raskin et al. (2012).[11] Double-blind, double-dummy, randomized, parallel group	Duloxetine vs escitalopram	Patients with MDD (n=483)	LS mean change from baseline in the Apathy Evaluation Scale, Clinician (AES-C) total score after 8 weeks of treatment	There was a statistically significant change from baseline in AES-C score for both duloxetine (-13.9) and escitalopram (-13.5) (p<0.001 for both). When compared to each other, there was no difference in the primary outcome (95% CI: -1.87 to 1.10; p= 0.612) There were no significant differences between the two groups on any measure (apathy, depression and functional outcomes).
Richard et al. (2012).[12] Double-blind, double-dummy, placebo controlled	Venlafaxine XR vs paroxetine vs placebo	Parkinson's disease patients with depression (n=115)	Change from baseline in HAM-D score after 12 weeks	There was no difference in the primary outcome between the paroxetine group (-6.2 points; 97.5% CI: 2.2 to 10.3) and the venlafaxine XR group (-4.2 points; 97.5% CI 0.1 to 8.4) (p=0.28). There were no significant differences between the two active groups in response or remission rates.

New Safety Alert/Indications: None

Horizon Scan: One antidepressant was identified on the AHRQ Healthcare Horizon Scanning Report. Amitifadine is a serotonin-norepinephrine-dopamine reuptake inhibitor in phase IIb/IIIa trials for the treatment of treatment-resistant MDD.[13]

New Drug Evaluations:

Vortioxetine (Brintellix®)
FDA approved indications: Treatment of Major Depressive Disorder (MDD)
Potential off-label use: Generalized Anxiety Disorder (has been studied in four short-term efficacy studies, but is not approved for this use)

Clinical Efficacy Data:

The approval of vortioxetine was based off of 10 short-term studies and 1 relapse-prevention study in adults to support the indication of treatment of major depressive disorder.[6] The trials included a total of 6,184 adult patients (ages 18-70 years) meeting DSM-IV-TR criteria for MDD, single episode or recurrent.

Table 2 provides a summary of the evidence findings for these studies. The primary outcome measure used to evaluate efficacy was the Montgomery-Asberg Depression Rating Scale (MADRS). Five of the short-term studies evaluated were conducted exclusively in the US[6]. Seven of the evaluated studies have been published[14–20]. Three longer-term studies have been published, the 24-week relapse-prevention study[21] and two open-label extension studies[22,23]. The manufacturer's dossier includes data for 12 short-term efficacy studies; 8 have positive results, 3 have negative results, and 1trial failed (neither vortioxetine nor the active control separated from placebo).[24] Results for one unpublished failed trial are not available.[24] Approval was based on the least squares (LS) mean change from baseline of MADRS or HAMD-24 scores compared to placebo. In US trials, only the 20 mg daily dose demonstrated statistical significance over placebo in change from baseline scores, although a trend toward efficacy was noted at lower doses in included studies.[6] The FDA recommends that patients are started at 10 mg daily and increased to a target daily dose of 20 mg as tolerated.[25] Non-US data shows statistical significance for lower doses of vortioxetine.[6] Of the published trials, only one studied the 20 mg daily dose.[6,20,24] Response and remission continue to be the most important clinical outcomes for patients.

Overall, vortioxetine appears to improve rates of response and remission when measured with MADRS or HAMD compared to placebo and the effect does not appear to be dose-dependent. Trials do not show a dose-response relationship. As an example, Henigsberg et al[15] studied three doses of vortioxetine and response rates were similar in all arms (1.90, 1.79, and 2.00 for 1 mg, 5 mg, and 10 mg, respectively). Remission rates were also similar at 1.55, 1.74, and 1.61 for the 1 mg, 5 mg and 10 mg groups, respectively. Of the published short-term efficacy studies, 2 had an overall quality rating of good, 4 were rated fair and one was of poor-fair methodological quality. Three of the four unpublished studies had a vortioxetine 20 mg arm, and two of these studies did not show that the 20 mg dose was statistically different than placebo in MADRS response or remission.

The baseline MADRS score of patients enrolled in short-term trials were in the low 30s on average, indicating moderate-to-severe MDD. A high percentage of participants were Caucasian, and a majority was female. In all but one study in elderly patients, the average age of participants was in the mid-40s. Extensive exclusion criteria included patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression. These characteristics of study participants make it hard to generalize these findings to a broader population.

One longer-term efficacy study evaluating relapse prevention was also conducted.[21] Patients were enrolled in a 12-week open-label, flexible dose treatment period and continued to the double-blind period if they were in remission (MADRS total score $\leq$10) at weeks 10 and 12 of the open-label treatment period.[21] During the double-blind period, included patients were randomized 1:1 to continue their stabilized dose (5 mg or 10mg) or switched to placebo. [21] A majority of the vortioxetine patients were on 10 mg daily.[21] The primary efficacy variable was time to relapse of depressive symptoms.[21] The proportion of patients who relapsed was lower in the vortioxetine group (15%) than the placebo group (30%) with a hazard ratio (HR) of 2.09 (95% CI: 1.35-3.23, p=0.0010).[21] This result may be biased toward vortioxetine because only patients who responded to vortioxetine during the single-blind run-in period were included in the double-blind treatment phase. There was a high rate of attrition in both groups.

While this drug is being promoted as having a new and novel mechanism of action, there is no evidence that it is more efficacious than other second generation antidepressants that are on the market. In the six trials where there was an active comparison (venlafaxine XR or duloxetine), vortioxetine did not have higher rates of response and remission than the active comparison. At low doses, there were no differences in response rates between vortioxetine and the active comparison, but when compared to 15 and 20 mg doses of vortioxetine, MADRS response rates were higher in the active control arms. There were no differences in remission rates at any dose of vortioxetine compared to the active control. There is a need for more head-to-head trials to truly understand vortioxetine's comparative effectiveness in this class.

Clinical Safety:

In the prescribing information, the most common adverse events are nausea, diarrhea and dry mouth; the most common serious adverse events are serotonin syndrome, abnormal bruising or bleeding, hypomania, or hypernatremia. It does not appear that side effects are dose-related; however there is an increase in withdrawals due to adverse events as the dose increases.

Two year-long open-label, single-arm extension studies evaluating a total of 1369 patients have been published.[22,23] In Alam et al, 70.6% of patients experienced a treatment-related adverse event, the most common being nausea (15.2%), headache (12.4%) and nasopharyngitis (9.8%).[23] Similar results were seen in the second extension study with 72.7% of patients experiencing an adverse event, the most common being nausea (19.8%), headache (15.3%) and nasopharyngitis (10.5%).[22] Serious adverse events occurred in 3.4% of patients in Baldwin et al and 3.5 % of patients in Alam et al.[22,23]

In the clinical program, all 6 deaths occurred in the vortioxetine treatment group.[6] The causes of death included 2 cancers, 1 suicide, 1 morphine toxicity, 1 road traffic accident, and 1 accidental death (an accidental fall from a balcony). [6] For the death from morphine toxicity and the accidental death, suicide could not be ruled out as a cause, according to the sponsor, due to limited information available.[6] All deaths were considered by the investigators as unrelated to vortioxetine treatment.[6]

Vortioxetine has not been studied in pediatric patients or patients with severe hepatic impairment. No subgroup analyses studying gender, race or ethnicity have been published.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Response*
2) Remission*
3) Relapse
4) Hospitalization
5) Quality of Life
6) Withdrawals due to adverse events
7) Major adverse events

*Secondary endpoints in vortioxetine trials

Primary Study Endpoint:

