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Literature Scan: Antidepressants

Date of Review: July 2016

Date of Last Review: September 2014
Literature Search: October 2014 – June 2016

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- A Cochrane review published in 2014 compared the efficacy and tolerability profile of paroxetine to tricyclic antidepressants (TCAs), other selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants. Most of the studies included in the analysis were at unclear or high risk of bias due to poor reporting of study characteristics or incomplete outcome reporting. Although some possibly meaningful differences between paroxetine and other antidepressants (ADs) were noted, no definitive conclusions can be drawn regarding the preference of one AD over another. There is no new comparative evidence between antidepressants that changes the previous conclusions.
- The Agency for Healthcare Research and Quality (AHRQ) funded a systematic review to evaluate the benefits and harms of second generation antidepressants (SGAs) compared to non-pharmacologic interventions such as cognitive behavioral therapy (CBT) or herbal supplements such as St. John's wort. The authors found low quality evidence with a high risk of bias and concluded both CBT and SGAs are reasonable choices for first line treatment of adults with depression.
- Several systematic reviews evaluated the safety and efficacy of antidepressants in specific populations such as post-partum women and patients with cancer, epilepsy or end stage renal disease. In the absence of robust and reliable evidence the authors were unable to draw effective conclusions regarding the impact of antidepressants in managing depression in these unique populations. More studies in each of these populations is needed to guide clinical practice.
- Two systematic evaluations focused on antidepressant therapy in pediatric patients concluded that selective serotonin reuptake inhibitors (SSRIs) are better tolerated with superior efficacy compared to TCA therapy. One systematic review concluded fluoxetine was best tolerated and the most effective for treating depression in children and adolescents. However, the quality of the studies ranged from low to moderate quality with unclear to high risk of bias.
- A retrospective cohort study conducted in children enrolled in the Tennessee Medicaid program found no evidence of increased suicide risk for sertraline, paroxetine, citalopram, escitalopram or venlafaxine compared with fluoxetine in children and adolescents.
- Vilazodone received an expanded indication from the Food and Drug Administration (FDA) in March 2015 for a lower 20 mg dose to treat major depressive disorder. An additional Phase III trial demonstrated the efficacy of the 20mg dose in treating major depressive disorder.
- New safety warnings were issued by the FDA after reports of orthostatic hypotension, falls and syncope were reported with therapeutic doses of duloxetine. An analysis of patients from all placebo controlled trials revealed that patients treated with duloxetine reported a higher rate of falls compared to patients treated with placebo.

Recommendations:

- There is no evidence of a difference in safety or efficacy between antidepressants and preference can be established on cost and patient specific factors. After the executive session, no changes to the PDL were made.

Previous Conclusions:

- There is low quality evidence that shows there are minimal differences in efficacy between first and second generation antidepressants. While some meta-analyses show a trend towards greater improvement with tricyclic antidepressants (TCAs) compared to selective serotonin receptor inhibitors (SSRIs), TCAs are no longer favored when only higher quality studies are considered.
- The safety profiles of antidepressants vary by class, and there is no comprehensive analysis that directly compares the rate and type of adverse events between first and second generation antidepressants. There is low quality evidence to show that SSRIs are more tolerable than TCAs, as a larger proportion of patients treated with TCAs withdrew treatment due to adverse events compared to those treated with SSRIs. MAOIs are associated with more drug-drug and food-drug interactions than any other class of antidepressants.

Previous Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.
- Recommend including first generation antidepressants to the voluntary PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions. Also maintain nefazodone as non-preferred due to hepatic safety concerns.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The Food and Drug Administration (FDA) website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, 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. Randomized controlled trials will not be identified and reviewed if there is ample evidence from high-quality systematic reviews.

