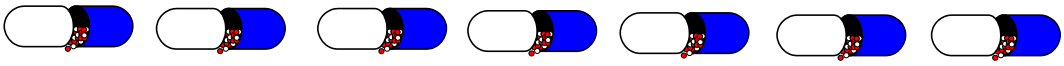
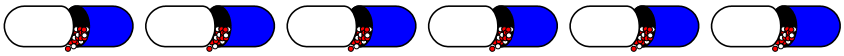


MISSOURI DUReport



DUR NEWSLETTER – DEPRESSION

I. INTRODUCTION[1]

Major depressive disorder (MDD) is a common health problem in patients treated in the primary care setting. Depression can be associated with a high level of functional disability and increased use of outpatient medical services. A 2-year follow-up study concluded that depressed patients may have substantial and long-lasting impairments in social and physical functioning that equals or exceeds those of patients with chronic medical conditions. Approximately 15% of patients with unrecognized or inadequately treated depression commit suicide; this is approximately 30 times the rate in nondepressed patients. Although adequate treatment reduces the risk of suicide and improves functioning and well-being, studies conducted in primary care settings suggest that even when depression is diagnosed accurately, few patients receive an adequate dose and duration of antidepressant treatment. The introduction of effective antidepressant drugs with more favorable adverse event profiles and relatively greater safety in an overdose situation has enabled more patients to be managed successfully.

II. EPIDEMIOLOGY[1]

- The true prevalence of depressive disorders in the United States is unknown. The National Comorbidity Survey (NCS) reported that 17% of the population studied had experienced a major depressive disorder in their lifetime, and more than 10% had an episode within the past 6 months.
- Depression is two to three times more frequent in females than in males.
- Although depression can occur at any age, adults 25 to 44 years of age experience the highest rates of major depression.

III. ETIOLOGY[2]

- Biologic contributors
    - Genetic predisposition plays a role in the development of MDD. Individuals with a family history of affective disorders, panic disorder, or alcohol dependence carry a higher risk for MDD.
    - Certain neurologic illnesses increase the risk of MDD. Examples include Parkinson's disease, stroke, multiple sclerosis, and seizure disorders.
    - Exposure to certain pharmacologic agents also increases the risk; medications such as reserpine or beta-blockers, as well as abused substances such as cocaine, amphetamine, narcotics, and alcohol are associated with higher rates of MDD.
    - Chronic pain, medical illness, and psychosocial stress also can play a role in both the initiation and continuation of MDD. The psychological component of these risk factors may be important. However, neurochemical hypotheses point to the deleterious effects of stress related substances such as cortisol on the neuronal substrate of mood in the CNS.

- Psychosocial contributors
    - While MDD can arise without any precipitating stressors, stress and interpersonal losses can increase risk. Psychodynamic formulations find that significant losses in early life predispose to MDD over the lifespan of the individual, as does trauma.

IV. DIAGNOSTIC CRITERIA

Major Depressive Episode DSM-IV Criteria[1, 3]
The essential feature of MDD is a clinical course that is characterized by one or more Major Depressive Episodes without a history of Manic, Mixed or Hypomanic Episodes. Episodes of Substance-Induced Mood Disorder or of Mood disorder Due to a General Medical Condition do not count toward a diagnosis of MDD. In addition, the episodes must not be better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder or Psychotic Disorder NOS.

Five (or more) of the following symptoms present during the same 2-week period which represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Exclude symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations. All symptoms except suicidal ideation must occur nearly every day.

- Depressed mood most of the day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, (as indicated by either subjective account or observation made by others)
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down)

- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) (not merely self-reproach or guilt about being sick)
- Diminished ability to think or concentrate, or indecisiveness, (either by subjective account or as observed by others)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation with a specific plan, or a suicide attempt or a specific plan for committing suicide.

