ANTIDEPRESSANT AGENTS

A. FDA Approved Indications (see Table 1) Documentation Required

1. MDD: all the agents on Table 1 except Clomipramine, Sarafem.
2. Major depressive disorder (MDD), FDA Approved in Children & Adolescents
    - Fluoxetine
    - Escitalopram

3. Anxiety Disorders:
    a. Generalized anxiety disorder (Doxepin, Escitalopram, Paroxetine, Paroxetine CR, Duloxetine, Venlafaxine, Venlafaxine XR
    b. Social anxiety disorder (Venlafaxine, Venlafaxine XR, Paroxetine, Paroxetine CR, Sertraline)
    c. Panic disorder (Fluoxetine, Paroxetine, Paroxetine CR, Zoloft, Venlafaxine, Venlafaxine XR)
    d. Obsessive compulsive disorder (Clomipramine, Fluoxetine, Fluvoxamine, Fluvoxamine CR, Paroxetine, Sertraline)
        - FDA Approved in Children & Adolescents ;
            - Clomimpramine
            - Fluoxetine
            - Fluvoxamine
            - Fluvoxamine CR
            - Paroxetine
            - Sertraline
    e. Posttraumatic stress disorder (Paroxetine, Sertraline)
    f. Bulimia nervosa (Prozac)
4. Premenstrual dysphoric disorder (Sarafem, Sertraline, Paroxetine CR)
5. Seasonal affective disorder (Bupropion XL)
6. Smoking Cessation: Zyban (Bupropion HCL SR)
8. Adjunctive therapy for MDD: Aripiprazole, Seroquel XR, Rexulti

B. Non-FDA Approved Indications, commonly used (Documentation Required)

1. Other depressive disorders
2. Attention deficit hyperactivity disorder
3. Autism
4. Eating disorders
5. Personality disorders
6. Insomnia
7. Chronic fatigue syndrome
8. Impulse control disorders
9. Somatoform disorders

C. Minimal Documentation (Documentation Required)

All standard outpatient & inpatient requirements

D. Maximum Dosage – see Medication Summary for MDD or Table 2 (Documentation Required)

1. Lower starting dose may be required in panic disorder due to patient sensitivity to stimulating effects
2. Higher doses may be required in the treatment of OCD
3. Applicable to Bupropion only:
   - When initiating treatment with bupropion, the dose of IR & SR formulation may be increased in 3 days to maximum daily dose of 400mg daily in divided doses for SR formulation and 450mg for the IR formulation.
   - When initiating treatment with the XL preparation, the dose may be increased in 4 days to a maximum daily dose of 450mg.
   - Bupropion IR, SR and XL are contraindicated with seizure disorder and eating disorder and should generally be avoided. However, if clinically indicated, treatment failure with other agents and detailed documentation of risks vs. benefits need to be documented**.**

E. Duration (Documentation Required)

1. Outpatient: Document rationale when making any medication change.
2. Inpatient: Document rationale when making more than 3 changes in any 7-day period.

F. Polypharmacy: Documentation Required (Refer to Purpose Section for exceptions)

When considering addition of more than one agent within a class, it is recommended to first titrate the initial agent to maximum tolerated dose; then provide clear supportive rationale for the additional agent(s).

i.e. 2 SSRIs, 2 SNRIs, One SSRI plus one SNRI. Trazodone for sleep is not counted towards poly-pharmacy.

G. Standard Laboratory and Examination Requirements

1. For Inpatient: Basic laboratory studies on admission
2. For Outpatient:
   - **Applicable to SNRIs only:** Monitor blood pressure at baseline and after each dose increase.
   - **Applicable to Remeron only:** Monitor total cholesterol and triglyceride annually.

     i. If Primary Care Provider is already monitoring total cholesterol and triglyceride, obtain results and document in progress note.

     ii. From Prescriber's Information: In US controlled studies, non-fasting cholesterol increased to $\geq$ 20% above the upper limits of normal in 15% of patients treated with Remeron, compared to 7% for placebo. Additionally, 6% of patients treated with

Remeron had non-fasting triglyceride increased to ≥ 500mg/dL compared to 3% for placebo.

