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Class Update: Second Generation Antidepressant Medications

EXECUTIVE SUMMARY:

Month/Year of Review: April 2012
New Product for review: vilazodone (Viibryd®)
Manufacturer: Forest Laboratories, Inc.
Last Oregon Review: June 2011 (Oregon HRC)

Dossier received: Yes

Source Document: DERP

Table 1. Current Voluntary PDL Preferred/Non-Preferred Antidepressants

Current Preferred Agents:		Current Non-Preferred Agents:
BUPROPION HCL TABLET	MIRTAZAPINE TAB RAPDIS	OLANZAPINE/FLUOXETINE (SYMBYAX)
BUPROPION HCL TABLET ER	MIRTAZAPINE TABLET	Fluoxetine DF (PROZAC WEEKLY)
CITALOPRAM HYDROBROMIDE SOLUTION	PAROXETINE HCL TABLET	Duloxetine (CYMBALTA)
CITALOPRAM HYDROBROMIDE TABLET	SERTRALINE HCL ORAL CONC	EFFEXOR XR
FLUOXETINE HCL CAPSULE	SERTRALINE HCL TABLET	Desvenlafaxine (PRISTIQ)
FLUOXETINE HCL SOLUTION	VENLAFAXINE HCL TABLET	VENLAFAXINE ER
FLUOXETINE HCL TABLET		NEFAZODONE
FLUVOXAMINE MALEATE TABLET		Paroxetine HCL (PAXIL CR)

Reason for Review:[1-6]

The Oregon Evidence-based Practice Center drug effectiveness review project (DERP) published their fifth updated drug class review of second generation antidepressant in March 2011 that included data through September 2010. This was reviewed by the Oregon Health Resources Commission in June 2011 and their conclusions are listed in Appendix 1.[1] This and other previous comparative effectiveness reviews have found that second generation antidepressants do not differ significantly in efficacy of major depressive disorder (MDD). Since the last OR review, however, a new antidepressant, vilazodone (Viibryd®), has been FDA approved and an update to the comparative effectiveness review on second-generation antidepressants in the treatment of adult depression was completed by the Agency for Healthcare Research and Quality (AHRQ).[3] The evidence-based practice guidelines endorsed by the American Psychiatric Association have not been updated since 2010 for the treatment of major

depressive disorder.[4] This update will examine the place in therapy for vilazodone, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines.

In addition, in August 2011, the FDA issued a Safety Alert regarding the link between abnormal heart rhythms and high dose citalopram (Celexa). Dose limits of 40mg/day have been advised.[5,6]

Issues:

- Is there any new evidence of effectiveness or harms that will support second generation antidepressant management strategies or changes?
- Is there any evidence that vilazodone is more effective or safer than currently available medications in the PDL drug class including subgroups of patients?
- What recommendations for management of the antidepressant class can be made? Should a dose limit be included for citalopram?

Conclusions

- 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.
- There is fair quality evidence that vilazodone is safe and effective for the treatment of MDD based on short-term placebo controlled trials. There is insufficient evidence to determine comparative effectiveness of vilazodone compared to other antidepressant medications.
- There is insufficient evidence to determine the effectiveness of vilazodone in the maintenance treatment of MDD, for the treatment of generalized anxiety disorder or other indications, as well as in pediatric patients or patients with severe hepatic impairment.
- 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.

Recommendations:

1. 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.
2. Evidence does not support superiority of vilazodone over other agents in this drug class. Recommend that is be listed as a non-preferred agent.
3. Include a dose limit of 40mg/day for citalopram.
4. 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.
    1. As an example, academic detailing can be use to promote appropriate utilization

I. Background

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) (with the exception of premenstrual disorder, which historically was untreated). TCAs and MAOIs sometimes are referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable; e.g., 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. Thus, first-generation antidepressants are no longer agents of choice in many circumstances.

Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, and escitalopram. The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine. Other agents used for treatment of MDD include, nefazodone,mirtazapine, and bupropion.

In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. The SNRIs are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist, nefazodone is believed to inhibit neuronal uptake of serotonin and norepineprhine, and bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. The recently approved antidepressant, vilazodone, combines properties of a SSRI with 5-hydroxytryptamine-1a ($5\text{-}HT_{1a}$) partial agonist activity. However, the clinical significance of this dual mechanism is unknown and it has not been shown to offer any unique efficacy or safety advantage over currently available treatments. Vilazodone is only approved and studied in the treatment of MDD, while other approved second generation antidepressants have multiple indications including GAD, social anxiety disorder, panic disorder, obsessive compulsive disorder, and post traumatic stress disorder.