Additional Considerations

- The symptoms do not meet criteria for a mixed episode.
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- The symptoms are not better accounted for by bereavement; i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

V. SCREENING TOOLS[5]

- Mental Status Exam (AMSIT)
  - Structured interview in which the clinician has an observational basis for evaluating a patient's appearance, behavior, speech, mood, affect, sensorium, memory, and intellectual functioning

- Hamilton Depression Scale (HAM-D)
  - Initially used to measure the efficacy of antidepressant medications given to severely depressed individuals in controlled clinical trials. This instrument has emerged as the gold standard of depression rating scales. The scale, however, was not designed for routine use in the general ambulatory care patient population and it fails to address a number of target symptoms required for a DSM-IV diagnosis of MDD.

- Beck Depression Inventory (BDI) Clinician and Patient-rated
  - A validated behavior rating scale. Does not address a number of target symptoms required for a DSM-IV diagnosis of MDD.

- Inventory for Depressive Symptoms (IDS) Clinician and Patient-rated
  - Can be completed in 10 to 15 minutes. It is a validated instrument used extensively in clinical and research setting in both formats. Does not address a number of target symptoms required for a DSM-IV diagnosis of MDD.

- Brief Inventory for Depressive Symptoms-Self Report (BIDS)
  - Brief, patient-rated scale, often distributed to patients in waiting rooms and doctors' offices. Does not address a number of target symptoms required for a DSM-IV diagnosis of MDD.

VI. TREATMENT[4, 5]

Table 1 – Phases of Depression - Goals[4*]

Phase of Depression	Goals
Acute Phase Goals (6-12 weeks)	• Ensure safety • Begin to resolve symptoms • Obtain adequate dose as soon as possible
Continuation Phase Goals (4-9 months)	• Prevent relapse • Ensure optimal response • Address adverse effects • Ensure compliance especially when symptoms resolve • Minimize polypharmacy
Maintenance Phase Goals (≥ 1 year)	• Prevent new episode (recurrence) • Potential candidates: three or more episodes of major depressive disorder or two episodes with confounders

*Adapted from Depression Guideline Panel, Depression in Primary Care, AHCPR, April 1993.

Table 2 - Classification of Antidepressant Pharmacotherapy by Presumed Mechanism of Action[5]

Mixed 5-HT/NE reuptake inhibitors	TCAs, venlafaxine
SSRIs	Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, esciltalopram
Selective NE reuptake inhibitors	Reboxetine
Mixed 5-HT effects	Trazodone, nefazodone
Mixed NE/DA reuptake inhibitors	Bupropion
Mixed 5-HT/NE effects	Mirtazapine
MAOIs	Phenelzine, tranylcypromine

5-HT-serotonin, NE-norepinephrine, DA-dopamine, TCAs-tricyclic antidepressants
SSRIs-selective serotonin reuptake inhibitors, MAOIs-monoamine oxidase inhibitors