H. Black Box Warning: Document Assessment of Following:

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Short –term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.

I. Warning & Precautions: Documentation Required

1. History of hypersensitivity to this class of drugs
2. Concomitant use of MAOIs, allow 14 days of drug holiday when switching from MAOIs to other antidepressants and vise versa. If on Fluoxetine, then wait 5 weeks before starting MAOIs.
3. Seizure disorder, current or prior diagnoses of bulimia or anorexia nervosa (applicable to Bupropion)
4. Tricyclic antidepressants are contraindicated during the acute recovery period after myocardial infarction
1. Agitation, anxiety and insomnia (Bupropion and other activating agents)
2. Doses >40mg of Citalopram
3. Activation of Psychosis and/or Mania
4. Kidney or liver impairment
5. Caution in elderly patients
6. Caution if volume depletion
7. Caution if cardiovascular disorder i.e. HTN, Arrhythmia, recent MI or CHF
8. Caution if seizure disorder
9. Caution if alcohol use
10. Caution if QT prolongation, congenital long QT syndrome or family history of QT prolongation*Electrolyte abnormalities uncorrected
11. Avoid abrupt withdrawal with SNRIs
12. Caution if increased IOP, glaucoma, controlled angle-closure
13. Caution if GI motility disorder
14. Caution if bleeding risk
15. Caution if hyponatremia
16. Caution if suicidal
17. Caution if substance use including alcohol use
18. Caution with slow or fast metabolizers or if smoking habit changes
19. Abrupt discontinuation with some of the antidepressants may result in nausea, headache and malaise. Refer to Package insert for each agent for details**.**

*** Risk of QT prolongation varies among different agents (see package insert for each agent)**

J. Drug-Drug Interactions, Pharmacology (Table 4) – Refer to www.epocrates.com Drug Interaction Check

Additional Comments/Hints:

1. A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance. A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance. A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance (Drug Interactions: Flockhart Table)

2. Approximately 8% of Caucasians lack the capacity to metabolize CYP2D substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about a 60% higher exposure to the total active moieties from a given dose of Abilify compared to EMs.

3. Co-administration of Abilify with known inhibitors of CYP2D6, such as Fluoxetine or Paroxetine in EMs, approximately doubles the plasma level of Abilify. Coadministration of Abilify with known inducers of CYP3A4, such as carbamazepine, may require doubling the Abilify dose. Dose adjustments should be considered when clinically indicated.

4. In general, the following medications with acronym (VMDCVE): Venlafaxine, Mirtazapine, Desvenlafaxine, Citalopram, Vilazodone and Escitalopram have fewer drug interactions. These agents are not completely devoid of effects on CYP450 system; however, they may lead to less clinically significant effects compared to other antidepressants such as: Fluoxetine, paroxetine, fluvoxamine, duloxetine and bupropion. (Current Psychiatry Vol. 11, No. 9)

5. Bupropion & Duloxetine are moderate inhibitors of 2D6 vs. Fluoxetine and Paroxetine which are potent inhibitors of 2D6 i.e. co-admin. Of bup & abilify may result in increased Abilify serum level. Also, when starting a patient on LAIs, consider the drug interactions since the LAI has a long t1/2.

6. Sertraline ≥150mg is a moderate inhibitor of 2D6. Also, sertraline may increase Lamotrigine levels by inhibition of uridine 5'-diphosphate glucuronosyltransferase 1A4.

7. Desvenlafaxine is the active metabolite of Venlafaxine and 45% excreted unchanged in the urine and only <5% metabolized by CYP3A4 so theoretically it may be more appropriate agent in patients with hepatic disease.

8. Some examples of potent inhibitors of 3A4 include: Antifungals, Suboxone, Clarithromycin, Reverse Transcriptase Inhibitors.

9. Some examples of moderate inhibitors of 3A4 include: Grapefruit juice, Verapamil, Diltiazem and Erythromycin, Fluvoxamine (weak inhibitor).

10. Some examples of potent inducers of 3A4 include: CBZ, Phenobarbital, Phenytoin, Rifampin, St. John' wort and Glucocorticoids.