New Systematic Reviews:

Comparative Assessments

Paroxetine Compared To Other Antidepressants

A 2014 Cochrane review compared the SSRI paroxetine with other antidepressants (ADs) to evaluate efficacy, safety, and tolerability in adults with depression.[1] One hundred fifteen RCTs involving 26,134 patients were included in the meta-analysis. Ninety nine (86%) of the 115 RCTs were double blinded. In 54 studies paroxetine was compared with TCAs including: dothiepin, nortriptyline, amitriptyline, imipramine, desipramine, maprotiline, mianserin, clomipramine, lofepramine, and doxepin.[1] Twenty-one trials compared paroxetine with other SSRIs including: sertraline, escitalopram, fluoxetine and fluvoxamine.[1] Forty studies evaluated paroxetine with other ADs including: trazodone, milnacipran, venlafaxine, nefazodone, reboxetine, bupropion, hypericum, tianeptine, mirtazapine, duloxetine, amisulpride, and agomelatine. The authors assessed the study methodology as poor with substantial unclear risk of bias. The evidence the reviewers found in terms of efficacy, acceptability and tolerability of paroxetine compared with certain antidepressants (ADs), was of low to moderate quality.[1] No statistically significant difference was noted in efficacy between paroxetine and TCAs as a class (OR: 1.04, 95% CI 0.92 to 1.17).[1] When number of people who responded to treatment with paroxetine was compared to SSRIs, a difference in favor of citalopram over paroxetine (OR: 1.54, 95% CI 1.04 to 2.28) was noted.[1] For the other ADs in the efficacy assessment, there was a trend in favor of paroxetine over reboxetine (OR: 0.82, 95% CI 0.66 to 1.02).[1] In head-to-head comparisons with TCAs, paroxetine was better tolerated than clomipramine (OR: 0.67, 95% CI 0.52) and imipramine (OR: 0.65, 95% CI 0.50 to 0.85).[1] The analysis of dropouts due to side effects revealed that amitriptyline (OR: 0.74, 95% CI 0.56 to 0.98), clomipramine (OR: 0.59, 95% CI 0.41 to 0.84), and imipramine (OR: 0.58, 95% CI 0.43 to 0.77) were significantly less well tolerated than paroxetine.[1] For the SRRI comparison, paroxetine was less well tolerated than fluoxetine (OR: 1.34, 95% CI 1.06 to 1.70).[1] No differences were found between paroxetine and the other SSRI's in terms of number of patients who experienced side effects (OR: 1.12, 95% CI 0.42-2.97).[1] For the assessment of other ADs and patient drop out due to side effects, a difference between paroxetine and reboxetine (OR: 0.38, 95% CI 0.17 to 0.86) was noted in favor of paroxetine; and a difference between paroxetine and tianeptine (OR: 3.38, 95% CI 1.31 to 8.71) was noted in favor of tianeptine.[1] Data from this review suggest some possible differences between paroxetine and other ADs, but the clinical meaning of these differences is uncertain, and no definitive implications for clinical practice can be drawn.[1] Although this Cochrane review included numerous studies, it is difficult to draw conclusions as to which antidepressant may be preferred over another agent. Patient tolerance and improvement in symptoms must be evaluated on a case by case basis when antidepressant therapy is warranted.

Second Generation Antidepressants Compared To Psychological and Complementary Treatments

A systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) focused on comparing second generation antidepressant (SGA) pharmacotherapy to alternative interventions such as cognitive behavioral therapy (CBT), herbal therapy such as St. John's wort, or exercise.[2] Forty three trials which compared the benefits and harms of SGAs with other treatments were included in the evidence synthesis. The authors rated 37% of the trials as having a high risk of bias.[2] When CBT was compared to SGAs, similar response rates were noted (44% vs. 46%; relative risk [RR], 0.90 [95% CI, 0.76 to 1.07]).[2] Remission rates were similar between CBT and SGA treatment groups (41% vs. 48%; RR, 0.98 [CI, 0.73 to 1.32]).[2] In both treatment groups, 16% of patients discontinued treatment (RR, 1.00 [CI, 0.55 to 1.81]).[2] Treatment discontinuations because of adverse events were numerically higher for patients on SGAs but did not reach statistical significance (8% vs. 3%; RR, 2.51 [CI, 0.40 to 15.46]) when compared to CBT.[2] Similar response rates for patients treated with SGAs or St. John's wort (52% vs. 54%; RR, 0.96 [CI, 0.83 to 1.11) were noted.[2] No statistically significant difference in remission rates (30% vs. 36%; RR, 0.85 [CI, 0.70 to 1.04]) was observed between SGAs and St. John's wort treatment groups.[2] Patients treated with antidepressants had a significantly higher risk for treatment discontinuation (16% vs. 12%; RR, 1.28 [CI, 1.01 to 1.62]) and discontinuation because of adverse events (7% vs. 4%; RR, 1.70 [CI, 1.12 to 2.60]) than those on St. John's wort.[2] No significant differences in remission rates were noticed with exercise. Based on the limited, weak evidence the authors concluded both CBT and SGAs are reasonable choices as first line therapy for patients with depression.[2]