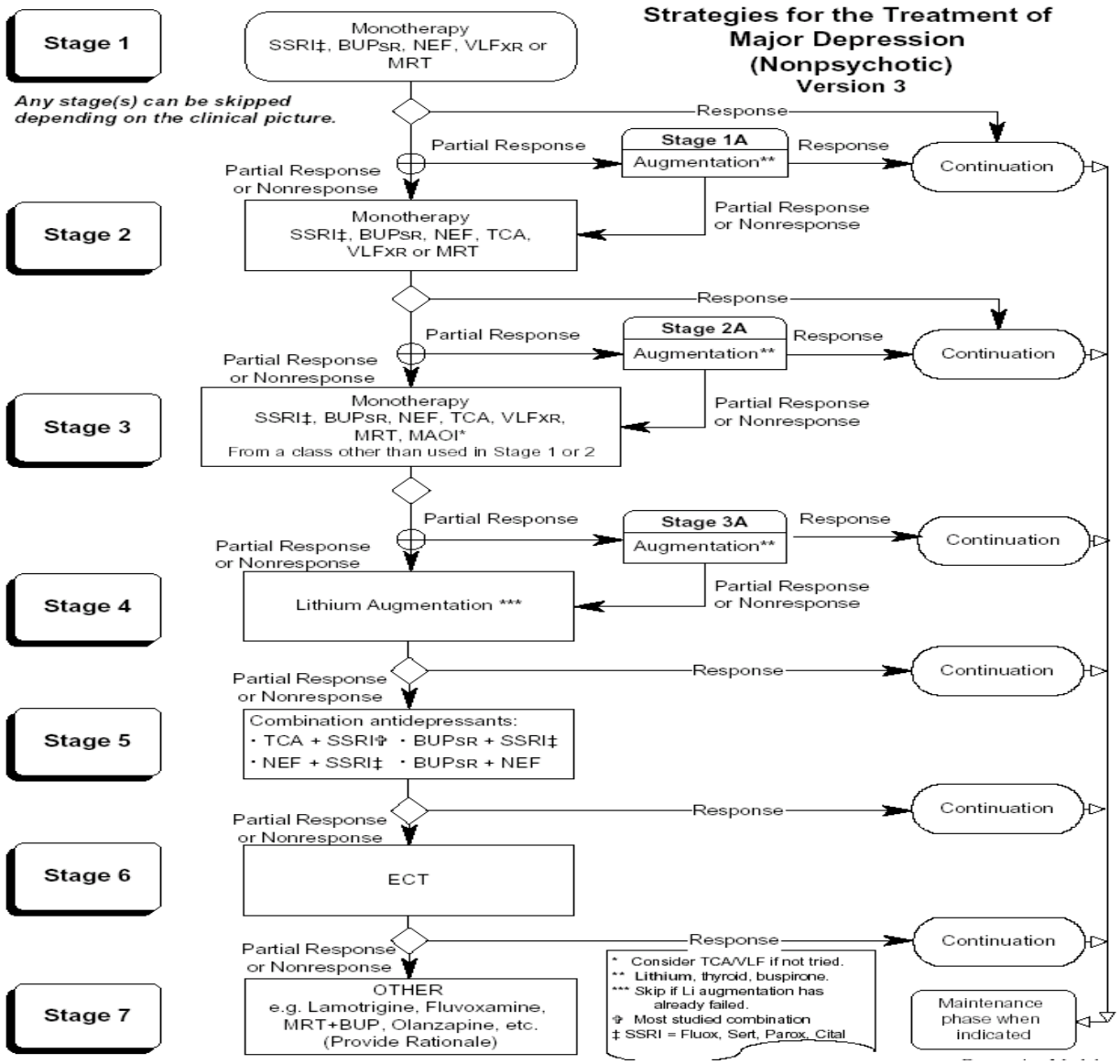
Antidepressant Treatment Duration - Highlights[5]

- Acute and continuation treatment recommended for all patients with MDD, minimal duration of treatment = 7 months
- Indefinite maintenance treatment is recommended if any one of the following criteria are met:
    - Three or more previous episodes (regardless of age)
    - Two or more previous episodes and age >50 yrs
    - One or more and age >60 yrs

Treatment Algorithm[6]**

TMAP

❖ *The Depression Algorithms*



From: Trivedi MH, Pigott T, Stegman K, Key T, O'Neal B, Baker S, Crismon L, Rush AJ. TMAP Procedural Manual. http://www.mhmr.state.tx.us/centraloffice/medicaldirector/mddman.pdf.
**See also: The Strategies for the treatment of Depression (*Psychotic*) and the At-A Glance Depression Medication Algorithm, Texas Medication Algorithm Project (TMAP) guidelines at http://www.mhmr.state.tx.us/centraloffice/medicaldirector/mddman.pdf
BUP-buproprion, BUP_{SR}-buproprion SR, NEF-nefazodone, VLF_{XR}-venlafaxine XR, MRT-mirtazapine, SSRI-selective serotonin reuptake inhibitor, TCA-tricyclic antidepressant, MAOI-monoamine oxidase inhibitor, ECT-electroconvulsive therapy.

VII. CHANGING PHARMACOLOGIC THERAPY

The following principles apply in determining the process of modifying antidepressant medications.