11. Oral contraceptives are metabolized by CYP3A4 (major) and CYP2C9. Potent inducers of CYP 3A4 may decrease efficacy of oral contraceptives and result in breakthrough bleeding. Caution is advised when starting a potent CYP3A4 Inducer.

12. Cigarette smoking accelerates the metabolism of certain drugs, particularly those primarily metabolized by cytochrome P450 1A2 (CYP1A2) such as Olanzapine, Clozapine and Benzodiazepines resulting in altered efficacy (Br J Clin Pharmacol. 2011 Nov; 72(5): 836–838)

13. Caffeine is both metabolized by the CYP1A2 enzyme and it inhibits it. Therefore, caffeine can interact with many psychiatric medications (i.e. Clozapine, Olanzapine and Fluvoxamine) and may lead to caffeine-related or medication-related side effects that may complicate psychiatric treatment.

K. Pregnancy or breast-feeding (See Table 3)

L. Adverse Effects: Documentation Required

Serious Adverse Effects:

- Suicidality
- Depression exacerbation
- Hypomania/mania
- Serotonin syndrome
- Abnormal bleeding/altered platelet fxn
- Anaphylaxis/anaphylactoid rxn
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Glaucoma, angle-closure
- Seizures
- Hyponatremia
- SIADH
- Hypoglycemia
- Hepatotoxicity
- Priapism

- Extrapyramidal sx
- QT prolongation
- Torsades de pointes
- Rhabdomyolysis
- Withdrawal sx if abrupt DC

Common Adverse Effects:

- Nausea
- Diarrhea
- Insomnia
- Xerostomia
- Fatigue
- Dizziness
- Somnolence
- Tremor
- Ejaculatory dysfxn
- Dyspepsia
- Agitation
- Anorexia
- Diaphoresis
- Libido decrease
- Constipation
- Abdominal pain
- Vomiting
- Sexual dysfxn
- Palpitations
- Visual disturbance
- Headache
- Anxiety

Attachments:

Table 1: FDA Approved Indication for Antidepressants
Table 2: Maximum Daily Dose
Table 3: Pregnancy and Lactation

Table 4: Drug Interactions, Pharmacology

References:

- Epocarates
- FDA package insert for various agents
- http://www.fda.gov/drugs/drugsafety/ucm283375.htm
-UpToDate, antidepressants
- The Cytochrome P450 System: What is it and Why Should I Care? https://nursing.unboundmedicine.com/nursingcentral/view/Davis-Drug-Guide/109519/all/The_Cytochrome_P450_System:_What_Is_It_and_Why_Should_I_Care_
- Psychotropic drugs- the effect of Smoking and Caffeine https://ww2.health.wa.gov.au/-/media/Files/Corporate/general-documents/WATAG/WAPDC/Smoking-and-caffeine-effects-on-antipsychotics.ashx
- Drug-drug interactions involving antidepressants: focus on desvenlafaxine https://pubmed.ncbi.nlm.nih.gov/29497300/
- Drug interactions: Flockhart Table https://edswi.org/wp-content/uploads/2018/02/Flockhart-Table-Medication-Metabolism.pdf
- The relevance of cytochrome P450 polymorphism in forensic medicine and akathisia-related violence and suicide. https://reader.elsevier.com/reader/sd/pii/S1752928X16300051?token=FC708108C2C14A1F7011799E43DC0B3ADEDD094AD28D52CDC5910590B64DCF489C8C58D3DD305C7F7D88950B023342F4
- Drug Interactions with Tobacco Smoke: https://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/drug-interactions.pdf
- Effect of Nicotine on Cytochrome P450 1A2 Activity: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243019/#:~:text=Cigarette%20smoking%20accelerates%20the%20metabolism,glucuronosyltransferases%20%5B1%2C%202%5D.

- Caffeine and psychiatric medication interactions: a review https://pubmed.ncbi.nlm.nih.gov/16206866/#:~:text=Thus%2C%20caffeine%20can%20interact%20with,that%20may%20complicate%20psychiatric%20treatment.