Antidepressants in Specific Populations

Epilepsy

Symptoms of depression such as low mood, tiredness, or apathy occur in approximately one third of patients with epilepsy.[3–5] Many prescribers are concerned that antidepressant therapy may exacerbate underlying seizures in their epileptic patients.[6] A Cochrane review reviewed the safety of antidepressants in treating depression and their effect on seizure recurrence.[7] The authors identified 8 studies for their review. Three RCTs and 5 non-randomized prospective cohort studies met the inclusion criteria. The five cohort studies were rated as low quality evidence with high risk of bias.[7] All the RCTs had unclear risk of bias.[7] When the data were combined into a meta-analysis to assess improvement in depression, the authors rated the quality of evidence as low.[7] Paroxetine was compared to doxepin in 67 patients.[7] The risk ratio for the proportion of patients with 50% improvement in depression scores for paroxetine versus doxepin was 1.16 (95% CI 0.88-1.52).[7] Venlafaxine was compared to no treatment in 64 patients.[7] The risk ratio for the proportion with a 50% or more improvement in depression scores for venlafaxine versus no treatment was 3.25 (95% CI 1.19 to 8.90).[7] The authors were unable to pool the data for a meta-analysis regarding seizure frequency due to either unreported data or substantial heterogeneity.[7] The authors concluded that robust evidence to evaluate the effectiveness of antidepressants in patients with epilepsy is currently unavailable. [7]

Cancer

Major depression among patients with cancer is estimated to occur in 15% of this population.[8] A 2015 Cochrane review sought to assess the effects and acceptability of antidepressants for treating depression in adults with cancer.[9] The authors identified 9 RCTs including 861 participants in their assessment. Fluoxetine, mianserin, amitriptyline, and desipramine were the antidepressants studied in the trials.[9] Overall the studies were rated as low quality with unclear to high risk of bias.[9] No statistically significant differences were noted between antidepressants as a class and placebo (standard mean difference (SMD) = -0.45 96% CI -1.01 to 0.11) or when SSRIs were compared to TCAs (SMD = -0.08 95% CI -0.34 to 0.18).[9] The authors found limited, reliable evidence to derive any effective conclusions regarding efficacy of antidepressants in cancer patients.[9]

End-Stage Renal Disease

Approximately 25% of adults with end-stage renal disease (ESRD) have some symptoms of depression.[10] Clearance of certain antidepressants (selegiline, amitriptyline, venlafaxine, desvenlafaxine, milnacipran, and bupropion) can be reduced by impaired renal function.[11] A 2016 Cochrane review updated a 2005 summary in order to evaluate the benefit and harms of antidepressants for treating depression in adults with ESRD treated with dialysis.[12] Adults aged 18 years and older with ESRD were included in the assessment. Depression was identified via interview or depression scale; patients with bipolar affective disorder were excluded. The following medications were studied: citalopram, escitalopram, fluoxetine and sertraline. The authors identified 4 studies in their update which involved 170 subjects. The authors rated the quality of the studies as low to medium quality with unclear to high risk of bias.[12] Most of the studies were placebo controlled and short term, limited to 12 weeks or shorter. Estimated effects on efficacy and safety outcomes were imprecise and difficult to generalize and the small number of studies limited the power of statistical testing.[12] The authors concluded there is insufficient evidence to identify effective treatments for depression in ESRD patients.[12]