1) Change in baseline MADRS total score
2) Change in baseline HAMD total score

Table 2. Vortioxetine Comparative Evidence Table

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

Alvarez et al, 2012[14] MC, R, DB, PG, PC 6-week Non-US	V5: Vortioxetine 5mg daily V10: vortioxetine 10mg P: placebo VEN: venlafaxine XR 225mg	Demographics: adults 18-65, mean age: 43 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; 18-65 years old; MADRS total score ≥30 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	ITT: V5: 10 V10: 100 P: 105 D: 112 Attrition: V5: 10 (9.3%) V10: 1 (18.0% P: 18 (16.7% VEN: 19 (16.9%	<u>Mean change from baseline in MADRS:</u> V5: -20.4* V10: -20.2* P: -14.5 VEN: -20.9* *difference from placebo p-value: <0.0001 <u>MADRS Response Rate:</u> V5: 72/108 (66.7%) V10: 68/100 (68%) P: 47/105 (44.8%) VEN: 81/112 (72.3%) V5 Vs P: RR 1.49, 95% CI (01.15-1.93) p-value 0.002 V10 Vs. P: RR 1.52, 95% CI (1.17-1.97) p-value <0.001 VEN Vs P: RR 1.62, 95% CI (1.26-2.063) p-value <0.001 <u>MADRS Remission Rate:</u> V5: 53/108 (49.1%) V10:49/100 (49%) P: 28/105 (26.7%) VEN: 62/112 (55.4%) V5 Vs P: RR 1.84; 95% CI 1.27-2.67; p-value <0.01 V10 Vs P: RR 1.84; 95% CI 1.26-2.67; p-value <0.01 VEN Vs P: RR 1.69; 95% CI 1.12-2.57; p-value <0.001	NA 22%/5 23%/5 17%/6 22.4%/5 22.3%/5 28.7%/4	<u>Withdrawals Due to Adverse Events:</u> V5: 3 (2.8%) V10: 7 (7.0%) P: 4 (3.7%) VEN: 16 (14.3%) V5 Vs P: RR 0.73, 95% CI (0.13-3.78) P-value 0.719 V10 Vs P: RR 1.84, 95% CI (0.50-7.34) p-value 0.365 VEN Vs P: RR 3.75, 95% CI (1.23-13.08) p-value 0.009 <u>Serious Adverse Events:</u> V5: 0 NS V10: 2 (2.0%) NS P: 0 VEN: 1 (<1%) NS	NS NS 10.6%/10 NS	**Quality Rating:** Good **Internal Validity:** <u>Selection:</u> Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. <u>Performance:</u> Patients, caregivers and investigators were blinded. Patients were given weekly wallet cards containing double-dummy capsules and instructed to take both capsules at the same time every day <u>Detection</u>: Raters were trained to increase inter-rater reliability and training was chaired by an experienced investigator. Patients were assessed by same investigator at each visit, whenever possible. <u>Attrition</u>: a modified intention-to-treat analysis was used for efficacy outcomes and full-analysis set used for safety outcomes. Total attrition was 15%; loss to follow-up very low (n=1) **External Validity:** <u>Recruitment:</u> Advertisements used in Australia, Canada, Finland, Malaysia and Sweden, otherwise unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited non-Caucasian patients which limits the generalizability of results <u>Setting:</u> 49 non-US outpatient sites in Australia, Canada, Asia and Europe <u>Outcomes:</u> The primary endpoint was mean change from baseline in MADRS total score at week 6

Baldwin et al, 2011[15] MC, R, DB, PC 8 weeks Europe, Asia, Africa	V2.5: vortioxetine 2.5 mg V5: vortioxetine 5 mg V10: vortioxetine 10 mg P: placebo DUL: duloxetine 60 mg	Demographics: adults 18-75, mean age: 45 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; 18-65 years old; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	FAS: V2.5: 155 V5: 15 V10: 151 P: 145 DUL: 149 Attrition: V2.5: 25 (16.1% V5: 33 (21.3% V10: 34 (22.5% P: 22 (15.2% DUL: 36 (24.2%	<u>Mean change from baseline in MADRS:</u> V2.5: -16.2 p-value: 0.219 V5: -16.5 p-value: 0.132 V10: -16.3 p-value: 0.185 P: -14.8 DUL: -16.8 p-value: 0.74 <u>MADRS Response:</u> V2.5: 84/155 (54.2%) V5: 87/155 (56.1%) V10: 88/151 (57.6%) P: 68/145 (46.9%) DUL: 85/149 (57.1%) V2.5 Vs P: RR 1.16 (95% CI 0.92-1.45) V5 Vs P: RR 1.20 (95% CI 0.96-1.49) V10 Vs P: RR 1.24 (95% CI 1.00-1.55) DUL Vs P: RR 1.14 (95% CI 0.87-1.50) <u>MADRS Remission:</u> V2.5: 51/155 (32.9%) V5: 56/155 (36.1%) C: 54/151 (35.8%) P: 49/145 (33.8%) DUL: 52/149 (34.9%) V2.5 Vs P: RR 0.97 (95% CI 0.71-1.34) V5 Vs P: RR 1.07 (95% CI 0.79-1.46) V10 Vs P: RR 1.06 (95% CI 0.77-1.45) DUL Vs P: RR 1.02 (95% CI 0.72-1.46)	NA NS NS NS NS NS NS NS NS	<u>Withdrawals Due to Adverse Events:</u> V2.5: 10 (6.5%) V5: 18 (11.6%) V10: 15 (9.9%) P: 12 (8.3%) DUL: 19 (12.8%) V 2.5 Vs. P: RR 0.80, 95% CI (0.33-1.92), p-value 0.66 V5 Vs P: RR 1.41, 95% CI (0.67-3.04), p-value 0.34 V10 Vs P: RR 1.18, 95% CI (0.54-2.61), p-value 0.691 DULVs P: RR 1.51, 95% CI (0.73-3.22) p-value 0.259 <u>Serious Adverse Events:</u> Not reported	NS NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. <u>Performance:</u> Double blind, double dummy <u>Detection:</u> Double-blind; Raters were trained to increase inter-rater reliability and training was chaired by an experienced investigator. Patients were assessed by same investigator at each visit, whenever possible; scales were given in local languages with validated translations <u>Attrition:</u> Overall attrition is 20%; higher in the duloxetine group (28%) due to unknown reasons **External Validity:** <u>Recruitment:</u> Advertisements used in several countries; unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian and some Asian patients which limits the generalizability of results <u>Setting:</u> 100 inpatient and outpatient centers from 20 countries (Australia, Canada, Europe and Asia) <u>Outcomes</u> Primary endpoint was an ANCOVA of the change from baseline in MADRS total score at week 8. Covariates were treatment and site factors and the baseline MADRS total score.

Jain et al, 2012[16] MC, R, DB, PC US 6-weeks US	V: Vortioxetine 5 mg P: placebo	Demographics: adults 18-75, mean age: 42 y/o; 60% female Inclusion Criteria: Patients with MDD major depressive episode of at least 3 months' duration according to DSM-IV-TR criteria; outpatient; baseline MADRS score ≥ 30 at baseline Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	N: V: 300 P: 300 Attrition: V: 56 (18.7% P: 64 (21.3%	<u>Mean change from baseline in MADRS:</u> V: -15.8 P: -15.4 p-value: 0.326 95% CI: -2.19 to 1.55 <u>HAMD24 Response Rate:</u> V: 135/292 (46.2%) P: 132/286 (46.2%) RR: 1.0, 95% CI (0.83-1.19) p-value: 0.984 <u>MADRS Remission Rate:</u> V: 85/292 (29.1%) P: 92/286 (32.2%) RR: 0.90, 95% CI (0.70-1.16) p-value: 0.418	NA NS NS	<u>Withdrawals Due to Adverse Events:</u> V: 9 (3.0%) P: 11 (3.7%) RR 0.82, 95% CI (0.32-2.10) p-value 0.821 <u>Serious Adverse Events:</u> V: 7 (2.3%) P: 4 (1.3%) RR 1.75, 95% CI (0.47-7.06) p-value 0.55	NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Centralized computer system used for randomization and medication assignment <u>Performance:</u> Study medication was identical in appearance and dispensed using unique identification numbers; double-blind <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability <u>Attrition:</u> Slightly higher attrition in placebo group (21% vs 19%) with more protocol deviations and patients withdrawn in placebo group. Loss to follow up high (n=39) **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability to population <u>Setting:</u> Outpatient sites in the US <u>Outcomes:</u> Primary outcome change from baseline in HAMD total score at week 6 which is difficult to determine the clinical significance of. Response and Remission were included as secondary outcomes.