SSRI's, SNRI's, and TCA's are also frequently recommended for the treatment of generalized anxiety disorder (GAD). In 2011, the National Institute for Health and Clinical Excellence (NICE) published a guideline on the management of adults with GAD in primary, secondary and community care.[7] These guidelines recommend that if drug treatment is needed, the most cost effective SSRI should be prescribed. NICE specifically recommends sertraline in the UK. If the first SSRI is not effective, recommendations include using an alternative SSRI or an SNRI, taking into account the side-effect profile and drug interaction potential, the risk of suicide and toxicity, and the tendency to produce a withdrawal syndrome when choosing an appropriate medication.

II. **Systematic Reviews**

AHRQ Comparative Effectiveness Review

The AHRQ review assessed evidence on comparative benefits and harms of second-generation antidepressants for treating acute, continuation, and maintenance phases of Major Depressive Disorder.[3] Overall, comparative efficacy and effectiveness of second-generation antidepressants did not differ substantially for treating patients with MDD. This included 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.
There was moderate quality of evidence that for acute phase treatment of MDD, clinical response and remission rates are similar among second-generation antidepressants. Consistent results from 17 mostly fair-quality studies indicate that the efficacy of second-generation antidepressants regarding quality of life does not differ among drugs. Consistent results from 7 fair-quality trials suggest that mirtazapine has a statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference favoring mirtazapine can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of a particular second-generation antidepressant compared with another. There was also moderate strength evidence based on 5 efficacy studies that demonstrated no statistically significant differences in preventing relapse or recurrence between escitalopram and paroxetine, fluoxetine, and setraline, fluoxeting and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine. Overall, there was low quality of evidence evaluating the management of treatment-resistant depression. Results from 3 trials support modestly better response and remission rates for venlafaxine than with comparator, but differences were generally not statistically significant.

There was high strength of evidence that overall, adverse events profiles are similar among second-generation antidepressants. Differences exist in the incidence of specific adverse events. Discontinuation rates were similar between SSRIs and other second-generation antidepressants (15% to 25%). Duloxetine and venlafaxine have a higher rate of discontinuation due to adverse events and venlafaxine has a lower rate of discontinuation due to lack of efficacy compared to the SSRI class. There was moderate strength evidence that mirtazapine causes greater weight gain than comparators, sertraline as a higher incidence of diarrhea, and trazodone has a higher rate of somnolence than comparators. There was insufficient evidence to draw conclusions on the comparative risk for suicidality, cardiovascular events, or seizures. Limitations of this review were that most trials were conducted in highly selected populations and were relatively short-term trials, publication bias might affect the estimates of some comparisons, and evidence within subgroups was limited.

Overall, 37% of patients with acute-phase MDD who received first-line treatment did not achieve response within 6 to 12 weeks, and 53% did not achieve remission. Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy or effectiveness and differences in onset of action and adverse events may be considered when choosing a medication.

A recent review by the Cochrane Collaboration assessed the evidence on the efficacy or mirtazapine compared with other antidepressive agents in the acute-phase treatment of MDD and concluded that mirtazapine was significantly more effective at two weeks than SSRI's (OR 1.57, 95% CI 1.3 to 1.88) and at the end of acute-phase treatment (OR 1.19, 95% CI 1.01 to 1.39). Mirtazapine was also more effective than venlafaxine at two

weeks (OR 2.29, 95% CI 1.45 to 3.59) and at the end of acute-phase treatment (OR 1.53, 95% CI 1.03 to 2.25). This was only based on two trials with a total of 415 participants. Mirtazapine was more likely to cause weight gain, increased appetite, and somnolence than SSRIs but less likely to cause nausea or vomiting and sexual dysfunction. One potential reason for these differences in acute-phase treatment of MDD is a faster onset of action when compared to the SSRI's

III. New Drug Review

FDA approved indications: Vilazodone is a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder.