Children and Adolescents

The prevalence of depression is estimated to be approximately 3 % for children (6-12 years old) and approximately 6 % for adolescents (13-18 years old).[13] Which antidepressants are safe and effective to use in children and adolescents is controversial. A meta-analysis was performed to compare the efficacy and acceptability of SSRIs versus TCAs in depressed children, adolescents, and young adults.[14] A literature search was conducted from 1970 to December, 2013. Five trials of moderate quality with a total of 422 patients were included in the review. The mean age of the patients was 15 years (range: 7-24 years).[14] The primary

efficacy outcome was the standardized mean difference (SMD) for change scores in depression rating scales. A negative value indicated more relief from depression.[14] The secondary measure was proportion of patients that responded to treatment. SSRIs were more effective than TCAs in primary efficacy (SMD = −0.52; 95% CI, −0.81 to −0.24; P = 0.0003). [14] Patients taking SSRIs had a significantly greater response to depressive symptoms than patients taking TCAs (RR = 1.55; 95% CI, 1.04 to 2.29; P = 0.03).[14] More patients taking TCAs discontinued treatment than patients taking SSRIs (35.8% vs 25.1%; RR = 0.70; 95% CI, 0.52 to 0.93; P = 0.02).[14] The authors concluded SSRI therapy had superior efficacy and was better tolerated compared with TCA therapy in young patients.[14]

Another systematic review searched published literature through May, 2015 to identify RCTs that studied antidepressant therapy in children and adolescents.[15] Mean overall change in depression symptoms and the proportion of patients who discontinued treatment due to any adverse events were the 2 outcomes evaluated by the reviewers. Thirty four trials including 5260 participants were included in the meta-analysis.[15] The following 14 antidepressants were studied: amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine. The authors rated the evidence as low quality as most of the studies as had moderate to high risk of bias.[15] Only 4 studies had low risk of bias.[16] Standardized mean difference (SMD) was calculated to evaluate effect size and odds ratio was calculated for tolerability. In terms of efficacy, only fluoxetine was better than placebo (SMD −0.51, 95% CI −0.99 to −0.03).[15] Nortriptyline was significantly less effective than seven other antidepressants and placebo (SMDs ranging between −1.65 and −1.14).[15] In terms of tolerability, fluoxetine was significantly better tolerated than duloxetine (OR 0.31, 95% CI 0.13 to 0.95) and imipramine (OR 0.23, 95% CI 0.04 to 0.78), and citalopram and paroxetine were significantly better tolerated than imipramine alone (OR 0.27, 95% CI 0.04 to 0.96 and OR 0.22,95% CI 0.08 to 0.87, respectively).[15] Imipramine was significantly less well tolerated than placebo (OR 5.49, 95% CI 1.96 to 20.86) as was venlafaxine (OR 3.19, 95% CI 1.01 to 18.70) and duloxetine (OR 2.80, 95% CI 1.20 to 9.42).[15] The authors concluded that fluoxetine was the best tolerated and most effective agent for treating depression in children and adolescents.[15] However, the evidence they based their conclusions upon was of low quality due to poor study methodology, risk of bias, and possible selective reporting.

Postnatal Depression

A 2001 Cochrane review focused on identifying evidence for treatment of postnatal depression. At that time, the authors found insufficient evidence to draw substantial conclusions to guide antidepressant therapy in postnatal depression.[17] A 2014 update aimed to address the effects of antidepressants in comparison with other treatments, placebo or usual treatment for postnatal depression. [18]The authors identified 6 RCTs to include in their qualitative synthesis. Three trials that compared SSRIs to placebo were robust enough for a pooled analysis.[18] Sertraline was evaluated in 3 studies; fluoxetine, paroxetine and nortriptyline were evaluated in 1 study each. Studies were rated as low quality with unclear to high risk of bias.[18] The meta-analysis that compared SSRI to placebo showed a 43% (RR 1.43, 95% CI 1.01-2.03) greater chance of response for the SSRI treated patients compared to those who received placebo.[18] The authors were unable to draw conclusions regarding the effectiveness of one antidepressant over another because most of the studies were underpowered to detect differences in efficacy.[18]

In 2014, the AHRQ sponsored a systematic review to evaluate antidepressant treatment of depression during pregnancy and the postpartum period.[19] The authors identified 15 observational studies that provided evidence on the safety and efficacy of antidepressants for depression in pregnancy.[19] The studies compared antidepressant treatment with no treatment in pregnant women. In postpartum women, antidepressants were compared alone to a combination of medication and non-pharmacologic therapy.[19] There was not enough evidence to draw conclusions on the comparative benefits or harms of antidepressants for improving depression symptoms, functional capacity, breast feeding, mother-infant interactions, or infant development.[19] The authors concluded that evidence regarding comparative benefits and harms of pharmacologic therapy for depression in pregnancy and post- partum women is largely inadequate and that studies focused on treating women with postnatal depression is essential.[19]