DIRECTIONS FOR UTILIZING THE FOLLOWING TABLE (Table 3):

- The first bullet point refers to the first drug being discontinued due to intolerance following a *brief exposure* (< 5 days). In this case the first drug can be stopped immediately and the second drug initiated.
- The second bullet refers to the first drug being discontinued after a *longer exposure* (> 7 days), due to symptomatic breakthrough or inadequate response. In this case the first drug should be **tapered** and the second drug started gradually (notable exception being a switch from an MAOI)

Table 3 - Guidelines for Combining and Switching Between Antidepressant Medications[6]

FROM	TO	PLAN
SSRI	SSRI	• Discontinue SSRI #1 and begin SSRI # 2 • Taper SSRI # 1 and initiate SSRI # 2
SSRI	TCA Bupropion	• Discontinue SSRI and begin TCA or bupropion • Taper SSRI and initiate TCA or bupropion gradually as tolerated to therapeutic dose range[1]
SSRI	Nefazodone Venlafaxine	• Discontinue SSRI and begin nefazodone or venlafaxine • Taper SSRI and initiate nefazodone or venlafaxine gradually as tolerated to therapeutic dose range
SSRI	MAOI	• **Discontinue SSRI. After a 5 week washout period for fluoxetine or a 2 week washout period for sertraline or paroxetine, MAOI therapy can safely be initiated.**
TCA Venlafaxine Nefazodone Bupropion	TCA	• Discontinue TCA # 1 (or venlafaxine, nefazodone, bupropion) by taper and then initiate TCA # 2 • Taper TCA # 1 (or venlafaxine, nefazodone, bupropion) while initiating TCA # 2 gradually as tolerated to therapeutic dose range.
TCA Venlafaxine Nefazodone Bupropion	SSRI	• Taper and discontinue TCA (or venlafaxine, nefazodone, bupropion) and then initiate SSRI • Taper TCA (or venlafaxine, nefazodone, bupropion) while initiating SSRI at a low dose
TCA Venlafaxine Nefazodone Bupropion	Nefazodone Venlafaxine Bupropion	• Discontinue TCA and initiate nefazodone, venlafaxine, or bupropion • Taper and discontinue TCA (or venlafaxine, nefazodone, bupropion) to initiate nefazodone, venlafaxine, or bupropion gradually as tolerated to therapeutic dose range
TCA	MAOI	• **Discontinue TCA. After a 2 week washout, MAOI therapy can be safely initiated.**
MAOI	MAOI	• **Discontinue MAOI # 1. After a 2 week washout, therapy with MAOI # 2 (or TCA, venlafaxine, nefazodone, or bupropion) can be safely initiated.**

[1] Both the TCAs and bupropion are associated with significant toxicity at elevated plasma concentrations. Because some SSRIs may increase the plasma concentrations of TCAs and bupropion, caution is indicated when co-administering these agents or when therapy with bupropion or a TCA is undertaken in close proximity to cessation of an SSRI.

DISCONTINUATION OF ANTIDEPRESSANTS[5]

Withdrawal syndrome

- Worse with paroxetine, venlafaxine
- Symptoms: dizziness, nausea, paresthesias, anxiety/ insomnia
- Onset: 36-72 hr
- Duration: 3-7 days
-

Taper schedule (for patients receiving long-term treatment)

- Fluoxetine: generally unnecessary
- Sertraline: decrease by 50 mg every 1-2 wk
- Paroxetine: decrease by 10 mg every 1-2 wk
- Citalopram: decrease by 10 mg every 1-2 wk
- Venlafaxine: decrease by 25-50 mg every 1-2 wk
- Nefazodone: decrease by 50-100 mg every 1-2 wk
- Bupropion: generally unnecessary
- Tricyclics: decrease by 10%-25% every 1-2 wk

ADDENDUM A

Side-Effect Profile of Selected Antidepressant drugs[1, 8]

	ACH Effects	Sedation	Orth. Hypoten.	Cardiac Arrhyth.	GI distress	Weight Gain
TCA's						
Tertiary amines						
Amitriptyline	++++	++++	++++	+++	+	++++
Doxepin	+++	++++	++	++	0	++++
Imipramine	+++	+++	++++	+++	+	++++
Secondary amines						
Desipramine	+	++	++	++	0	+
Nortriptyline	++	++	+	++	0	+
Tetracyclics						
Mirtazapine	+	+++	0	0	0	+++
Triazolopyridines						
Nefazodone	+	+	0	0	+	0
Trazodone	0	++++	+++	+	+	++
Aminoketone						
Bupropion	0	0	0	+	+	0
SSRI's						
Citalopram	0	0	0	0	+++	+
Fluoxetine	0	0	0	0	+++	+
Fluvoxetine	0	0	0	0	+++	+
Paroxetine	+	+	0	0	+++	++
Sertraline	0	0	0	0	+++	+
SNRI						
Reboxetine	+	0	+	0	No info	No Info
5-HT/NE reuptake Inhibitor						
Venlafaxine	+	+	0	+	+++	0

