North Dakota Medicaid

Drug Utilization Review Board

Drug Class Review

Antidepressant Agents

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North Dakota Department of Human Services
Pharmacotherapy Review
Antidepressant Medications
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I. Overview

Drugs with clinically useful antidepressant effects include the tricyclic antidepressants (TCAs), tetracyclic antidepressants, trazodone, bupropion, serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin and norepinephrine reuptake inhibitor (SSNRI), nefazodone, selective serotonin reuptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). Antidepressants are used for treating patients with conditions in diagnostic categories classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM); these include depressive disorders-Major Depressive Disorder (MDD) and dysthymic disorder, generalized anxiety disorder (GAD), Obsessive Compulsive Disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder (SAD)[i].

In 1985, Bupropion was approved for the treatment of major depressive disorders. In 1987, the FDA approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline (1991), paroxetine (1992), citalopram (1999), fluvoxamine (2000), and escitalopram (2002). The SNRIs were first introduced to the market in 1993 with the approval of venlafaxine. Nefazodone was approved in 1994 and Mirtazapine was approved in 1996. Duloxetine, a SSNRI was approved for the treatment of MDD and diabetic peripheral neuropathic pain (DPNP) in 2004.

Since their introduction, the second-generation antidepressants have established a prominent role in the pharmaceutical market**. The top 15 therapeutic classes accounted for 64.31% of North Dakota Medicaid prescription sales in the first quarter of 2007 and the antidepressant class ranked third among this group.** Table 1 lists the medications that will be included in this review.

Table 1. Antidepressant Medications in this Review

Generic Name	Brand Name
Fluoxetine	Prozac®, Prozac weekly®, Sarafem®
Sertraline	Zoloft®
Paroxetine	Paxil®, Paxil CR®
Citalopram	Celexa®
Fluvoxamine	Luvox®
Escitalopram	Lexapro®
Duloxetine	Cymbalta®
Venlafaxine	Effexor®, Effexor XR®
Bupropion	Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Zyban®
Mirtazapine	Remeron®
Nefazodone	Serzone®

II. Current Treatment Guidelines

Clinical Guideline	Recommendation
American Psychiatric Association (APA): Practice guideline for the treatment of patients with **major depressive disorder**	**Acute** **First line:** SSRIs, desipramine, nortriptyline, bupropion,

(MDD)[ii]	venlafaxine. Selection is based first on the safety and tolerability of the agents for the individual patient, then on patient preference, clinical data, and cost. **Second line:** MAOIs, restricted to patients unresponsive to other options. **Continuation** Continue therapy to prevent relapse. **Maintenance** Continue therapy that was effective in the acute and continuation phases at the same dose. **Duration of treatment:** Adequate trial of therapy requires 4 to 6 weeks of treatment before judging efficacy.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **generalized anxiety disorder (GAD)**[iii]	**First line:** Antidepressants–SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or least-sedating TCAs. **Second line:** Buspirone **Adjunct therapies:** • Benzodiazepines: consider as first-line therapy agent in an acute anxiety reaction. Use as adjunct agent in acute exacerbations of GAD or sleep disturbances during the initiation of antidepressant therapy. Patient should be stabilized on antidepressant therapy for > 4 weeks before benzodiazepines are slowly tapered (over 4-8 weeks). • Hydroxyzine: consider use in acute anxiety states.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **panic disorder**[iv]	**Acute** **First line:** SSRIs, initiated at low dose. **Second line:** Concomitant use of a benzodiazepine for a limited period (< 8 weeks) may be considered to help initiate treatment with a SSRI. **Maintenance** Limited evidence suggests that once patient is in full remission, the therapeutic dose may be reduced slowly. **Second line (non-responders):** If patient fails to respond at the maximum tolerated dose of a SSRI, or if partial response was observed and the SSRI well tolerated, switch to another SSRI. If SSRI not tolerated, initiate trial with a benzodiazepine or tricyclic antidepressant (TCA). **Third line:** Monoamine oxidase inhibitor (MAOI) or valproate. **Duration of treatment:** 8 to 12 weeks of treatment is considered an