ANTIDEPRESSANT AGENTS

Table 1: FDA-Approved Indications for Antidepressants

Agents	Brand	MDD	PMDD[1]	GAD	OCD	PD[2]	SAD[3]	PTSD	Bulimia Nervosa	SAD[4]
MAOIs										
Isocarboxazid	Marplan	X								
Phenelzine	Nardil	X								
Selegiline patch	Emsam	X								
Tranylcypromine	Parnate	X								
TCAs										
Amitriptyline	Elavil	X								
Amoxapine	Asendin	X								
Clomipramine	Anafranil				X[5]					
Desipramine	Norpramin	X								
Doxepin	Sinequan	X		X						
Imipramine	Tofranil	X								
Maprotiline	Ludiomil	X								
Nortriptyline	Pamelor	X								
Protriptyline	Vivactil	X								
SSRIs										
Escitalopram	Lexapro	X[5]		X						
Citalopram	Celexa	X[5]								
Fluoxetine	Prozac	X[5]			X[5]	X			X	
	Sarafem		X							
Fluvoxamine	Fluvoxamine				X[5]					
	Fluvoxamine ER				X[5]					
Paroxetine	Paxil	X			X	X	X	X		
	Paxil CR	X	X			X	X			
Sertraline	Zoloft	X	X	X	X[5]	X	X	X		
Vilazodone	Viibryd	X								
SNRIs										
Desvenlafaxine	Pristiq	X								
Duloxetine	Cymbalta	X		X[5]						
Levomilnacipran	Fetzima	X								
Venlafaxine	Effexor	X		X		X	X			
	Effexor XR	X		X		X	X			
Others										
Aripiprazole	Abilify	X								
Brexiprazole	Rexulti	X								
Bupropion	Wellbutrin	X								
	Wellbutrin XL	X								X[5]
Esketamine	Spravato	X								
Mirtazapine	Remeron	X								
Quetiapine XR	Seroquel XR	X								
Trazodone	Desyrel	X								
Trazodone ER	Oleptro	X								
Vortioxetine	Brintellix	X								

[1]Premenstrual dysphoric DO; [2]Panic DO; [3]Social Anxiety DO; [4]Seasonal Affective DO; [5]Adult, Children & Adolescent

ANTIDEPRESSANT AGENTS

Table 2: Maximum Daily Dose

Agent	Brand	Adult	Children & Adolescents
MAOIs			
Isocarboxazid	Marplan	60 mg	non-FDA approved
Phenelzine	Nardil	90 mg	non-FDA approved
Selegiline Transdermal	Emsam	12 mg	non-FDA approved
Tranylcypromine	Parnate	60 mg	non-FDA approved
TCAs			
Amitriptyline	Elavil	300 mg	non-FDA approved
Amoxapine	Asendin	600 mg	non-FDA approved
Clomipramine	Anafranil	250 mg	OCD: 25-200 mg (≥ 10yo)
Desipramine	Norpramin	300 mg	non-FDA approved
Doxepin	Sinequan	300 mg	non-FDA approved
Imipramine	Tofranil	300 mg	non-FDA approved
Maprotiline	Ludiomil	225 mg	non-FDA approved
Nortriptyline	Pamelor	150 mg	non-FDA approved
Protriptyline	Vivactil	60 mg	non-FDA approved
SSRIs			
Citalopram	Celexa	40 mg	non-FDA approved
Escitalopram	Lexapro	20 mg	MDD: 10-20mg (12-17yo)
Fluoxetine	Prozac	80 mg	MDD:20mg(8-18yo), OCD:60mg(7-17yo)
	Prozac Weekly	90 mg	non-FDA approved
	Sarafem	80 mg	non-FDA approved
Fluvoxamine	Luvox, Luvox CR	300 mg	OCD: 200 mg (8-11yo) 300 mg (12-17yo)
Paroxetine	Paxil	60 mg	non-FDA approved
	Paxil CR	75 mg	non-FDA approved
Sertraline	Zoloft	200 mg	OCD: 25-200 mg (6-12 yo), 50-200mg (13-17y.o)
Vilazodone	Viibryd	40mg	non-FDA approved
SNRIs			
Desvenlafaxine	Pristiq	50 mg	non-FDA approved
Duloxetine	Cymbalta	120 mg	GAD: 30-120mg (7-17yo), Fibro.: 30-60mg (13-17yo)
Levomilnacepran	Fetzema	120 mg	Non-FDA approved
Venlafaxine	Venlafaxine	375 mg	Non-FDA approved
	Effexor XR	225 mg	non-FDA approved
Others			
Aripiprazole[1]	Abilify	15 mg	Irritability: Autism associated, 2-15mg (6 to 17y.o), Tourette Synd. 2-10mg (8-18yo<50mg, 2-20mg 8-18yo >50kg)
Brexiprazole[1]	Rexulti	3mg	non-FDA approved
Bupropion	Wellbutrin, Wellbutrin XL	450 mg	non-FDA approved
	Wellbutrin SR	400 mg	non-FDA approved
Esketamine[1]	Spravato	28mg	non-FDA approved
Mirtazapine	Remeron	45 mg	non-FDA approved
Quetiapine XR[1]	Seroquel XR	300mg	non-FDA approved
Trazodone	Desyrel	600 mg	non-FDA approved
Trazodone ER	Oleptro	375mg	non-FDA approved
Vortioxetine	Brintellix	20mg	non-FDA approved