Clinical Trial Data

Efficacy: The efficacy of vilazodone was established in two Phase III short term (eight-week), randomized, placebo-controlled, multicenter studies using a dose titrated up to 40 mg/day.[8,9] The trials included a total of 891 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 the two studies. There are no head-to-head comparative trials with any other antidepressants. The primary measure used to evaluate efficacy was the Montgomery-Asberg Depression Rating Scale (MADRS). This scale measures the effect of treatment on depression severity by measuring the severity of a number of symptoms at baseline and during the course of treatment. These symptoms include mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness. Limited information is available defining a clinically meaningful change in the MADRAS score. Measurements were conducted at baseline and weeks 1, 2, 3, 6 and 8. Both studies demonstrated a significant improvement in patients on vilazodone according to the MADRS scale compared to placeb. The least-squres mean difference between groups in change from baseline in one study (trial 07) was -2.5 (SE = 0.96; 95% CI, -4.4 to -0.6; p=0.009). In the second study (trial 04) the least squares mean difference from placebo in change from baseline was -3.2 (SE=0.99; 95% CI, -5.1 to -1.2; p=0.001). In the second trial, patients were allowed to stay on the 20 mg/day dose if they could not tolerate 40 mg/day. Forty-one patients were maintained on this dose due to reasons of intolerability (28 in vilazodone group and 13 in placebo group).

Vilazodone has also been studied in five, 8-week Phase II studies in patients with MDD (none are fully published). Three of these studies included active comparators (fluoxetine or citalopram) and all used the change from baseline to endpoint on the Hamilton Depression Rating Scale (HAM-D_{17}) as the primary endpoint. These studies evaluated vilazodone doses ranging from 5 to 100 mg/day, with most patients dosed at ≤ 20 mg/day (however only two used fixed-dose designs that were informative about dose response). No statistically significant differences were observed between vilazodone and placebo or between the active comparator and placebo in the ITT analyses.

Safety and Tolerability: Commonly observed adverse effects (incidence ≥5% and at least twice the rate of placebo) include: diarrhea (28% vilazodone vs 9% placebo), nausea (23% vilazodone vs 5% placebo), vomiting (5% vilazodone vs 1% placebo), and insomnia (6% vilazodone vs 2% placebo). The gastrointestinal adverse events and insomnia tend to occur early in treatment. Other adverse events with an incidence of at least 2% and at least twice the placebo rate include: gastroenteritis, paresthesia, tremor, abnormal dreams, restlessness, decreased libido, abnormal orgasm, delayed ejaculation, erectile dysfunction, feeling jittery, palpitations, and increased appetite.

Pharmacology: Vilazodone is an indolaklylamine that binds with high affinity to the serotonin reuptake site (SSRI). It also has high affinity for 5HT1a Receptors and is a 5HT1A receptor partial agonist. The mechanism of antidepressant effect is not known but is thought to be related to enhancement of serotonergic activity in the central nervous system through its SSRI effect. The net effect of the partial agonist activity is not known.

Consideration in Subpopulations:
Pediatrics: Vilazodone has not been studied in patients less than 18 years of age.
Geriatrics: Vilazodone has not been studied in patients older than 70 years of age. No dose adjusted is necessary for renal impairment or mild to moderate hepatic impairment. Patients with severe hepatic impairment have not yet been studied.
Gender, race, ethnicity: No subgroup analyses have been published.

Comparative Clinical Efficacy:

Relevant Endpoints for Depression:

Response*
Remission*
Relapse
Hospitalization
Quality of Life
Withdrawals due to adverse events
Major adverse events
*Secondary endpoints in vilazodone trials

Study Primary Endpoints:

Khan, et al: Change in baseline at week 8 in Montgomery-Asberg Depression Rating Scale (MADRS)

Rickels, et al: Change in baseline at week 8 in Montgomery-Asberg Depression Rating Scale (MADRS)