	adequate trial. If remission is maintained, consider stopping treatment after 12-24 months.
American Psychiatric Association (APA): Practice guideline for the treatment of **patients with acute stress disorder and posttraumatic stress disorder (PTSD)**[v]	**First line:** SSRIs. **Second line:** TCAs and MAOIs. Concomitant use of a benzodiazepine in reducing anxiety and improving sleep. **Third line:** Second generation antipsychotic medications (e.g., olanzapine, quetiapine, risperidone). Anticonvulsant medications (e.g., divalproex, carbamazepine, topiramate, lamotrigine), alpha-2-adrenergic agonists, and beta-adrenergic blockers may also be helpful in treating specific symptom **clusters in individual patients. Duration of treatment:** Adequate trial of therapy requires 3 months of treatment. If treatment is effective and remission maintained, duration of therapy may be extended to 12 months or longer.
The Expert Consensus Guideline Series: Treatment of **obsessive-compulsive disorder (OCD)**[vi]	**First line (mild OCD, or young patients):** Cognitive behavior therapy (CBT) alone if mild OCD **Second line (more severe):** CBT plus a serotonin receptor inhibitor, or a serotonin receptor inhibitor alone (guideline specifically lists clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline). Generally clomipramine is used after failure of 2-3 trials of the other selective-serotonin reuptake inhibitors. **Third line:** Venlafaxine, MAOIs, clonazepam **Duration of treatment:** It is recommended to wait 8-13 weeks before making changes to the medication regimen.
Consensus Statement from the International Consensus Group on Depression and Anxiety: **social anxiety disorder (SAD)**[vii]	**Pharmacological treatment recommendation:** SSRI. Most studies conducted with paroxetine. Dose should be initiated at 20 mg/day for 2-4 weeks and then titrated to obtain a response. **Duration of treatment:** Adequate trial of therapy requires 6 to 8 weeks of treatment. If treatment is effective and remission maintained, minimum duration of therapy is 12 months. Note: there is no clinical evidence that benzodiazepines, TCA, or β-blockers as a class are effective for treatment of social anxiety disorder**.**

III. Drugs, recommended doses, and FDA-approved (labeled) uses[viii]

Class	Generic Name	Trade Name	Dosage Forms	Labeled Uses
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine	Prozac®; Prozac Weekly®; Sarafem®	10, 20, 40mg caps; 10mg tabs; 4 mg/ml solution; 90 mg pellets (weekly)	MDD (adult/ped); OCD; premenstrual dysphoric disorder (PMDD); Panic disorder
	Sertraline	Zoloft®	25, 50, 100mg tabs; 20 mg/ml solution	MDD (adult); OCD; Panic disorder; SAD; GAD; PTSD; PMDD
	Paroxetine	Paxil®; Paxil CR®	10, 20, 30, 40 mg tabs; 2 mg/ml solution; 12.5, 25, 37.5 mg CR tabs	MDD (adult); OCD; Panic disorder; SAD; GAD; PTSD; PMDD
	Citalopram	Celexa®	10, 20, 40 mg tabs; 1, 2 mg/ml solution	MDD
	Fluvoxamine	Luvox®	25, 50, 100 mg tabs	OCD (peds ≥ 8 years of age/adults)
	Escitalopram	Lexapro®	10, 20 mg tabs ; 1 mg/ml	MDD; GAD
Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)	Duloxetine	Cymbalta®	20, 30, 60 mg caps	MDD; (DPNP)
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	Venlafaxine	Effexor®; Effexor XR®	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps	MDD; GAD; Panic disorder; SAD
Other second-generation antidepressants	Bupropion	Wellbutrin®; Wellbutrin SR®; Wellbutrin XL®; Zyban®	75, 100 mg tabs; 50, 100, 150, 200 mg SR tabs; 150, 300 mg XL tabs	MDD; Seasonal affective disorder
	Mirtazapine	Remeron®	15, 30, 45 mg tabs; 15, 30, 45 mg ODT	MDD
	Nefazodone	Serzone®	50, 100, 150, 200, 250 mg tabs	MDD