[1]FDA maximum dosing for the diagnosis of Adjunctive Therapy for MDD

Table 3: Pregnancy and Lactation Information

Agents	Brand	Pregnancy Category	Nursing Mother
Amitriptyline	Elavil	caution advised in 3rd trimester; risk of teratogenicity not expected based on human data, though risk of neonatal withdrawal sx based on limited human data w/ other TCAs; possible dose-dependent risk of teratogenicity based on conflicting animal data at doses higher than MRHD	may use while breastfeeding; low risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Amoxapine	Asendin	consider avoiding use in 1st trimester; inadequate human data available to assess risk, though risk of neonatal withdrawal sx based on limited human data w/ other TCAs; no known risk of teratogenicity based on animal data, though risk of embryo-fetal toxicity based on animal data at 1-10x recommended human dose	consider alternative while breastfeeding; inadequate human data available to assess risk of infant harm; no human data available to assess effects on milk production
Aripiprazole	Abilify	caution advised in 3rd trimester; risk of teratogenicity not expected based on human data, though risk of neonatal extrapyramidal and withdrawal sx based on human data w/ antipsychotics	caution advised while breastfeeding; no known risk of infant harm based on limited human data; inadequate human data available, though theoretical decr. milk production based on decr. prolactin levels
Brexiprazole	Rexulti	Adequate & well-controlled studies have not been conducted with REXULTI in pregnant women to inform drug associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like REXULTI, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms	Lactation studies have not been done. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REXULTI and any potential adverse effects on the breastfed infant from REXULTI or from the underlying maternal condition.
Bupropion	Wellbutrin	caution advised during pregnancy; risk of congenital heart defects inconclusive, though no known risk of other teratogenicity based on human data	caution advised while breastfeeding; possible risk of infant seizures, though inadequate human data to fully assess risk; no human data available to assess effects on milk production
Citalopram	Celexa	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	consider alternative while breastfeeding, though may cont. if used during pregnancy; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data
Clomipramine	Anafranil	caution advised during pregnancy, esp. in 1st and 3rd trimesters; risk of teratogenicity and neonatal withdrawal sx based on human data	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Desipramine	Norpramin	caution advised during pregnancy, esp. in 3rd trimester; inadequate human data available to assess risk, though risk of neonatal withdrawal sx based on limited human data; possible risk of teratogenicity based on conflicting human and animal data w/ imipramine	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Desvenlafaxine	Pristiq	caution advised during pregnancy, esp. in 3rd trimester; no human data available; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on limited human data w/ venlafaxine; risk of maternal postpartum hemorrhage based on human data w/ SNRIs	consider alternative while breastfeeding, though may cont. if used during pregnancy; low risk of infant harm based on limited human data and drug properties; inadequate human data available to assess effects on milk production
Doxepin	Sinequan	caution advised during pregnancy, esp. in 3rd trimester; possible risk of teratogenicity based on limited human data; risk of neonatal withdrawal sx based on limited human data w/ other TCAs	use alternative while breastfeeding; possible risk of infant CNS and resp. depression based on limited human data; no human data available to assess effects on milk production