Safety

Risk of Suicide

A retrospective cohort study including 36,842 children enrolled in Tennessee Medicaid between 1995 and 2006 compared the risk for medically treated suicide attempts among new users of sertraline, paroxetine, citalopram, escitalopram and venlafaxine to new users of fluoxetine.[20] The mean age of new users of the antidepressants included in the study was 14.0 years.[20] Diagnosis of record included major depressive disorder (47.4%), attention deficit disorder, conduct disorder and anxiety.[20] The rate of confirmed suicide attempts for current users of the study drugs ranged from 24.0 per 1000 person-years (paroxetine) to 29.1 Per 1000 person-years (citalopram).[20] For users of sertraline, paroxetine, citalopram, escitalopram, and venlafaxine, the adjusted rate of suicide attempts did not differ significantly from that for users of fluoxetine (24.8 per 1000 person years).[20] The authors found no evidence of increased suicide risk for sertraline, paroxetine, citalopram, escitalopram or venlafaxine compared with fluoxetine in children and adolescents.[20]

Sexual Dysfunction

An AHRQ funded systematic review evaluated the risk of treatment-emergent sexual dysfunction (TESD) in patients that were taking SGAs.[21] Sixty three studies (58 RCTs and five observational studies) with low to moderate risk of bias were included in the assessment.[21] Based on network meta-analyses of 66 pairwise comparisons from 37 RCTs, most comparisons showed a similar risk of SD among included SGAs.[21] However, credible intervals were wide and included differences that would be considered clinically relevant.[21] The authors observed three main patterns: bupropion had a statistically significantly lower risk of TESD than some other SGADs, and both escitalopram and paroxetine showed a statistically significantly higher risk of TESD.[21]

New Guidelines:

In 2005, the National Institute for Clinical Excellence (NICE) and National Collaborating Centre for Mental Health (NCCMH) initially published guidelines focused on caring for children and young people aged 5 to 18 years with depression.[22] The guidelines were updated as of March, 2015 to reflect new evidence in two areas:

- The psychological therapies for the treatment of depression in children and young people.
- The use of antidepressant treatment and psychological therapy, either alone or together for the treatment of depression in children and young people.

The updated guidelines recommend CBT for all children and young adults with mild depression. For initial treatment of moderate to severe depression, CBT in combination with fluoxetine is recommended for young people 12-18 years of age. At the time of publication, fluoxetine did have UK marketing authorization for use in patients aged 12-18 years without a previous trial of psychological therapy that was ineffective.[22] In addition, in the UK fluoxetine was only approved to use in children aged 8 years and older.[22]

AHRQ supports the 2014 revisions to the 2008 Working Group of the Clinical Practice Guideline on the Management of Depression on Adults published by the Galician Health Technology Assessment Agency and Spanish Ministry of Health.[23, 24] Significant recommendations include:

- Patients with chronic and/or recurrent depression are recommended a combination of drug therapy and cognitive behavioral therapy.[23]
- The initial selection of drug therapy should be based mainly on the side effect profile and tolerability, safety and pharmacological properties, as well as other factors such as previous response to treatment, cost and patient preferences.[23]
- SSRIs are antidepressants with the most evidence and better risk/benefit ratio, and should be considered as the first choice of treatment.[23]
- Although there is evidence of the efficacy of St. John's Wort in the treatment of mild to moderate depression, its use is not recommended for the following reasons:
  –Lack of knowledge about of the active ingredients, mechanisms of action and persistence of the antidepressant effect.
  –A lack of standardization of the dose.