*adapted from Pharmacotherapy, a Pathophysiologic Approach, 5th edition. Mcgraw-Hill; 2002: 1243-1264 and Drug Information Handbook, 10th edition. Hudson, OH Lexicomp; 2002: 1482-1483.

0=none +=very low ++=low +++=moderate ++++=high

ADDENDUM B

DRUG INTERACTIONS DUE TO CYTOCHROME P450 (CYP) ISOENZYME SYSTEMS

Knowing which drugs are metabolized by each cytochrome P450 isoenzyme and the drugs that influence those enzymes can help in predicting drug-drug interactions. The following tables are meant to serve as one tool in the prediction of drug-drug interactions with antidepressants. It is important to understand that other parameters may also influence these drug interactions.

DEFINITIONS[9]

Substrate: drug metabolized by the enzyme system
Inducer: drug that will increase the synthesis of CYP450 enzymes, may decrease levels of the substrate
Inhibitor: drug that will decrease the metabolism of a substrate by the CYP450 enzyme system, may increase levels of the substrate

CLINICAL SIGNIFICANCE[8]

Points to consider when predicting drug interactions

- Alternative elimination pathways may minimize clinical significance of CYP pathway
- Active metabolites can affect the CYP system (e.g. fluoxetine, sertraline)
- Wide therapeutic range may limit clinical significance of CYP pathway (e.g. TCA's)

The following tables may be used together to predict potential drug interactions:

TABLE 1 - NEWER ANTIDEPRESSANTS AND CYTOCHROME (CYP) P450 ENZYME INHIBITORY POTENTIAL[1**]

	1A2	2C	2D6	3A4
Tetracyclics				
Mirtazapine	0	0	0	0
Triazolopyridines				
Nefazodone	0	0	0	++++
Aminoketone				
Bupropion	0	0	0	0
SSRIs				
Citalopram	0	0	0	+++
Fluoxetine	0	++	++(++++)*	++(++)*
Fluvoxetine	++++	++	0	++
Paroxetine	0	0	++++	0
Sertraline	0	++(++)*	+(++)*	+(+)*
SNRI				
Reboxetine	0	0	0	0
5-HT/NE Reuptake Inhibitor				
Venlafaxine	0	0	0	0

*inhibitory potential of major metabolite
**adapted from Depressive Disorders In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy, a Pathophysiologic Approach, 5th edition. Mcgraw-Hill; 2002: 1243-1264.
SSRIs-selective serotonin reuptake inhibitors, SNRI-selective norepinephrine reuptake inhibitor, 5-HT-serotonin, NE-norepinephrine

TABLE 2 - COMMON ANTIDEPRESSANTS THAT INTERACT WITH P450 ENZYMES[8*]
(Antidepressive agents are indicated in bolded text)