Table 2. Vilazodone Comparative Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
Khan, et al. Multicenter, DB, PC, PG, RCT Vilazodone vs Placebo	1. Vilazodone 40mg 2. Placebo Dosed QD	Adult patients (18-70 yrs); DSM-IV-TR criteria for MDD, single episode or recurrent Mean age 42 y/o 56% female Excluded:	240 241	8-weeks	<u>MADRS total score (change from baseline to week 8):</u> Vilazodone 40mg = -13.3 Placebo = -10.8 Mean difference -2.5 95% CI (-4.4 to -0.6) p-value = 0.009 <u>Response Rate*</u> Vilazodone 101 (43.7%) Placebo 70 (30.3%)	N/A Response: ARR 13.4% NNT=7.5	<u>Discontinuations due to adverse events:</u> Vilazodone: 12 (5.1%) Placebo: 4 (1.7%) RR 3.0, 95% CI (0.9 to 10.9) P=0.042 <u>Severe Adverse events:</u> Vilazodone: 15 (6.4%) Placebo: 13 (5.6%) RR 1.1, 95% CI (0.5 to 2.5)	ARI 3.4% NNH 29 NS	Fair; *Placebo controlled, short-term trial, not head-to-head* *Manufacturer sponsored trial* *No information on methods of allocation concealment*

		Excluded: history of schizophrenia, bipolar, or substance dependence, current psychotherapy within previous 12 weeks			RR 1.44 95% CI (1.1-1.9) P=0.003 <u>Remission Rate**</u> Vilazodone 63 (27.3%) Placebo 47 (20.3%) RR 1.3 95% CI (0.95-1.9) P=0.08 *Response rate defined as ≥50% decrease from baseline in MADRS **Remission rate defined as MADRS score <10	Remission: NS	P=0.7		*Patients with significant comorbid conditions that might interfere with trial participation excluded at the investigator's discretion* *Total Discontinuation Rate 19%(similar between groups)* *No measures of QOL*
Rickels, et al. Multicenter, DB, PC, PG, RCT	1. Vilazodone 40mg 2. Placebo	Adult patients (18-70 yrs); DSM-IV-TR criteria for MDD, single episode or recurrent Mean age 40y/o 63% female Excluded: history of schizophrenia, bipolar, or substance dependence, current psychotherapy, patients with serious suicidal risk, patients with clinically significan cardiac, renal, neurologic, hepatic, metabolic or pulmonary disease	205 205	8-weeks	<u>MADRS total score (change from baseline to week 8):</u> Vilazodone 40mg = -12.9 Placebo = -9.6 Mean difference -3.2 95% CI (-5.1 to -1.2) p-value = 0.001 <u>Response Rate*</u> Vilazodone: 80 (40%) Placebo : 56(28%) RR 1.44 95% CI (1.07-1.9) P=0.01 *Response rate defined as ≥50% decrease from baseline in MADRS	N/A Response ARR 12% NNT=8.1	<u>Discontinuations due to adverse events:</u> Vilazodone: 19 (9.3%) Placebo: 10 (4.9%) RR 1.9, 95% CI(0.9-4.3) P=0.085 <u>Serious adverse events:</u> Vilazodone: 5 (2.4%) Placebo: 5 (2.5%) RR 1.0 95% CI (0.3-4.0) P=0.99	NS NS	Fair; *Placebo controlled, not head-to-head* *No information on methods of allocation concealment* *Manufacturer sponsored tria* *Short-term trial* *Total Dropout rate25% (similar between groups)* *Extensive exclusion criteria* *No measure of QOL*

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Table 3. Vilazodone Dose & Availability

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10mg	Tab	PO	Daily	N/A	N/A (not studied in severe hepatic disease)	Not Established	Not Established	Should be given with food Should be titrated (10mg X 7 days; 20mg X 7 days; then 40mg/day)
20mg	Tab	PO	Daily					
40mg	Tab	PO	Daily					

Table 4. Vilazodone Pharmacokinetics

Parameter	Result
Oral Bioavailability	72% w/food
Tmax	4-5 hours
Protein Binding	96-99%
Elimination	Extensively metabolized Feces 2% Urine 1%
Half-Life	25 hours
Metabolism	CYP3A4 (major); 2C19 (minor); 2D6 (minor) No active metabolites

IV. Safety Alert for Citalopram

In August 2011, the FDA issued a Safety Alert regarding the link between abnormal heart rhythms and high dose citalopram (Celexa). Further clarification of recommendations was posted March 2012.[5,6] Changes in the electrical activity of the heart (prolongation of the QT interval) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood. Studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day. Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day. The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes. The FDA recommends the following:

- Citalopram causes dose-dependent QT interval prolongation.
- Citalopram should no longer be prescribed at doses greater than 40 mg per day.
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure.
- Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval.

- The maximum recommended dose of citalopram is 20 mg per day for patients with hepatic impairment, patients who are older than 60 years of age, patients who are CYP 2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet) or another CYP2C19 inhibitor, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.