IV. Pharmacokinetic parameters related to drug-drug interactions[ix]

Drug	Protein Binding	Substrate of	Inhibits
Citalopram	80%	Major: CYP2C19; CYP3A4 Minor: CYP2D6	Weak: CYP1A2; CYP2B6; CYP2C19; CYP2D6
Escitalopram	56%	Major: CYP2C19; CYP3A4	CYP2D6
Fluoxetine	94.5%	Major: CYP2C8/9; CYP2D6 Minor: CYP1A2; CYP2B6; CYP2C19; CYP2E1; CYP3A4	Strong: CYP2D6 Moderate: CYP1A2 Weak: CYP2B6; CYP2C8/9; CYP3A4
Fluvoxamine	80%	Major: CYP1A2; CYP2D6	Strong: CYP1A2; CYP2C19 Weak: CYP2B6; CYP3A4; CYP2D6; CYP2C8/9
Paroxetine	95%	Major: CYP2D6	Strong: CYP2D6 Moderate: CYP2B6 Weak: CYP1A2; CYP2C19; CYP2C8/9; CYP3A4
Sertraline	98%	Major: CYP2C19; CYP2D6 Minor: CYP2B6; CYP3A4; CYP2C8/9	Moderate: CYP2C19; CYP2D6; CYP2B6; CYP3A4 Weak: CYP1A2; CYP2C8/9
Mirtazapine	85%	Major: CYP1A2; CYP2D6; CYP3A4 Minor: CYP2C8/9	Weak: CYP1A2; CYP3A4
Venlafaxine	27%	Major: CYP2D6; CYP3A4 Minor: CYP2C8/9; CYP2C19	Weak: CYP2B6; CYP2D6
Bupropion	84%	Major: CYP2C8/9 Minor: CYP1A2; CYP2A6; CYP2C8/9; CYP2D6; CYP2E1; CYP3A4	Weak: CYP2D6
Nefazodone	>99%	Major: CYP2D6; CYP3A4	Strong: CYP3A4 Weak: CYP1A2; CYP2B6; CYP2D6

V. Medication Drug Interactions[x]

SSRIs used in conjunction with another highly plasma protein-bound drug may affect the concentration of either the SSRI or the other drug and result in drug interactions. When administered with other serotonergic medications, SSRIs have the potential to cause serotonin syndrome, which results from over stimulation of the central and peripheral serotonin receptors and is characterized by nausea, vomiting, flushing, and diaphoresis. In more severe cases, hyperreflexia, myoclonus, muscular rigidity, hyperthermia and autonomic instability may occur. The following table lists significant drug interactions for the SSRIs.

Precipitant drug	Object Drug		SSRI Interactions
Barbiturates	SSRIs Paroxetine	↓	Phenobarbital decreased the AUC and half-life of paroxetine by 25% and 38% respectively.

Precipitant drug	Object Drug		SSRI Interactions
Cimetidine	SSRIs	↑	Cimetidine increased steady-state paroxetine concentrations by ~50%. Cimetidine increased sertraline AUC (50%), Cmax (24%), and half-life (26%). Citalopram and escitalopram AUC (43%) and Cmax (39%) also increased. Adjust paroxetine dosage as needed.
Cyproheptadine	SSRIs Fluoxetine Paroxetine	↓	The pharmacologic effects of SSRIs may be decreased or reversed.
Linezolid	SSRIs	↑	A serotonin syndrome has been reported to occur after coadministration of linezolid and paroxetine. It may be prudent to allow at least 2 weeks after stopping linezolid before giving an SSRI.
MAO inhibitors	SSRIs	↑	Serious, sometimes fatal, reactions have occurred in patients receiving SSRIs in combination with a MAOI or who have recently discontinued the SSRI and are then started on an MAOI.
Phenytoin	SSRIs Paroxetine	↓	Phenytoin reduced the AUC and half-life of paroxetine by 50% and 35% respectively. Also, paroxetine reduced the AUC of phenytoin by 12%, and sertraline, fluoxetine, and fluvoxamine may increase hydantoin levels.
SSRIs Fluoxetine Fluvoxamine Sertraline	Hydantoins	↑ ↓	
Smoking	SSRIs Fluvoxamine	↓	Smokers had a 25% increase in the metabolism of fluvoxamine.
L-tryptophan	SSRIs	↑	Concurrent use with fluoxetine or paroxetine may produce symptoms related to both central toxicity (eg, headache, sweating, dizziness, agitation, restlessness) and peripheral toxicity (eg, GI distress, nausea, vomiting). Concomitant use is not recommended. Tryptophan may enhance the serotonergic effects of fluvoxamine; use the combination with caution. Severe vomiting has been reported with the coadministration of fluvoxamine and tryptophan.
St. John's wort	SSRIs Paroxetine Sertraline	↑	Increased sedative-hypnotic effects may occur. Avoid concurrent use.