–The variability of different commercial preparations, which may have different amounts and proportions of its components and may not be therapeutically equivalent.[23]

The American College of Physicians (ACP) developed guidelines to provide evidence on the comparative effectiveness of depression treatment with SGAs versus nonpharmacological therapy.[25] Based on moderate quality evidence, ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient.[25]

New Formulations/Indications:
Viibryd® (vilazodone) received an expanded indication from FDA in March 2015 for a lower 20 mg dose to treat adults with major depressive disorder.[26] When Viibryd was initially FDA approved in 2013, the recommended dose was 40mg once a day with food based on 3 Phase III studies. An additional Phase III trial demonstrated the efficacy of the 20mg dose in treating major depressive disorder. No dose related adverse reactions were reported with either 20 or 40mg doses of Viibryd.[26]

New FDA Safety Alerts:
Cymbalta® (Duloxetine): November 2014: New warnings and precautions describe that orthostatic hypotension, falls, and syncope have been reported with therapeutic doses of Cymbalta.[27]
Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure as well as other factors that may increase the underlying risk of falls. In an analysis of patients from all placebo-controlled trials, patients treated with Cymbalta reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in blood pressure. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking Cymbalta at doses above 60 mg daily.[27]
Consideration should be given to dose reduction or discontinuation of Cymbalta in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during Cymbalta therapy. Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As elderly patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported.[27]

Brintellix® (vortioxetine): July 2015: Drug Safety Communication - Brand Name Change to Trintellix®, to Avoid Confusion with Antiplatelet Drug Brilinta (ticagrelor).[28] In a Med Watch Alert, FDA warned that name confusion between Brintellix and Brilinta had resulted in prescribing and dispensing errors since Brintellix was approved in September 2013. Due to continued reports of name confusion between the two medicines used for very different purposes, FDA worked with Brintellix manufacturer Takeda Pharmaceuticals to change the drug's brand name.[28]

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	GENERIC	BRAND	PDL	CARVED OUT
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	TABLET	WELLBUTRIN	BUPROPION HCL	Y	Y
ORAL	TABLET ER	BUPROPION HCL SR	BUPROPION HCL	Y	Y
ORAL	TABLET	BUPROPION HCL	BUPROPION HCL	Y	Y
ORAL	TABLET ER	WELLBUTRIN SR	BUPROPION HCL	Y	Y
ORAL	TABLET	CELEXA	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	TABLET	CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	SOLUTION	CITALOPRAM HBR	CITALOPRAM HYDROBROMIDE	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	TABLET	ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	Y	Y
ORAL	TABLET	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	SOLUTION	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	TABLET	LEXAPRO	ESCITALOPRAM OXALATE	Y	Y
ORAL	SOLUTION	FLUOXETINE HCL	FLUOXETINE HCL	Y	Y
ORAL	TABLET	FLUOXETINE HCL	FLUOXETINE HCL	Y	Y
ORAL	TABLET	SARAFEM	FLUOXETINE HCL	Y	Y
ORAL	TABLET	FLUVOXAMINE MALEATE	FLUVOXAMINE MALEATE	Y	Y
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	MAPROTILINE HCL	MAPROTILINE HCL	Y	Y
ORAL	TAB RAPDIS	MIRTAZAPINE	MIRTAZAPINE	Y	Y
ORAL	TAB RAPDIS	REMERON	MIRTAZAPINE	Y	Y
ORAL	TABLET	MIRTAZAPINE	MIRTAZAPINE	Y	Y
ORAL	TABLET	REMERON	MIRTAZAPINE	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	TABLET	PAROXETINE HCL	PAROXETINE HCL	Y	Y
ORAL	TABLET	PAXIL	PAROXETINE HCL	Y	Y
ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	ORAL CONC	SERTRALINE HCL	SERTRALINE HCL	Y	Y
ORAL	ORAL CONC	ZOLOFT	SERTRALINE HCL	Y	Y
ORAL	TABLET	SERTRALINE HCL	SERTRALINE HCL	Y	Y
ORAL	TABLET	ZOLOFT	SERTRALINE HCL	Y	Y
ORAL	CAPSULE	SURMONTIL	TRIMIPRAMINE MALEATE	Y	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y