Appendix 1

Previous Conclusions by HRC Second Generation Antidepressants[1,2]:

Drug Classes included in review

- SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
- SNRIs: desvenlafaxine, duloxetine, venlafaxine
- Others: bupropion, mirtazapine, nefazodone, trazodone

Limitation of the evidence:

- Study durations were short (mostly 6-12 weeks) compared to the usual duration of treatment (9-12 months).
- High dropout rates
- No effectiveness studies
- Depression in children is not as well studied as in adults

Conclusions:

	Good Evidence	Fair Evidence	Insufficient Evidence
Efficacy, Adults	No significant difference in overall efficacy among second generation antidepressants in adults with MDD.	Second generation antidepressants were no better than placebo for MDD in patients with comorbid conditions including methadone maintained opioid addiction, cocaine abuse, HIV, multiple sclerosis, arthritis, diabetes, cancer or substance abuse disorder.	To determine a comparative difference in efficacy among the studied agents for dysthymia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder and late luteal phase dysphoric disorder.
Efficacy, children and adolescents	Citalopram and fluoxetine are the only two agents studied shown to be better than placebo. Sertraline, venlafaxine, and paroxetine were shown to be no better than placebo. In patients ≤18 years the risk of self-harm increased with SSRIs vs. TCAs. There were no statistically significant differences among SSRIs. A systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk/benefit profile in pediatric populations.	Second generation antidepressants were no better than placebo for comorbid alcohol use disorder in adolescents.	

Adverse Effects	Black Box Warning: 1. Nefazone and active liver disease. 2. All included drugs carry a black box warning regarding suicidality. The risk of suicidality is not increased in adult patients ≥ age 18. Higher rate of nausea and vomiting with venlafaxine. Higher rate of discontinuation with venlafaxine and duloxetine.	Sexual Side Effects: 1. Higher risk: paroxetine, sertaline and mirtazapine 2. Lower risk: bupropion and nefazodone Greater weight gain with mirtazapine and paroxetine than with sertraline and fluoxetine.	
Subgroups	A large meta-analysis of paroxetine vs. placebo suggests that the response rate is lower in Hispanic and Asian populations compared to White and Black populations for MDDs in adults, anxiety disorders, and post menstrual dysphoric disorder.	A retrospective cohort study of women ≥66 years with breast cancer shows that use of paroxetine increased the risk of death from breast cancer among women taking tamoxifen. There is insufficient data to assess the risk for other medications in this class.	To determine a comparative difference among agents in this class based on subpopulations of age, comorbidities, ethnicity or gender.

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REFERENCES

1. Health Resources Commission. Second generation antidepressants. June 2011. Available at: www.oregon.gov/OHPPR/HRC/index.shtml. Accessed: January 3, 2012.

2. Gartlehner G, Hansen RA, Reichenpfader U, et al. Drug class review: Second generation antidepressants. Update 5. Available at: http://derp.ohsu.edu/about/final-document-display.cfm. Accessed January 3, 2012.

3. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772-785.

4. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. American Psychiatric Association. November 2010. Available at: http://psychiatryonline.org/guidelines.aspx. Accessed March 15, 2012.

5. Drug Safety Communication. Celexa (citalopram hydrobromide): Drug Safety Communication - Abnormal Heart Rhythms Associated With High Doses. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm269481.htm. Accessed March 15, 2012.

6. Drug Safety Communication. Celexa (citalopram hydrobromide) - Drug Safety Communication: Revised Recommendations, Potential Risk of Abnormal Heart Rhythms. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm297624.htm?source=govdelivery Accessed March 28, 2012.

7. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. National Institute for Health and Clinical Excellence. January 2011. Available at: http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf. Accessed March 15, 2012.

8. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotnergic agent for the treatment of major depressive disorder. J Clin Psychiatry. 2011;72(4):441-447.

9. Rickels K, Athanasiou M, Robinson DS, et al. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(3):326-333.

10. Laughren TP, Gobburu J, Temple RJ, et al. Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant. J Clin Psychiatry. 2011;72(9):1166-1173.

11. FDA Center for Evaluation and Research. Application Number: 022567Orig1s000 (vilazodone). Summary review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000SumR.pdf. Accessed February 7, 2012.

12. Formulary submission dossier for Viibryd. Forest Laboratories, Inc. 2011