Henigsberg et al, 2012[17] MC, R, DB, PG, PC 8-weeks Europe, Asia, Africa	V1: Vortioxetine 1 mg V5: Vortioxetine 5 mg V10: vortioxetine 10mg P: placebo	Demographics: adults 18-75, mean age: 46 y/o; 63% female Inclusion Criteria: Patients with MDD major depressive episode of at least 3 months' duration according to DSM-IV-TR criteria; outpatient; baseline MADRS score ≥ 26 at baseline Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	FAS: V1: 140 V5: 140 V10: 140 P: 140 Attrition: V1: 13 (9.3%) V5: 11 (7.8%) V10: 18 (12.8%) P: 13 (9.3%)	Mean change from baseline in MADRS: V1: -14.82 p-value: N/A V5: -15.42 p-value: <0.001 V10: -16.23 p-value: <0.001 P: -11.30 MADRS Response Rate: V1: 65 (46.8%) V5: 61 (43.9%) V10: 68 (48.9%) P: 34 (24.5%) V1 Vs P: RR 1.90 (95% CI 1.35, 2.67); p-value <0.001 V5 Vs P: RR 1.79 (95% CI 1.27, 2.54); p-value = 0.001 V 10 Vs P: RR 2.00 (95% CI 1.43, 2.80); p-value <0.001 HAMD24 Response Rate: V1: 66 (47.5%) V5: 63 (45.3%) V10: 69 (49.6%) P: 32 (23.0%) V1 Vs P: RR 1.71 (95% CI 1.17, 2.55); p-value =0.004 V5 Vs P: RR 1.66 (95% CI 1.13, 2.49); p-value= 0.008 V10 Vs P: RR 1.77 (95% CI 1.21, 2.63); p-value =0.002 MADRS Remission Rate: V1: 36 (25.9%) V5: 40 (28.8%) V10: 37 (26.6%) P: 23 (16.5%) V1 Vs P: RR 1.55 (95% CI 0.97, 2.48); p-value = 0.003 V5 Vs P; RR 1.74 (95% CI 1.10, 2.74); p-value <0.001 V10 Vs P; RR 1.61 (95% CI 1.01, 2.56); p-value = 0.002	NA 22.3%/5 19.4%/6 24.4%/4 24.5%/4 22.3%/5 26.6%/4 9.4%/11 6.3%/16 6.1%/17	Withdrawals Due to Adverse Events: V1: 3 (2.1%) V5: 1 (0.7%) V10: 5 (3.6%) P: 2 (1.4%) Serious Adverse Events: V1: 1 (<1%) V5: 1 (<1%) V10: 5 (3.6%) P: 2 (1.4%)	NS NS	**Quality Rating:** Poor-Fair **Internal Validity:** Selection: Randomization occurred, no details were given. No allocation concealment details were given. Performance: Double-blind, blinding was maintained throughout the study; all study medication was identical in appearance and dispensed using unique identification numbers. Detection: Lack of detail and known inter-rater variability with no details for controlling for variability. Attrition: Stated modified intention to treat analysis conducted, but did not use. <10% total attrition, loss to follow-up low. **External Validity:** Recruitment: Unclear Patient Characteristics: Extensive exclusion criteria Setting: Outpatient sites in Europe, Africa, Asia Outcomes: Primary outcome change from baseline in HAMD total score and MADRS total score at week 8

Mahablesh-warker et al, 2013[18] MC, R, DB, PG, PC US 8-weeks	V2.5: vortioxetine 2.5 mg V5: vortioxetine 5 mg P: placebo DUL: duloxetine 60 mg	Demographics: adults 18-75, mean age: 42 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥22 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	ITT: V2.5: 146 V5: 15 P: 149 DUL: 149 Attrition: V2.5: 54 (32.3% V5: 31 (20.3% P: 42 (27.3% DUL: 33 (21.6%	<u>Mean change from baseline in HAMD24:</u> V2.5: -12.04 p-value: 0.138 V5: -11.08 p-value: 0.577 P: -10.50 DUL: -13.47 p-value: 0.005 <u>HAMD24 Response Rate:</u> V2.5: 60 (41.1%) V5: 58 (37.9%) P: 48 (32.2%) DUL: 76 (51.0%) V2.5 Vs P: RR 1.28, 95% CI (0.93-1.76) p-value: 0.118 V5 Vs P: RR 1.18, 95% CI (0.85-1.64) p-value: 0.335 DUL Vs P: 1.58, 95% CI (1.18-2.13) p-value: 0.001 <u>MADRS Remission Rate:</u> V2.5: 33 (22.6%) V5: 32 (20.9%) P: 33 (22.1%) DUL: 51 (34.2%) V2.5 Vs P: RR 1.02, 95% CI (0.65-1.61) p-value 0.925 V5 Vs P: RR 0.94, 95% CI 0.60-4.50) p-value 0.794 DUL Vs P: RR 1.55, 95% CI (1.04-2.31) p-value 0.28	NA NS NS 18.8%/6 NS NS NS	<u>Withdrawals Due to Adverse Events:</u> V2.5: 7 (4.5%) V5: 12 (7.8%) P: 7 (4.5%) DUL: 17 (11.2%) <u>Serious Adverse Events:</u> V2.5: 0 V5: 4 (2.6%) P: 2 (1.3%) DUL: 2 (1.3%)	NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Randomization schedule developed by Takeda and investigators were informed of each patient's coded treatment allocation by an interactive voice-activated system. <u>Performance:</u> Participants and investigators were blinded to treatment allocation for duration of study; identical capsules used <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> High attrition. Overall 26% attrition (35.3% on V2.5 group, 27.6% in DUL group). Overall loss to follow-up high (n=43). **External Validity:** <u>Recruitment:</u> advertisement posters, brochures, doctor-to-patient letters and websites <u>Patient Characteristics:</u> Extensive exclusion criteria <u>Setting:</u> 49 outpatient clinics in the US <u>Outcomes</u>: LS Mean change from baseline in HAMD24 total score after 8 weeks

Katona et al, 2012[19] MC, R, BD, PC US and non-US 8-weeks	V: Vortioxetine 5 mg P: Placebo D: Duloxetine 60mg	Demographics: adults ≥65, mean age: 70 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening, abnormal vital signs	FAS: V: 154 P: 145 D: 147 Attrition: V: 20 (12.8% P: 17 (11.7% D: 23 (15.2%	<u>Mean change from baseline in MADRS:</u> V: -13.7 p-value: 0.0011 P: -10.3 D: -15.8 p-value: <0.0001 <u>MADRS Response Rate:</u> V: 92 (59.7%) P: 52 (35.9%) D: 104 (70.7%) V Vs P: RR 1.67, 95% CI (1.28-2.17) p-value <0.001 D Vs P: RR 1.97, 95% CI (1.55-2.50) p-value <0.001 <u>HAMD24 Response Rate:</u> V: 82 (53.2%) P: 51 (35.2%) D: 93 (63.3%) V Vs P: RR 1.51, 95% CI (1.15-2.01) p-value <0.01 D Vs P: RR 1.80, 95% CI (1.39-2.33) p-value <0.001 <u>MADRS Remission Rate:</u> V: 52 (33.8%) P: 30 (20.7%) D: 69 (46.9%) V Vs P: RR 1.63, 95% CI (1.09-2.48) p-value <0.05 D Vs P: RR 2.27, 95% CI 1.57-3.34) p-value <0.001 <u>HAMD17 Remission Rate:</u> V: 45 (29.2%) P: 28 (19.3%) D: 51 (34.7%) V Vs P: RR 1.51, 95% CI (0.98-2.37) p-value <0.05 D vs P: RR1.80, 95% CI 1.81-2.77) p-value <0.01	NA 24%/4 35%/3 18%/6 28%/4 13%/8 24%/4 10%/10 15%/7	<u>Withdrawals Due to Adverse Events:</u> V: 10 (6.4%) P: 6 (4.1%) D: 15 (9.9%) V Vs P: RR 1.56, 95% CI (0.34-4.75) p-value: 0.875 D Vs P: RR 2.40, 95% CI (0.90-6.82) p-value 0.16 <u>Serious Adverse Events:</u> V: 1 (<1%) p-value: NS P: 4 (2.8%) D: 1 (<1%) p-value: NS	23%/43 6%/17 NW	**Quality Rating:** Good **Internal Validity:** <u>Selection:</u> Eligible patients assigned to double-blind treatment according to computer-generated randomization list; details of randomization were contained in a set of sealed opaque envelopes. Sequentially enrolled patients were assigned the lowest randomization number available in blocks of six at each site <u>Performance:</u> All investigators, trial personnel and patients were blinded to treatment assignment; double-dummy design used <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall low attrition. Loss to follow-up low (n=2) **External Validity:** <u>Recruitment:</u> Advertisements used to recruit patients in Sweden, Finland; otherwise unknown <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. <u>Setting:</u> 81 outpatient settings in Canada, Finland, France, Germany, Sweden, Ukraine and the US <u>Outcomes</u>: ANCOVA of the mean change from baseline in HAMD24 total score at week 8