Precipitant Drug	Object Drug		SSRI Interactions
SSRIs	Alcohol	↔	Although potentiation of impairment of mental and motor skills caused by alcohol has not occurred, concurrent use is not recommended in patients.
SSRIs	Antidepressants, tricyclic	↑	Plasma TCA levels may be increased; use caution when coadministering. Monitor TCA levels; may need to reduce TCA dose.
SSRIs Fluoxetine Fluvoxamine Sertraline	Benzodiazepines	↑	Clearance of benzodiazepines metabolized by hepatic oxidation may be decreased; those metabolized by glucuronidation are unlikely to be affected. Coadministration of alprazolam and fluoxetine or fluvoxamine has resulted in increased alprazolam levels and decreased psychomotor performance. Halve the initial alprazolam dose, and titrate to the lowest effective dose. Avoid coadministration of fluvoxamine and diazepam.
SSRIs	Beta blockers	↑	Certain SSRIs may inhibit the metabolism of certain beta blockers. Concurrent use of citalopram or escitalopram and metoprolol produced an increase in metoprolol levels. Fluvoxamine administered with propranolol produced a 5-fold increase in propranolol Cmin. If propranolol or metoprolol is given with fluvoxamine, reduce the initial beta blocker dose.
SSRIs Fluoxetine Fluvoxamine	Buspirone	↓	Effects of buspirone may be decreased; plasma concentrations may be increased with fluvoxamine but clinical response may be decreased. Paradoxical worsening of OCD or serotonin syndrome has occurred.
SSRIs Fluoxetine Fluvoxamine	Carbamazepine	↑	Serum carbamazepine levels may be increased with fluoxetine or fluvoxamine, possibly resulting in toxicity. The clearance of citalopram and escitalopram may be increased. The therapeutic effect of sertraline may be decreased.
Carbamazepine	SSRIs Citalopram Escitalopram Sertraline	↓	
Citalopram, Fluoxetine, Fluvoxamine, Sertraline	Clozapine	↑	Elevated serum clozapine levels have occurred. Closely monitor patients on concomitant admin.

Precipitant Drug	Object Drug		SSRI Interactions
SSRIs Fluoxetine Fluvoxamine	Cyclosporine	↑	Elevated cyclosporine concentrations were reported in case reports during concomitant administration.
SSRIs Paroxetine	Digoxin	↓	Paroxetine decreased the AUC of digoxin by 15%. The coadministration of paroxetine and digoxin should be undertaken with caution.
SSRIs Fluvoxamine	Diltiazem	↑	Bradycardia has occurred with concurrent use.
SSRIs Fluoxetine Fluvoxamine	Haloperidol	↑	Serum concentrations of haloperidol may be increased. Closely monitor patients on concomitant therapy.
SSRIs Citalopram	Ketoconazole	↓	Coadministration decreased ketoconazole Cmax (21%) and AUC (10%).
SSRIs Citalopram Escitalopram Fluoxetine Fluvoxamine Sertraline	Lithium	↑ ↓	Lithium levels may be increased or decreased by fluoxetine with possible neurotoxicity and increased serotonergic effects. In healthy volunteers, sertraline did not affect lithium levels. It is recommended that plasma lithium levels be monitored following initiation of sertraline, fluoxetine, citalopram, and escitalopram with appropriate adjustments to lithium dose. Concurrent use may enhance serotonergic effects of SSRIs. Use caution when coadministering. Lithium may enhance the serotonergic effects of fluvoxamine. Use with caution in combination; seizures have been reported.
Lithium	SSRIs	↑	
SSRIs Fluvoxamine	Methadone	↑	Significantly increased methadone concentrations have occurred. One patient developed opioid intoxication; another had opioid withdrawal symptoms with fluvoxamine discontinuation.
SSRIs Fluvoxamine	Mexiletine	↑	Mexiletine serum levels may be elevated, increasing the risk of side effects.
SSRIs	NSAIDs	↑	The risk of GI adverse effects may be increased. If possible, avoid.
SSRIs Fluoxetine Fluvoxamine	Olanzapine	↑	Olanzapine plasma concentrations may be elevated. Observe the patient closely.