Subfamily	Substrates	Inducers	Inhibitors
1A2	Acetaminophen, **amitriptyline**, antipyrene, caffeine, clomipramine, clozapine, **imipramine**, olanzapine, propranolol, tacrine, theophylline, (R)-warfarin, zileuton	Charcoal-broiled food, omeprazole, smoking	Ciprofloxacin, enoxacin, **fluvoxamine**, macrolides[1], mexiletine, tacrine, zileuton
2C9/10	Celecoxib, diclofenac, dronabinol, flubiprofen, hexobarbital, ibuprofen, losartan, (R)-mephenytoin, montelukast, naproxen, phenytoin, piroxicam, tolbutamide, torsemide, (S)-warfarin	Barbiturates, carbamezapine, phenytoin, primidone, rifampin	Amiodarone, clopidrogrel, disulfuram, efavirenz, fluconazole, **fluoxetine**, fluvastatin, metronidazole, miconazole (IV), ritonavir, sulfamethoxazole, sulfaphenazole, sulfinpyrazone, zafirlukast
2C19	**Amitriptyline**, clomipramine, diazepam, hexobarbital, **imipramine**, lansoprazole, mephenytoin, mephobarbital, omeprazole, pantoprazole, phenytoin, propranolol, rabeprazole	Rifampin	Efavirenz, felbamate, **fluoxetine**, **fluvoxamine**, omeprazole, ritonovir, ticlidopine
2D6	Chlorpheniramine, codeine, debrisoquine, dextromethorphan, flecainide, **fluoxetine**, galantamine, haloperidol, hydrocodone, loratadine, metoprolol, mexiletine, **paroxetine**, perphenazine, propafenone, propranolol, risperidone, thioridazine, timolol, tramadol, **trazodone**, **TCA's**, **venlafaxine**, voriconazole		Amiodarone, chloroquine, cimetidine, diphenhydramine, **fluoxetine**, haloperidol, **paroxetine**, perphenazine, propoxyphene, quinidine, ritonavir, **SSRI's[2]**, terbinafine, thioridazine
3A3/4	Alfentanil, alprazolam, amiodarone, **amitriptyline**, amlodipine, androgens, astemizole, atorvastatin, benzphetamine, bepridil, bromocriptine, **buspirone**, carbamezapine, cilostazol, cisapride, clomipramine, clonazepam, cocaine, corticosteroids, cyclosporine, dapsone, dexamethasone, diazepam, diltiazem, disopyramide, doxorubicin, ergotamine, erythromycin, ethinyl estradiol, ethosuxamide, etoposide, felodipine, fentanyl, fexofenadine, finasteride, galantamine, hydrocortisone, ifosfamide, imatinib, imipramine, indinavir, isradipine, itraconazole, ketoconazole, lidocaine, losartan, lovastatin, miconazole, midazolam, mifepristone, montelukast, **nefazodone**, nelfinavir, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendapine, omeprazole, paclitaxel, pimozide, pioglitazone, progesterone, propafenone, quinidine, quinine, rifabutin, ritonavir, saquinavir, **sertraline**, sibutramine, sildenafil, simvistatin, sirolimus, tacrolimus, tamoxifen, teniposide, testosterone, theophylline, triazolam, troleandomycin, verapamil, vinca alkaloids, voriconazole, (R)-warfarin, zolpidem	Aminoglutethimide, barbiturates, carbamezapine, corticosteroids, efavirenz, griseofulvin, phenytoin, primidone, rifabutin, rifampin, sulfinpyrazone	Cyclophosphamide, cyclosporine, delavirdine, diltiazem, fluconazole, **fluvoxamine**, grapefruit juice, ifosfamide, indinavir, itraconazole, ketoconazole, macrolides[1], metronidazole, miconazole (IV), **nefazodone**, nelfinavir, nicardipine, nifedipine, quinidine, ritonavir, verapamil, zafirlukast

[1]CYP3A4 enzyme inhibition by macrolide antibiotics varies by drug: troleandomycin>erythromycin> clarithromycin>azithromycin=didithromycin=0
[2]CYP2D6 enzyme inhibition by SSRI varies by drug: paroxetine=fluoxetine>>sertraline>citalopram>fluvoxamine
*Adapted from the Handbook of Clinical Drug Data, 10th edition. McGraw-Hill Companies Inc.; 2002: 1019-1023.