Duloxetine	Cymbalta	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on limited human data; risk of maternal postpartum hemorrhage based on human data	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; effects on milk production inconclusive based on conflicting human data
Escitalopram	Lexapro	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	consider alternative while breastfeeding, though may cont. if used during pregnancy; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data
Esketamine	Spravato	SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes	Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.
Fluoxetine	Prozac	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	consider alternative while breastfeeding, though may cont. if used during pregnancy; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data
Fluvoxamine	Luvox	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	may use while breastfeeding; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data
Imipramine	Tofranil	caution advised during pregnancy, esp. in 3rd trimester; possible risk of teratogenicity based on conflicting human data; possible risk of neonatal withdrawal sx based on limited human data	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Isocarboxazid	Marplan	consider avoiding use during pregnancy; inadequate human data available to assess risk; no known risk of teratogenicity based on limited animal data; possible risk of vasoconstriction based on drug's mechanism of action	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Levomilnacipran	Fetzima	caution advised during pregnancy, esp. in 3rd trimester; inadequate human data available, though risk of neonatal withdrawal sx or serotonin syndrome based on human data w/ other SNRIs; no known risk of teratogenicity, though risk of embryo-fetal toxicity, incl. delayed skeletal ossification and decr. fetal wt based on animal data at 8x and 16x MRHD; risk of maternal postpartum hemorrhage based on human data w/ SNRIs	consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Maprotiline	Ludiomil	may use during pregnancy; inadequate human data available to assess risk, though risk of fetal harm not expected based on limited human data; no known risk of teratogenicity based on animal data at 1.3x MRHD	consider alternative while breastfeeding; inadequate human data available to assess risk of infant harm; no human data available to assess effects on milk production
Mirtazapine	Remeron	caution advised during pregnancy, esp. in 3rd trimester; inadequate human data available to assess risk, though risk of teratogenicity not expected based on limited human data; risk of neonatal withdrawal sx or serotonin syndrome based on human data w/ SSRIs; no known risk of fetal harm based on animal data at 3x MRHD	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Nortriptyline	Pamelor	caution advised during pregnancy, esp. in 3rd trimester; possible risk of teratogenicity based on conflicting human data; possible risk of neonatal withdrawal sx based on limited human data	may use while breastfeeding; may give 30-50 mg/day PO divided qd-qid; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Paroxetine	Paxil	weigh risk/benefit during pregnancy, consider alternate SSRI; risk of teratogenicity in 1st trimester and neonatal withdrawal sx or serotonin syndrome in 3rd trimester based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	may use while breastfeeding; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data