Boulenger et al, 2013[21] MC, R, DB, PG, PC Non-US 8-weeks	V15: Vortioxetine 15mg V20: vortioxetine 20mg P: Placebo D: duloxetine 60 mg	Demographics: adults18-75, mean age: 46 y/o; 66% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening	FAS: V15: 149 V20: 151 P: 158 D: 146 Attrition: V15: 3 (23.0% V20: 2 (17.2% P: 25 (15.8% D: 16 (10.9%	Mean change from baseline in MADRS: V15: -17.2 p-value: <0.001 V20: -18.8 p-value: <0.001 P: -11.7 D: -21.2 p-value: <0.001 MADRS Response Rate: V15: 85 (57.0%) V20: 93 (61.6%) P: 51 (32.3%) D: 108 (74.0%) V15 Vs P: RR 1.77, 95% CI (1.35-2.33) p-value <0.0001 V20 Vs P: RR 1.91. 95% CI (1.47-2.45) p-value <0.0001 D Vs P: RR 2.29, 95% CI (1.81-2.89) p-value <0.0001 MADRS Remission Rate: V15: 52 (34.9%) V20: 58 (38.4%) P: 30 (19.0%) D: 79 (54.1%) V15 Vs P: RR 1.84, 95% CI (1.22-2.79) p-value 0.0016 V20 Vs P: RR 2.02, 95% CI (1.54-3.04) p-value 0.0002 D Vs P: RR 2.85, 95% CI (1.99-4.14) p-value <.0001	NA 24.7%/4 29.3%/3 41.7%/2 15.9%/6 19.4%/5 35.1%/3	Withdrawals Due to Adverse Events: V15: 10 (6.7%) V20: 17 (11.3%) P: 7 (4.4%) D: 7 (4.8%) V15 Vs P:RR 1.52, 95% CI (0.55-4.33), p-value 0.382 V20 Vs P: RR 2.54, 95% CI (1.03-6.63), p-value 0.032 D Vs P: RR 1.08, 95% CI (0.35-3.36) p-value 1.0 Serious Adverse Events: V15: 0 V20: 2 (1.3%) P: 0 D: 3 (2.0%) NS	NS 6.9%/15 NS NS	**Quality Rating:** Fair **Internal Validity:** Selection: Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. Performance: double-dummy design used Detection: Double-blind; Raters were trained to increase inter-rater reliability in MADRS, MINI, CGI, HAMA, and DESS scales. Attrition: Attrition overall was acceptable, however the V15 group had a higher level of attrition than other groups, with high numbers of patients withdrawn due to adverse events, lack of efficacy, and undefined. **External Validity:** Recruitment: Advertisements used in some countries, otherwise not described. Patient Characteristics: Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. Setting: Outpatient settings in 13 countries in Europe and South Africa Outcomes: Change from baseline in MADRS total score at week 8

Boulenger et al, 2012[21] MC, R, DB, PC Non-US Period I: 12-weeks Period II: 24-weeks	Period I: Open label, acute Tx V: Vortioxetine 5mg or V10 mg (flexible-dose) Period II: Relapse Prevention V: vortioxetine fixed dose (5 or 10 mg) P: placebo	Demographics: adults ≥65, mean age: 70 y/o; 65% female, 78.2% Caucasian Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening	Period I: N=639 Period II: V: 204 P: 192 Attrition: Period I: 37.4% Period II: V: 79 (38.3% P: 88 (41.2%	Period I: MADRS Response Rate: 75.7% MADRS Remission Rate: 68.7% Period II: Relapse Rate: V: 12.7% P: 23.4% HR 2.0, 95% CI 1.26-3.21 P=0.0035	NA NA NA	Withdrawals due to adverse events: Period I: 54/639 (8.4%) Period II: 16/206 (7.8%) vs. 5/194 (2.6%) Serious Adverse Events: Period I: NR Period II: V: 7 (3.4%) P: 4 (2.1%)	NA 0.052/ 20 NA 0.013/ 77	**Quality Rating:** Poor **Internal Validity:** Selection: All patients received open-label vortioxetine for 12 weeks and then were randomized to placebo or vortioxetine for 24 weeks. Patients were randomized based on a computer-generation randomization list, details were unknown to any investigators and contained in a set of sealed opaque envelopes. At each study center, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four Performance: All investigators, trial personnel and participants were blinded to treatment for the duration of the study. Medication was given as encapsulated tablets or matched placebo. Detection: Rater training was undertaken to increase inter-rater reliability and chaired by an experienced investigator. Only those investigators who had actively participated in training sessions prior to inclusion of patients into the study and received certification were allowed to rate patients. Scales were used in local language versions. Attrition: High overall attrition **External Validity:** Recruitment: Advertisements used in 9 countries, otherwise unclear Patient Characteristics: Extensive exclusion criteria Setting: 66 outpatient settings in 17 countries (Europe, Asia, Canada, and Australia Outcomes: Time to relapse of MDD (MADRS score of >10) within the first 24 weeks of the double-blind period.

Baldwin et al 2012[22]	A: vortioxetine 2.5-10 mg	Demographics: adults 18-75, mean age: 46 y/o; 68% female Inclusion Criteria: Patients enrolled in Baldwin et al 2011 if investigator judged that 12 months of therapy was indicated Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	N=535 Attrition: A: 207 (38.7%	MADRS Response at week 52 (LOCF): 84.3% MADRS Remission at 52 weeks (LOCF): A: 71.2%	NA NA	Withdrawals due to adverse events: A: 42/535 (7.9%) Serious Adverse Events: A: 18/535 (3.4%)	NA NA	**Quality Rating:** Poor As an open-label, single-arm study, this does not constitute an adequate, well-controlled study

Alam et al[23] 2013	A: vortioxetine 2.5-10 mg	Demographics: adults 18-75, mean age: 46 y/o; 68% female; 83% Caucasian Inclusion Criteria: Patients enrolled in Mahableshwarker et a 2013l or Henigsberg et al 2012 and if investigator judged that 12 months of therapy was indicated Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, experienced a continuing moderate or severe adverse events related to treatment from the original acute trial, or using disallowed medications	N= 836 Attrition: 310 (37%)	MADRS Response at week 52 (LOCF): 60.2% MADRS Remission at 52 weeks (LOCF): A: 61.7%	NA NA	Withdrawals due to adverse events: A: 49/836 (7.9%) Serious Adverse Events: A: 29/836 (3.5%)	NA NA	**Quality Rating:** Poor As an open-label, single-arm study, this does not constitute an adequate, well-controlled study

levomilnacipran (Fetzima®)

FDA approved indications: Treatment of MDD

Clinical Efficacy Data:

Levomilnacipran is the active enantiomer of milnacipran, an SNRI approved for use in fibromyalgia.[29] The approval of levomilnacipran in July 2013 was based on three 8-week, placebo-controlled RCTs in adults with MDD.[5,26–28] Two additional studies have been published, one short term efficacy study and one longer-term safety study.[28,30]The trials included a total of 2,243 adult patients (ages 18-70 years) meeting DSM-IV-TR criteria for MDD, single episode or recurrent. Table 3 provides a summary of the evidence findings for the two studies. The primary measure used to evaluate efficacy was change from baseline in total MADRS score. Response and remission rates remain the most relevant clinical efficacy endpoints in treating MDD.