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Top 25 Products Ranked by Paid and Detail Drugs

Drug Class/Drug	Cost	Paid	Rx	User Months	Cost PUPM	Paid PUPM	Cost/Rx	Paid/Rx	% Pgm Cost	% Pgm Paid	% View Cost
OLANZAPINE	$57,286,201	$55,986,371	189,267	183,940.00	$311.44	$304.37	$302.67	$295.81	6.4%	6.3%	16.4%
RISPERIDONE	$32,566,330	$29,644,966	196,117	189,463.00	$171.89	$156.47	$166.06	$151.16	3.7%	3.3%	9.3%
QUETIAPINE	$19,443,944	$18,366,877	107,637	103,168.00	$188.47	$178.03	$180.64	$170.64	2.2%	2.1%	5.6%
CELECOXIB	$16,821,692	$17,464,081	168,020	170,663.00	$98.57	$102.33	$100.12	$103.94	1.9%	2%	4.8%
ATORVASTATIN	$15,270,032	$16,010,018	194,713	200,222.00	$76.27	$79.96	$78.42	$82.22	1.7%	1.8%	4.4%
GABAPENTIN	$15,957,029	$15,948,741	141,533	140,847.00	$113.29	$113.23	$112.74	$112.69	1.8%	1.8%	4.6%
SERTRALINE	$16,387,680	$15,277,907	211,574	211,845.00	$77.36	$72.12	$77.46	$72.21	1.8%	1.7%	4.7%
OXYCODONE	$14,881,759	$14,572,561	75,732	66,454.00	$223.94	$219.29	$196.51	$192.42	1.7%	1.6%	4.3%
DIVALPROEX	$14,814,648	$14,452,672	152,918	150,057.00	$98.73	$96.31	$96.88	$94.51	1.7%	1.6%	4.2%
PAROXETINE	$15,354,716	$14,401,530	188,097	187,431.00	$81.92	$76.84	$81.63	$76.56	1.7%	1.6%	4.4%
VENLAFAXINE	$10,942,429	$10,303,100	111,957	110,486.00	$99.04	$93.25	$97.74	$92.03	1.2%	1.2%	3.1%
CLOPIDOGREL	$9,688,754	$10,123,942	91,882	93,006.00	$104.17	$108.85	$105.45	$110.18	1.1%	1.1%	2.8%
CITALOPRAM	$10,112,006	$9,759,493	150,707	149,671.00	$67.56	$65.21	$67.10	$64.76	1.1%	1.1%	2.9%
ROFECOXIB	$8,877,051	$9,239,405	112,597	114,077.00	$77.82	$80.99	$78.84	$82.06	1%	1%	2.5%
SIMVASTATIN	$8,879,071	$9,171,800	81,440	83,648.00	$106.15	$109.65	$109.03	$112.62	1%	1%	2.5%
AMLODIPINE	$8,444,549	$9,101,417	168,145	169,809.00	$49.73	$53.60	$50.22	$54.13	1%	1%	2.4%
FENTANYL PRODUCTS	$8,728,021	$8,692,258	41,282	33,337.00	$261.81	$260.74	$211.42	$210.56	1%	1%	2.5%
LANSOPRAZOLE	$9,556,665	$8,350,804	75,304	74,333.00	$128.57	$112.34	$126.91	$110.89	1.1%	0.9%	2.7%
SALMETEROL/ FLUTICASONE INH	$9,294,064	$8,102,003	73,834	74,445.00	$124.84	$108.83	$125.88	$109.73	1%	0.9%	2.7%
BUPROPION	$8,715,455	$8,057,786	102,933	103,097.00	$84.54	$78.16	$84.67	$78.28	1%	0.9%	2.5%
TOPIRAMATE	$8,527,763	$7,941,334	46,520	45,128.00	$188.97	$175.97	$183.31	$170.71	1%	0.9%	2.4%
MIRTAZAPINE	$7,375,881	$7,303,554	104,704	103,046.00	$71.58	$70.88	$70.45	$69.75	0.8%	0.8%	2.1%
AZITHROMYCIN	$8,260,794	$7,258,482	231,186	219,170.00	$37.69	$33.12	$35.73	$31.40	0.9%	0.8%	2.4%
EPOETIN ALFA	$7,291,166	$7,256,488	26,077	7,558.00	$964.72	$960.13	$279.60	$278.27	0.8%	0.8%	2.1%
TRAMADOL: WITHOUT APAP	$6,631,688	$7,090,629	148,951	128,802.00	$51.49	$55.05	$44.52	$47.60	0.8%	0.8%	1.9%
Totals:	$350,109,386	$339,878,221	3,193,127	3,113,702.00	$112.44	$109.16	$109.64	$106.44	39.4%	38%	100%