Phenelzine	Nardil	consider avoiding use during pregnancy; inadequate human data available to assess risk; risk of embryo-fetal toxicity based on limited animal data at greater than MRHD; possible risk of vasoconstriction based on drug's mechanism of action	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Protriptyline	Vivactil	caution advised during pregnancy, esp. in 3rd trimester; no human data available, though risk of neonatal withdrawal sx based on limited human data w/ other TCAs; no known risk of teratogenicity based on animal data at >10x recommended human dose	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Quetiapine XR	Seroquel XR	There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. SEROQUEL XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	SEROQUEL XR was excreted into human milk. Because of the potential for serious adverse reactions in nursing infants from SEROQUEL XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother's health.
Selegiline Transdermal	Emsam	consider avoiding use during pregnancy; inadequate human data available to assess risk; no known risk of teratogenicity based on limited animal data, though risk of embryo-fetal toxicity based on animal data at 60x and 64x MRHD; possible risk of vasoconstriction based on drug's mechanism of action	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Sertraline	Zoloft	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on human data; risk of neonatal persistent pulmonary HTN or autism inconclusive	SSRI of choice while breastfeeding; start 25 mg PO qd x5-7 days, then may incr. by 25-50 mg/day qwk to max 200 mg/day; low risk of infant harm based on human data; effects on milk production inconclusive based on conflicting human data
Tranylcypromine	Parnate	consider avoiding use during pregnancy; inadequate human data available to assess risk; no known risk of teratogenicity based on limited animal data; risk of decr. uteroplacental blood flow and vasoconstriction based on animal data and drug's mechanism of action	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Trazodone	Desyrel	caution advised during pregnancy, esp. in 3rd trimester; inadequate human data available, though risk of teratogenicity not expected based on limited human data; risk of neonatal withdrawal sx or serotonin syndrome based on human data w/ SSRIs; no known risk of teratogenicity based on animal data at doses of 75 mg/kg and 210 mg/kg	may use while breastfeeding; no known risk of infant harm based on limited human data; no human data available to assess effects on milk production
Trazodone ER	Oleptro	Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30 – 50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 – 50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Oleptro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. "	Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when Oleptro is administered to a nursing woman.
Venlafaxine	Effexor	caution advised during pregnancy, esp. in 3rd trimester; risk of fetal harm low, though risk of neonatal withdrawal sx or serotonin syndrome based on limited human data	consider alternative while breastfeeding, though may cont. if used during pregnancy; low risk of infant harm based on limited human data and drug properties; inadequate human data available to assess effects on milk production
Vilazodone	Viibryd	caution advised during pregnancy, esp. in 3rd trimester; no human data available, though risk of neonatal withdrawal sx or serotonin syndrome based on human data w/ SSRIs; risk of neonatal persistent pulmonary HTN or autism inconclusive based on human data w/ SSRIs; no known risk of teratogenicity based on animal data at 17x and 48x MRHD	consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

Vortioxetine	Brintellix	caution advised during pregnancy, esp. in 3rd trimester; no human data available, though risk of neonatal withdrawal sx or serotonin syndrome based on human data w/ SSRIs; risk of neonatal persistent pulmonary HTN or autism inconclusive based on human data w/ SSRIs; no known risk of teratogenicity based on animal data at 58x and 77x MRHD	consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