Response rates appear to be similar for the 40 mg and 80 mg doses in available studies, but there was an increase in MADRS response with the 120 mg dose. MADRS remission rates were similar among all doses, although data is limited. MADRS response rates were similar between the two doses of levomilnacipran

studied in the Bakish et al study with RRs of 1.43 (95% CI 1.10-1.86) and 1.34 (95% CI 1.05-1.78) for the 40 mg and 80 mg groups, respectively.[27] MADRS remission RRs were 1.67 (95% CI 1.12-2.51) and 1.80 (95% CI 1.22-2.68) for the 40 mg and 80 mg groups, respectively. In Asnis et al, which studied three doses of levomilnacipran, only the 120mg group had a statistically significant MADRS response rate (RR 1.42; 95% CI 1.05-1.94), while no group was statistically significant for MADRS remission rates.[31] A third short-term efficacy study titrated patients from levomilnacipran SR 25 mg daily to either 75 mg or 100 mg daily based on tolerance; both MADRS response (RR 1.34; 95% CI 1.18-1.66)and MADRS remission (RR 1.78; 95% CI 1.40-2.28) outcomes were statistically significant.[30]The flexible-dose study grouped all doses of levomilnacipran together which limits our ability to fully appraise this study for efficacy.[31]

The baseline MADRS score of patients enrolled in Montgomery et al and Bakish et al was 30 (moderate-to-severe MDD). In Asnis et al, the baseline MADRS score was 36, indicating a slightly more sever patient population. A high percentage of participants in all trials were Caucasian, mostly female and in their early 40s. Extensive exclusion criteria included patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression. These characteristics of study participants make it hard to generalize these findings to a broader population.

No head-to-head studies or studies with an active comparator have been published. Levomilnacipran has not been studied in pediatric patients or patients with severe hepatic impairment. Dose adjustments should be made for patients with renal insufficiency. No subgroup analyses studying gender, race or ethnicity have been published.

Clinical Safety:

The most common adverse events seen in trials as compared to placebo were nausea, constipation, hyperhidriosis, tachycardia, erectile dysfunction, increased heart rate and urinary hesitation.[5] The two dose-related adverse reactions were urinary hesitation and erectile dysfunction.[5]

One long-term, open-label extension study of levomilnacipran including 825 patients has been published to examine safety and tolerability.[28] In this study, 13.0% of patients withdrew from the study due to adverse events. The most common adverse events seen were headache (22.2%), nausea (16.2%), upper respiratory tract infection (13.2%), hyperhidrosis (10.9%), constipation (9.6%), nasopharyngitis (8.5%), dizziness (8,1%), insomnia (8.0%), tachycardia (7.6%), dry mouth (7.2%), and erectile dysfunction (5.6% of men). Serious adverse events occurred in 4.0% of patient and no deaths occurred.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Response*
2) Remission*
3) Relapse
4) Hospitalization
5) Quality of Life
6) Withdrawals due to adverse events
7) Major adverse events

*Secondary endpoints in levomilnacipran trials

Primary Study Endpoint:

1) Change in baseline Montgomery-Asberg Depression Rating Scale (MADRS)

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Date: May 2014

Table 3. Levomilnacipran Comparative Evidence Table

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Montgomery et al, 2013[30] MC, DB, PC, PG, RCT 10 weeks	L: levomilnacipran SR 75 mg or 100 mg P. Placebo	Demographics: Adult patients (18-70 yrs); mean age 44.5 y/o; 66.5% female; 91% white Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥1 month; HAMD17 score >22/SDS score ≥10 with at least 1 subscale ≥6 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; substance abuse (last 6 months); physical condi39ons; pregnancy; allergy/nonresponse to milnicipran; psychotherapy sessions previous 6 months; ECT (preceding 3 months); concomitant psychotropic medicine	Full Analysis Set (FAS): L: 276 P: 277 Attrition: L: 57 (20.2%) P: 70 (24.9%)	<u>Difference in MADRS total score from baseline vs placebo, LOCF (week 10):</u> LS mean difference: -3.7 95% CI (-5.2 to -2.1) p-value: <0.0001 <u>MADRS Response Rate*</u>: L: 163 (59.1%) P: 117 (42.2%) RR 1.34; 95% CI 1.18-1.66; p-value: <0.0001 <u>MADRS Remission Rate*</u>: L: 128 (46.4%) P: 72 (26.0%) RR 1.78; 95% CI (1.40-2.28); p-value: <0.0001	NA 17%/ 6 20.4%/ 5	<u>Withdrawals Due to Adverse Events:</u> L: 26 (9.4%) P: 18 (6.5%) RR 1.44, 95% CI (0.78-2.69) p-value 0.272 <u>Serious Adverse Events:</u> L: 3 (1.1%) P: 9 (3.2%) RR 0.35, 95% CI (0.08-1.39) p-value 0.143	NS NS	**Quality Rating:** Fair **Internal Validity: RoB** <u>Selection:</u> Patients were randomized by a computer-generated list of numbers that were blindly linked to test drug or placebo; groups in each study center were balanced according to severity of baseline MADRS score (<30 or ≥30). Blinding information was contained in sealed decoding envelopes. <u>Performance:</u> Double-blind design used. During titration, patients received an equivalent number of identical-looking active or placebo capsules. Patients assigned to active treatment were titrated from 25 mg to 75 mg over 11 days. If good tolerance was discerned by telephone assessment, the 100mg active target dose was initiated on day 12 and maintained for the study duration. <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall attrition high, more loss in the placebo group due to insufficient therapeutic response and worsening of MDD. **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. <u>Setting:</u> 68 sites in Europe, India, and South Africa <u>Outcomes</u>: MADRS total score change from baseline to week 10