ORAL	TAB ER 24H	APLENZIN	BUPROPION HBR	V	Y
ORAL	TAB ER 24H	BUPROPION XL	BUPROPION HCL	V	Y
ORAL	TAB ER 24H	FORFIVO XL	BUPROPION HCL	V	Y
ORAL	TAB ER 24H	WELLBUTRIN XL	BUPROPION HCL	V	Y
ORAL	CAPSULE	CLOMIPRAMINE HCL	CLOMIPRAMINE HCL	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24H	PRISTIQ ER	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	IRENKA	DULOXETINE HCL	V	Y
ORAL	SOLUTION	ESCITALOPRAM OXALATE	ESCITALOPRAM OXALATE	V	Y
ORAL	SOLUTION	LEXAPRO	ESCITALOPRAM OXALATE	V	Y
ORAL	CAPSULE DR	FLUOXETINE DR	FLUOXETINE HCL	V	Y
ORAL	CAPSULE DR	PROZAC WEEKLY	FLUOXETINE HCL	V	Y
ORAL	CAP ER 24H	FLUVOXAMINE MALEATE ER	FLUVOXAMINE MALEATE	V	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	TABLET	MARPLAN	ISOCARBOXAZID	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TABLET	NEFAZODONE HCL	NEFAZODONE HCL	V	Y
ORAL	CAPSULE	BRISDELLE	PAROXETINE MESYLATE	V	Y
ORAL	ORAL SUSP	PAXIL	PAROXETINE HCL	V	Y
ORAL	TAB ER 24H	PAROXETINE HCL	PAROXETINE HCL	V	Y
ORAL	TAB ER 24H	PAXIL CR	PAROXETINE HCL	V	Y
ORAL	TABLET	PEXEVA	PAROXETINE MESYLATE	V	Y
ORAL	TABLET	NARDIL	PHENELZINE SULFATE	V	Y
ORAL	TABLET	PHENELZINE SULFATE	PHENELZINE SULFATE	V	Y
TRANSDERM	PATCH TD24	EMSAM	SELEGILINE	V	Y
ORAL	TABLET	PARNATE	TRANYLCYPROMINE SULFATE	V	Y
ORAL	TABLET	TRANYLCYPROMINE SULFATE	TRANYLCYPROMINE SULFATE	V	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	TAB DS PK	VIIBRYD	VILAZODONE HCL	V	Y
ORAL	TABLET	VIIBRYD	VILAZODONE HCL	V	Y
ORAL	TABLET	AMOXAPINE	AMOXAPINE	V	Y
ORAL	TAB DS PK	SAVELLA	MILNACIPRAN HCL	V	Y
ORAL	TABLET	SAVELLA	MILNACIPRAN HCL	V	Y
ORAL	TAB ER 24H	OLEPTRO ER	TRAZODONE HCL	V	Y
ORAL	TABLET	TRAZODONE HCL	TRAZODONE HCL	V	Y

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 6, 2016

1. *exp Depressive Disorder, Major/dt [Drug Therapy] 6533*
2. *Depression/ or Long-Term Synaptic Depression/ or Depression, Postpartum/*
3. *exp Anxiety/dt [Drug Therapy] 3037*
4. *exp Premenstrual Dysphoric Disorder/dt [Drug Therapy] 5*
5. *Citalopram/ 3647*
6. *escitalopram.mp. 1424*
7. *Fluoxetine/ 5913*
8. *Fluvoxamine/ 1311*
9. *Paroxetine/ 3085*
10. *Sertraline/ 2294*
11. *Duloxetine Hydrochloride/ 1231*
12. *Desvenlafaxine Succinate/ 216*
13. *levomilnacipran.mp. 26*
14. *Bupropion/ 2287*
15. *mirtazapine.mp. 1564*
16. *nefazodone.mp. 626*
17. *vortioxetine.mp. 105*
18. *Vilazodone Hydrochloride/ 70*
19. *Venlafaxine Hydrochloride/ 2095*
20. *Amitriptyline/ 1898* *21*
21. *Imipramine/ 1972*
22. *Desipramine/ 1356*
23. *Doxepin/ 270*
24. *Maprotiline/ 151*
25. *Nortriptyline/ 724*
26. *Protriptyline/ 17*
27. *Trimipramine/ 73*
28. *Clomipramine/ 1035*
29. *Isocarboxazid/ 9*
30. *Phenelzine/ 184*
31. Selegiline/ 1190
32. *Tranylcypromine/ 269*
33. *7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 24873*
34. *limit 33 to (humans and yr="2014 -Current") 1354*
35. *1 or 2 or 3 or 4 75231*
36. *limit 35 to (humans and yr="2014 -Current") 11698*
37. *33 and 36 387*
38. *limit 37 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) 194*