ANTIDEPRESSANT AGENTS

Table 4: Drug Interactions, Pharmacology

Agent	Brand	Metabolism; CYP (Substrate)	$t_{1/2}$ (hr)	Comments
MAOIs				
Isocarboxazid	Marplan	unknown	unknown	
Phenelzine	Nardil	Hepatic: CYP450 Unknown	11.6	
Selegiline Transdermal	Emsam	Substrate: 2C19 (Primary), 2B6, 2C9, 1A2, 2A6, 3A4/5		active metabolites
Tranylcypromine	Parnate	Hepatic: CYP450 Unknown	2.5	active metabolites
TCAs				
Amitriptyline	Elavil	Substrate: 2D6 (Primary), 1A2, 2C19, 3A4	10-26 (18-44 hr nortript.)	active metabolites, includes nortriptyline
Amoxapine	Asendin	Hepatic: CYP450 Unknown	8 (30 hr hydroxyamox.)	active metabolite
Clomipramine	Anafranil	Substrate: CYP3A4 & 2C19	32 (69 desmethylclomip.)	active metabolite
Desipramine	Norpramin	Substrate: 2D6 (primary), 2C19	12-27	
Doxepin	Sinequan	Substrate:2C19 (Primary), 1A2, 2C9, 2D6	6-8 (28-52 metabolite)	active metabolite
Imipramine	Tofranil	Substrate:2D6 (Primary), 1A2, 2C19, 3A4	12-25	active metabolite: desipramine
Maprotiline	Ludiomil	Substrate: 2D6	43 (60-90 d-methylmapro.)	active metabolite
Nortriptyline	Pamelor	Substrate:2D6 (primary), 1A2, 2C19, 3A4	18-44	active metabolite
Protriptyline	Vivactil	CYP450: unknown	67-89	
SSRIs				
Citalopram	Celexa	Substrate: 2C19(primary), 2D6, 3A4	35	MDD 20mWg for 2C19 poor metabolizers & pts>60y.o., Inhibits 2D6 (Weak)
Escitalopram	Lexapro	Substrate: 2C19 (primary), 2D6, 3A4	27-32	$t_{1/2}$ ↑ 50% for elderly, Inhibits: 2D6 (Weak)
Fluoxetine	Prozac	Substrate: 2D6 (primary), 2C9, 2C19, 3A4	4-6 days (fluox.); 9.3 days (norfluox.)	Inhibits: 2D6(Potent), 2C9, 2C19, 3A4(mod.), 1A2 (mild)
Fluvoxamine	Luvox	Substrate: 2D6 (primary), 1A2	15.6	Inhibits: 1A2 & 2C19 (potent), CYP2C9 & 3A4(mod.), 2D6 (mild)
Paroxetine	Paxil	Substrate: 2D6	21	Inhibits: 2D6 (potent), 2B6 (potent)
Sertraline	Zoloft	Substrate: 2C19 (primary), 2D6, 3A4	26	Inhibits: 2D6(mild if dose<100mg/d, potent ≥150mg/d, 1A2 & 2C9 & 2C19 & 3A4 (weak)
Vilazodone	Viibryd	Substrate: 3A4 (Primary), 2C19, 2D6	25	Dose=20mg when co-admin. with CYP3A4 strong inhibitors. The effect of CYP3A4 inducers on VIIBRYD has not been evaluated
SNRIs				
Desvenlafaxine	Pristiq	Substrate: 3A4 (minor), UGT	11	$t_{1/2}$ is 23h for ESRD
Duloxetine	Cymbalta	Substrate: 1A2(major), 2D6	12	Inhibits 2D6(mod.) & 1A2
Levomilnacipran	Fetzema	Substrate: 3A4 (primary), 2C8, 2C19, 2D6, 2J2	12	Dose Adj. needed when co-admin. With strong CYP3A4 inhib. (e.g. Ketocon.) or inducers (See PI for details)
Venlafaxine	Effexor	Substrate: 2D6 (primary), 3A4	5 (11 desmethylvenla.)	Active metabolite, Inhibits: 2D6 & 3A4 (Weak)

ANTIDEPRESSANT AGENTS Cont'd

Table 4: Drug Interactions, Pharmacology

Agent	Brand	Metabolism; CYP	$t_{1/2}$ (hr)	Comments
Others				
Aripiprazole[1]	Abilify	Substrate: 2D6,3A4	75 (2D6 Extensive Metabol.); 146 (2D6 Poor Metabolizer)[2]	2D6 Poor Metabolizers ↑active drug exposure by 60%
Brexiprazole	Rexulti	Substrate: 2D6, 3A4		Dose adj. needed with mod. To severe hepatic failure & poor metabolizers and cod-admin with 2D6 & 3A4 inducers & inhibitors (See PI for details)
Bupropion	Wellbutrin	Substrate: 2B6	21	Active metabolite, Inhibits 2D6 (moderate, can inc. Abilify level)
Mirtazapine	Remeron	Substrate: Glucuronidation, 2D6, 1A2, 3A4	20-40	Active metabolite, Caution in elderly
Quetiapine XR	Seroquel XR	Substrate: 3A4	7-12	Caution with elderly, hepatic & renal impairment. Dosage adj. needed when co-admin with 3A4 inhibitors & inducers. (See PI for details)
Trazodone, Trazodone ER	Desyrel& Oleptro	Substrate: 3A4	Biphasic: 3-6; 5-9	Active metabolite, dosage adj. may be needed with 3A4 inducers & inhibitors (see PI for details).
Vortioxetine	Brintellix	Substrate: 2D6 (primary), 3A4/5, 2C19, 2C9, 2A6, 2C8, 2B6	66	Dose adj. may be needed with potent 2D6 inhibitors or inducers. (See PI for details)

[1] Adjunctive Therapy for MDD

[2] Poor Metabolizers lack the capacity to Metabolize 2D6 substrates due to genetically dysfunctional 2D6 enzyme versus Extensive Metabolizers, who have normal enzyme function