Asnis et al, 2013[26]	L40: levomilnacipran SR 40m mg L80: levomilnacipran SR 80m mg L120: levomilnacipran SR 120m mg P: placebo	Demographics: Adult patients (18-65 yrs); mean age 41 y/o; 64% female; 75% white Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥8 weeks; MADRS score ≥30, BMI ≥18 and ≤40 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; lifetime history of manic/hypomanic episode; substance abuse (last 6 months); medical conditions; suicide risk; pregnancy; allergy/nonresponse to milnicipran, other SNRIs/ SSRIs; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	mITT: L40: 176 L80: 177 L120: 176 P: 175 Attrition: L40: 48 (27.0%) L80: 58 (32.4%) L120: 63 (35.0%) P: 38 (21.6%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L40: -8.6 (vs. P: p-value NS) L80: -9.7 (vs. P: p-value <0.05) L120: -9.7 (vs. P: p-value <0.05) P: -7.2 <u>MADRS Response Rate*</u>: L40: 64 (36.4%) L80: 66 (37.3%) L120: 73 (41.5%) P: 51 (29.1%) L40 VS P: RR 1.25; 95% CI (0.91-1.72); p-value NS L80 VS P: RR 1.27; 95% CI (0.93-1.76); p-value NS L120 VS. P: RR 1.42; 95% CI (1.05-1.94); p-value 0.019 <u>MADRS Remission Rate*</u>: L40: 38 (21.6%) L80: 37 (20.9%) L120: 36 (20.5%) P: 34 (19.4%) L40 VS P: RR 1.11; 95% CI (0.72-1.73); p-value NS L80 VS P: RR 1.08; 95% CI (0.69-1.68); p-value NS L120 VS P: RR 1.05; 95% CI (0.67-1.65); p-value NS	NA NS NS 12.4%/ 8 NS NS NS	<u>Withdrawals Due to Adverse Events:</u> L40: 13 (7.3%) L80: 26 (14.5%) L120: 12 (6.7%) P: 3 (1.7%) L40 Vs P: RR 4.065, 95% CI (1.112-17.842), p-value 0.020 L80 Vs P: RR 7.620, 95% CI (4.274-31.414), p-value <0.001 L120 Vs. P: RR 3.733, 95% CI (1.007-16.551), p-value=0.033 <u>Serious Adverse Events:</u> L40: 2 (1.1%) L80: 1 (0.6%) L120:0 P: 0 All arms vs. P: NS	5.6%/ 18 12.8%/ 8 5%/ 20 NS	**Quality Rating:** Fair **Internal Validity: RoB** <u>Selection:</u> Patients were randomized by a computer generated list of numbers. <u>Performance:</u> Investigators and patients were blinded to allocation throughout treatment and down-taper periods. Patients were assigned to identically appearing treatment. Blinding was maintained via a secured randomization code list. <u>Detection:</u> Double blind. Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> High attrition in the levomilnacipran groups, especially due to adverse events and withdrawal of consent **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability <u>Setting:</u> 38 US outpatient centers <u>Outcomes</u>: MADRS total score mean change from baseline at week 8

Bakish et al, 2013[27]	L40: Levomilnacipran SR 40 L80: Levomilnacipran SR 80 P: placebo	Demographics: adult patients 18-75 yrs; mean age 43; 63% female; 74% white Inclusion Criteria: DSM-IV-TR criteria for recurrent MDD, current episode of MDD 6 weeks-12 months; 5 or fewer episodes of MDD within previous 5 years; MADRS score ≥26, CGI-S score ≥4; BMI ≥18 and≤40 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; lifetime history of manic/hypomanic episode; substance abuse (last 6 months); medical conditions; suicide risk; pregnancy; allergy/nonresponse to milnicipran, other SNRIs/ SSRIs, or levomilnicipran; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	ITT: L40: 185 L80: 187 P: 185 Attrition: L40: 40 (21.6%) L80: 45 (24.1%) P: 31 (16.7%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L40: -13.1 (vs. P: p-value = 0.025) L80: -13.1 (vs. P: p-value = 0.024) P: -10.7 <u>MADRS Response Rate*</u>: L40: 90 (49%) L80: 88 (47%) P: 63 (34%) L40 vs P: RR 1.43; 95% CI (1.10-1.86) p-value = 0.004 L80 vs P: RR 1.34; 95% CI 1.05-1.78) p-value = 0.010 <u>MADRS Remission Rate*</u>: L40: 55 (30%) L80: 60 (32%) P: 33 (18%) L40 vs P: RR 1.67; 95% CI (1.12-2.51) p-value = 0.012 L80 vs P: RR 1.80; 95% CI (1.22-2.68) p-value = 0.002	NA 15%/7 13%/ 8 12%/ 8 14%/ 7	<u>Withdrawals Due to Adverse Events:</u> L40: 12 (6.4%) L80: 19 (10.1%) P: 3 (1.6%) L40 Vs. P: RR 3.817, 95% CI (1.029-16.925); p-value: 0.032 L80 Vs. P: RR 5.780, 95% CI 1.668-24.400); p-value: 0.001 <u>Serious Adverse Events:</u> L40: 0 L80: 0 P: 0 All vs. P: NS	4.8%/ 21 8.5%/ 12 Ns	**Quality Rating:** Fair **Internal Validity: RoB** <u>Selection:</u> Allocation was performed using a computer-generated randomization numbers and treatment assignments were made using a web-response system <u>Performance:</u> Identically appearing treatments with labels corresponding to the sequence of treatment assignment were supplied. All study personnel and patients were blinded to treatment for the entire study period. <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall high attrition (23%), with more attrition in the levomilnacipran groups due to more adverse events and more protocol violations **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability <u>Setting:</u> 51 outpatient centers in the US and Canada <u>Outcomes</u>: Change from baseline in MADRS total score at week 8

Sambunaris et al, 2014[31] MC, DB, PC, PG, RCT	L: levomilnacipran SR 40-120 mg P: Placebo	Demographics: Adult patients (18-80 yrs); mean age 45 y/o; 65% female Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥4 weeks; MADRS score ≥30, BMI ≥18 and ≤40 Exclusion Criteria: current of history of psychiatric or personality disorders; lifetime history of major psychiatric diagnosis;medical conditions; suicide risk; pregnancy; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	mITT: L: 215 P: 214 Attrition: L: 54 (24.9%) P: 54 (20.7%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L: -13.9 P: -11.4 Difference: -2.53; 95% CI: (-4.557, -0.549) p-value: 0.0127 <u>MADRS Response Rate*</u>: L: 90 (41.9%) P: 63 (29.4%) RR 1.42, 95% CI (1.09-1.87) p-value: 0.0083 <u>MADRS Remission Rate*</u>: L: 37 (17.2%) P: 39 (18.2%) RR 0.94, 95% CI (0.61-1.46) p-value: 0.441	NA 12.4%/8 NS	<u>Withdrawals Due to Adverse Events:</u> L: 17 (7.8%) P: 7 (3.2%) RR 2.313, 95% CI (0.926-6.071) p-value 0.059 <u>Serious Adverse Events:</u> L: 2 (<1%) P: 3 (1.4%) NS	NS NS	**Quality Rating: Poor-Fair** **Internal Validity: RoB** <u>Selection:</u> Patients randomized by a computer generated list of numbers <u>Performance</u>: Patients assigned to identically appearing treatment that corresponded to the sequence of randomization numbers; investigators and patients were blinded to treatment assignment. Levomilnacipran was titrated up based on response but no details were given about how placebo was matched when patients were titrated, or if both groups were assess at each time point and medication was adjusted accordingly. <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall high attrition. Higher attrition in levomilnacipran group due to more withdrawals due to adverse events **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> No details given <u>Setting:</u> 23 US outpatient centers <u>Outcomes</u>: Change from baseline in MADRS total score at week 8

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Appendix 1: Specific Drug Information: Vortioxetine

CLINICAL PHARMACOLOGY:

PHARMACOKINETICS[25]

Parameter	Result
Oral Bioavailability	75%
Protein Binding	98%
Elimination	Urine (59%); feces (26%)
Half-Life	~66 hours
Metabolism	Hepatic through CYP450, primarily CYP 2D6, and gloconic acid conjugation

DOSE & AVAILABILITY[25]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5 mg, 10 mg, 20 mg	PO	Daily	Initial: 10 mg once daily; increase to 20 mg once daily as tolerated; consider 5 mg once daily for patients who do not tolerate higher doses. Maintenance: 5-20 mg once daily.	None	Mild-to-moderate: no adjustment Severe: Do not use (has not been studied)	Has not been studied	Same as adult	• May be taken without regard to meals • If switiching from MAOI, 14 days should elapse before starting vortioxetine

DRUG SAFETY[25]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning: Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults **(18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. **Vortioxetine is not approved for use in children.**

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Contraindications: Hypersensitivity to vortioxetine or any component; use of MAO inhibitors concurrently or within 21 days of discontinuing vortioxetine or within 14 days of discontinuing the MAO inhibitor; initiation of vortioxetine in a patient receiving linezolid or intravenous methylene blue.

Cautions: use caution in elderly patients; may have higher risk of SIADH or hyponatremia

Warnings and Precautions:

Serotonin syndrome: Potentially life-threatening serotonin syndrome (SS) has occurred with serotonergic antidepressants (eg, SSRIs, SNRIs), particularly when used in combination with other serotonergic agents (eg, triptans, TCAs, fentanyl, lithium, tramadol, buspirone, St John's wort, tryptophan) or agents that impair metabolism of serotonin (eg, MAO inhibitors intended to treat psychiatric disorders, other MAO inhibitors [ie, linezolid and intravenous methylene blue]). Monitor patients closely for signs of SS such as mental status changes (eg, agitation, hallucinations, delirium, coma); autonomic instability (eg, tachycardia, labile blood pressure, diaphoresis); neuromuscular changes (eg, tremor, rigidity, myoclonus); GI symptoms (eg, nausea, vomiting, diarrhea); and/or seizures. Discontinue treatment (and any concomitant serotonergic agent) immediately if signs/symptoms arise.

Discontinuation syndrome: Abrupt discontinuation or interruption of antidepressant therapy has been associated with a discontinuation syndrome. Symptoms arising may vary with antidepressant however commonly include nausea, vomiting, diarrhea, headaches, lightheadedness, dizziness, diminished appetite, sweating, chills, tremors, paresthesias, fatigue, somnolence, and sleep disturbances (eg, vivid dreams, insomnia). Greater risks for developing a discontinuation syndrome have been associated with antidepressants with shorter half-lives, longer durations of treatment, and abrupt discontinuation. For antidepressants of short or intermediate half-lives, symptoms may emerge within 2-5 days after treatment discontinuation and last 7-14 days.

Mania/hypomania: May precipitate a mixed/manic episode in patients at risk for bipolar disorder. Use with caution in patients with a family history of bipolar disorder, mania, or hypomania. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Vortioxetine is not FDA approved for the treatment of bipolar depression.**

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Vortioxetine may be confused with duloxetine, fluoxetine, paroxetine, venlafaxine

Appendix 2: Specific Drug Information : Levomilnacipran

CLINICAL PHARMACOLOGY: Levomilnacipran

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	92%
Protein Binding	22%
Elimination	Renal (58% excreted unchanged)
Half-Life	12 hours
Metabolism	CYP3A4 (major)

DOSE & AVAILABILITY[5]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
20mg 40mg 80mg 120mg	oral	Daily	Start with 20 mg/day for 2 days, the increase to 40 mg/day, may increase by 40 mg/day every 2 days. Maximum recommended dose is 120mg/day	CrCl 30-59 mL/min: do not exceed 80 mg/day CrCl 15-29 mL/min: do not exceed 40mg/day ESRD: do not use	none	Safety and efficacy not established in patients <18 years old	No dose adjustment	• If switiching from MAOI, 14 days should elapse before starting levomilnacipran • When used with a strong CYP3A4 inhibitor, dose should not exceed 80 mg/day • Not approved for the management of fibromyalgia

DRUG SAFETY[5]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning: Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults. Monitor all patients started on antidepressants for worsening and emergence of suicidal thoughts and behaviors. This is based on a pooled analysis of 24 short-term studies of 9 antidepressant drugs in children and adolescents on antidepressants. All antidepressants carry this warning.

Contraindications: Known hypersensitivity to any component of the drug; the use of MAOIs within 14 days of starting or 7 days of stopping treatment with levomilnacipran; uncontrolled narrow-angle glaucoma due to increased risk of mydriasis when used concomitantly with levomilnacipran

Warnings and Precautions: There is an increased risk of serotonin syndrome with SSRIs and SNRIs, particularly when used with other serotonergic drugs and with drugs that impair the metabolism of serotonin (MAOIs, linezolid and IV methylene blue). SNRIs, including levomilnacipran, have been associated with increase s in blood pressure; in short-term trials with levomilnacipran, there was a mean increases in systolic BP of 3 mmHg and diastolic BP of 3.9 mmHg, compared to no change in the placebo group. Levomilnacipran was associated with a mean increase in heart rate of 7.4 beats per minute (bpm) in trials compared to a decrease of 0.3 bpm in placebo-treated patients. Urinary hesitation occurred in 4-6% of levomilnacipran patients compared to no patients in the placebo groupin short-term studies. Patients should not abruptly discontinue levomilnacipran due to adverse events following abrupt discontinuation.

Pregnancy/Lactation: Pregnancy Category C. No teratogenic effects were observed when levomilnacipran was administered to pregnant rats or rabbits at doses up to 8 and 16 times the maximum recommended human dose (MRHD). Fetal body weights were reduced in rats, and skeletal ossification was delayed in both rats and rabbits at this dose; these effects were not observed in either species at doses up to 2.5 and 5 times the MHRD. However, no studies have been performed with pregnant women so the drug should be used during pregnancy only if needed. It is not known if levomilnacipran is present in human milk; studies have shown that it

does pass into the milk of lactating rats. Therefore, breastfeeding women should decide to discontinue nursing or discontinue the drug based on the risks and benefits.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Levomilnacipran may be confused with milnacipran, levonunolol, levocarnitine, levocetirizine, levodopa, levofloxacin, levoleucovorin, levonogestrel, levorphanol, levothyroxine, and levomefolate.

Appendix 3: Abstracts of potentially relevant randomized controlled trials and systematic reviews

Bose, A., J. Tsai, et al. (2012). "Early non-response in patients with severe depression: escitalopram up-titration versus switch to duloxetine." Clin Drug Investig **32**(6): 373-85.
BACKGROUND: Comparative evidence for second-step treatment strategies in severe depression is scarce. Up-titrating a well-tolerated selective serotonin reuptake inhibitor (SSRI) versus switching to a serotonin norepinephrine reuptake inhibitor (SNRI) after initial SSRI non-response are possible treatment options. It is often unclear whether relevant tolerability and efficacy differences exist between SSRI up-titration versus switch to an SNRI. OBJECTIVE: The objective of this study was to evaluate tolerability and efficacy of up-titration of escitalopram versus switch to duloxetine in patients who failed to respond to escitalopram 10 mg/day. METHODS: This was an active-controlled, parallel-group, double-blind, randomized study in a general community comparing escitalopram and duloxetine in patients with severe depression; patients who did not respond (<50% Montgomery-Asberg Depression Rating Scale [MADRS] improvement) to 2 weeks of single-blind escitalopram 10 mg/day during the lead-in period were randomized to 8 weeks of double-blind treatment. 571 male and female outpatients aged 18-65 years with severe depression (MADRS total score >/=30) participated in the study and received at least one dose of escitalopram 10 mg/day in the single-blind lead-in phase. During the double-blind randomized phase, 474 patients who did not respond to lead-in escitalopram were randomized and received treatment with escitalopram 20 mg (n = 229) or duloxetine 60 mg (n = 245). Treatment was single-blind escitalopram 10 mg/day during a 2-week lead-in followed by 8-week double-blind escitalopram 20 mg/day or duloxetine 60 mg/day. The main outcome measure was time to all-cause premature study discontinuation. RESULTS: There was no difference in time to all-cause discontinuation between groups (hazard ratio escitalopram/duloxetine = 0.95 [95% CI 0.64, 1.41]; p = 0.727). Treatment with escitalopram compared with duloxetine resulted in significant improvement in MADRS total score at the end of week 8 (least squares mean difference [LSMD] = -1.87 [95% CI -3.60, -0.14]; p = 0.034) using last observation carried forward (LOCF) analysis. Significantly more escitalopram (54%) than duloxetine (42%) patients achieved remission (MADRS </=10) by week 8 (p = 0.013). Adverse events were similar between the two treatment groups. CONCLUSION: In initial non-responders to escitalopram 10 mg/day, dose escalation to 20 mg/day provided better efficacy than switching to duloxetine 60 mg/day, while discontinuations for any reasons and adverse events were similar. CLINICAL TRIAL REGISTRATION: Registered at ClinicalTrials.gov as NCT00384436.

Jonas, D. E., K. Cusack, et al. (2013). *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)*. Rockville MD.
To assess efficacy, comparative effectiveness, and harms of psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). MEDLINE(R), Cochrane Library, PILOTS, International Pharmaceutical Abstracts, CINAHL(R), PsycINFO(R), Web of Science, Embase, U.S. Food and Drug Administration Web site, and reference lists of published literature (January 1980-May 2012). Two investigators independently selected, extracted data from, and rated risk of bias of relevant trials. We conducted quantitative analyses using random-effects models to estimate pooled effects. To estimate medications' comparative effectiveness, we conducted a network meta-analysis using Bayesian methods. We graded strength of evidence (SOE) based on established guidance.

We included 92 trials of patients, generally with severe PTSD and mean age of 30s to 40s. High SOE supports efficacy of exposure therapy for improving PTSD symptoms (Cohen's d -1.27; 95% confidence interval, -1.54 to -1.00); number needed to treat (NNT) to achieve loss of diagnosis was 2 (moderate SOE). Evidence also supports efficacy of cognitive processing therapy (CPT), cognitive therapy (CT), cognitive behavioral therapy (CBT)-mixed therapies, eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy for improving PTSD symptoms and/or achieving loss of diagnosis (moderate SOE). Effect sizes for reducing PTSD symptoms were large (e.g., 28.9- to 32.2-point reduction in Clinician-Administered PTSD Scale [CAPS]; Cohen's d ~ -1.0 or more compared with controls); NNTs were </= 4 to achieve loss of diagnosis for CPT, CT, CBT-mixed, and EMDR. Evidence supports the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms (moderate SOE); effect sizes were small or medium (e.g., 4.9- to 15.5-point reduction in CAPS compared with placebo). Evidence for paroxetine and venlafaxine also supports their efficacy for inducing remission (NNTs ~8; moderate SOE). Evidence supports paroxetine's efficacy for improving depression symptoms and functional impairment (moderate SOE) and venlafaxine's efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). Risperidone may help PTSD symptoms (low SOE). Network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective than most medications for reducing PTSD symptoms, but analysis was based largely on indirect evidence and limited to one outcome measure (low SOE). We found insufficient head-to-head evidence comparing efficacious treatments; insufficient evidence to verify whether any treatment approaches were more effective for victims of particular trauma types or to determine comparative risks of adverse effects. Several psychological and pharmacological treatments have at least moderate SOE supporting their efficacy: exposure, CPT, CT, CBT-mixed therapies, EMDR, narrative exposure therapy, fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine.

Raskin, J., T. George, et al. (2012). "Apathy in currently nondepressed patients treated with a SSRI for a major depressive episode: outcomes following randomized switch to either duloxetine or escitalopram." J Psychiatr Res **46**(5): 667-74.
Apathy in the context of treated major depressive disorder (MDD) is a common but understudied symptom. This multicenter, double-blind, randomized study investigated whether switching from a selective serotonin reuptake inhibitor (SSRI) to a serotonin-norepinephrine reuptake inhibitor (SNRI), compared with switching to another SSRI, improved apathy symptoms in patients who had been treated with a SSRI for MDD for >/= 3 months, were no longer depressed (Montgomery-Asberg Depression Rating Scale [MADRS] total score </= 15), and continued to have apathy (Apathy Evaluation Scale-- Clinician rated version [AES-C] total score >30). Following 8 weeks of treatment, both the duloxetine (SNRI, 244 patients) and escitalopram (SSRI, 239 patients) groups significantly improved from baseline on the AES-C total score (least squares mean change [standard error]: duloxetine -13.9 [0.54]; escitalopram -13.5 [0.54], both P < 0.001), and on the secondary apathy, depression, and functional outcomes. There were no significant differences between the two groups on any measure, including AES-C total score (least squares mean difference [95% confidence interval]: -0.4 [-1.87 to 1.10], P = 0.612; primary objective). There was a significant within-group improvement in apathy in the subgroup who received escitalopram before and during the study. There were few differences in safety between the two groups. This study did not support the hypothesis that switching from a SSRI to a SNRI has a beneficial effect on apathy symptoms. However, given the study limitations, it is possible that more specific targeting of the noradrenergic pathway would be of benefit.

Richard, I. H., M. P. McDermott, et al. (2012). "A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease." Neurology **78**(16): 1229-36.
OBJECTIVE: To evaluate the efficacy and safety of a selective serotonin reuptake inhibitor (SSRI) and a serotonin and norepinephrine reuptake inhibitor (SNRI) in the treatment of depression in Parkinson disease (PD). METHODS: A total of 115 subjects with PD were enrolled at 20 sites. Subjects were randomized to receive an SSRI (paroxetine; n = 42), an SNRI (venlafaxine extended release [XR]; n = 34), or placebo (n = 39). Subjects met DSM-IV criteria for a depressive disorder, or operationally defined subsyndromal depression, and scored >12 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Subjects

were followed for 12 weeks (6-week dosage adjustment, 6-week maintenance). Maximum daily dosages were 40 mg for paroxetine and 225 mg for venlafaxine XR. The primary outcome measure was change in the HAM-D score from baseline to week 12. RESULTS: Treatment effects (relative to placebo), expressed as mean 12-week reductions in HAM-D score, were 6.2 points (97.5% confidence interval [CI] 2.2 to 10.3, p = 0.0007) in the paroxetine group and 4.2 points (97.5% CI 0.1 to 8.4, p = 0.02) in the venlafaxine XR group. No treatment effects were seen on motor function. CONCLUSIONS: Both paroxetine and venlafaxine XR significantly improved depression in subjects with PD. Both medications were generally safe and well tolerated and did not worsen motor function. CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that paroxetine and venlafaxine XR are effective in treating depression in patients with PD.

Santaguida, P. L., G. MacQueen, et al. (2012). *Treatment for Depression After Unsatisfactory Response to SSRIs*. Rockville MD.
A comparative effectiveness review was undertaken to evaluate treatment strategies in patients who failed to respond to selective serotonin reuptake inhibitors (SSRIs) as first-line treatment. The efficacy (benefits and harms) of monotherapy approaches (dose escalation, increased duration, or switch) or combined therapies were evaluated. Efficacy in the context of subgroups was also evaluated. Recommendations in Clinical Practice Guidelines (CPGs) from 2004 to April 2011 were compared. MEDLINE(R), Embase(R), CINAHL(R), PsychINFO(R), AMED (Allied and Complementary Medicine), Cochrane Database of Systematic Reviews, and Cochrane Central(R) were searched from 1980 to April 13, 2011. An extensive grey literature search was also undertaken, including publications of drug regulatory agencies. Systematic review methodology was employed.Eligibility criteria included English studies of adults (aged >/=18 years) or adolescents and children (8-18 years) with major depressive disorder, dysthymia, or subsyndromal depression, who had an inadequate response to an SSRI at entry into the study. Comparative study designs were eligible. Publications focusing only on treatment algorithms were not considered to be CPGs. From 46,884 citations, there were 44 studies and 27 guidelines that were eligible. Key Questions 1 and 2 (KQ1-a and KQ2): Forty-one studies included adults and three studies included adolescents; all included subjects with major depressive disorder except for one with adult dysthymia and subsyndromal patients alone. A limited number of studies (n=11) evaluated monotherapy strategies and these showed no differences among approaches. Although there were more studies evaluating monotherapy relative to combined therapies (n=33), the types of add-on agents were numerous and showed no relative differences; the exception was the addition of risperidone to an SSRI. KQ 3: Seven studies evaluated the impact of disease type, disease severity, previous comorbidities, age, gender, and race on treatment outcomes and showed no clear trend. KQ4: From 18 CPGs for adults, the majority did not provide specific recommendations for monotherapy strategies; for combination therapies, although specific agents were specified, there was variability across CPGs when recommending agents and strategies. Recommendations were more consistent for the CPGs for adolescents (n=7). There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. All but 2 of 44 studies showed no relative differences in response and remission rates. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit with combined therapy. The majority of studies were not designed to assess superiority of the strategies. Inconsistency and lack of clarity for clinical actions were noted when comparing CPGs.