Precipitant Drug	Object Drug		SSRI Interactions
SSRIs Fluoxetine Fluvoxamine Paroxetine	Phenothiazines	↑	Plasma phenothiazine concentrations may be elevated, increasing the pharmacologic and adverse effects, including life-threatening cardiac arrhythmias. Thioridazine is contraindicated with fluvoxamine, fluoxetine, and paroxetine (see Contraindications).
SSRIs Fluvoxamine Sertraline	Pimozide	↑	Concurrent use of sertraline and pimozide 2 mg produced a mean increase in pimozide AUC and Cmax of » 40%, increasing the risk of life-threatening cardiac arrhythmias. Because of pimozide's narrow therapeutic index, administration with sertraline or fluvoxamine is contraindicated.
SSRIs Paroxetine	Procyclidine	↑	Paroxetine increased the AUC, Cmax, and Cmin of procyclidine by 35%, 37%, and 67%, respectively. Reduce procyclidine dose if anticholinergic effects occur.
SSRIs Fluoxetine	Propafenone	↑	Coadministration of fluoxetine and propafenone produced elevated propafenone plasma levels. Certain SSRIs may inhibit the metabolism (CYP2D6) of propafenone.
SSRIs Paroxetine	Risperidone	↑	Coadministration may increase risperidone concentrations, increasing the risk of side effects. Serotonin syndrome may occur.
SSRIs Fluoxetine	Ritonavir	↑	The AUC of ritonavir may be increased. Serotonin syndrome may occur.
SSRIs Fluvoxamine	Ropivacaine	↑	Ropivacaine plasma concentrations may be elevated; the pharmacologic effects may be prolonged, increasing the risk of toxicity.
SSRIs Fluvoxamine Sertraline	Sulfonylureas Glimepiride Tolbutamide	↑	Fluvoxamine and sertraline have been shown to decrease the clearance of tolbutamide. Fluvoxamine also has been shown to increase the peak plasma concentration of glimepiride.
SSRIs	Sumatriptan	↑	Weakness, hyperreflexia, and incoordination have occurred with coadministration. Observe patient closely.
SSRIs	Sympathomimetics	↑	Increased sensitivity to the effect of sympathomimetics and increased risk of serotonin syndr.

Precipitant Drug	Object Drug		SSRI Interactions
SSRIs Fluvoxamine	Tacrine	↑	Plasma tacrine concentrations may be elevated, increasing the pharmacologic and cholinergic adverse effects.
SSRIs Fluvoxamine Paroxetine	Theophylline	↑	Clearance of theophylline may be decreased by 3-fold when coadministered with fluvoxamine; reduce dosage. Elevated theophylline levels have occurred with paroxetine. It is recommended that theophylline levels be monitored when these drugs are concurrently administered.
SSRIs Fluoxetine Paroxetine	Trazodone	↑	Plasma trazodone levels may be elevated, resulting in increased pharmacologic and toxic effects. If coadministration cannot be avoided, start with a low dose of the SSRI or trazodone.
SSRIs	Warfarin	↑	A pharmacodynamic interaction of altered anticoagulant effects including increased bleeding diathesis with unaltered prothrombin time (PT) may occur with paroxetine or fluoxetine. Coadministration of sertraline and warfarin and citalopram and warfarin has resulted in an 8% and 5% increase in PT, respectively, and delayed PT normalization. Fluvoxamine increased warfarin plasma levels by 98%; PT was prolonged. Monitor PT. Use caution with coadministration and monitor patient.
SSRIs Sertraline	Zolpidem	↑	Coadministration of sertraline and zolpidem produced a shortened onset of action of zolpidem and an increased effect.

↑ = object drug increased. ↓ = object drug decreased. ↔ = undetermined effect.

Clinically Significant Drug Interactions: Mirtazapine, Venlafaxine

Interacting Drug	Mirtazapine	Venlafaxine
Alprazolam	Monitor	
Amiodarone	Monitor[b]	
Carbamazepine	Monitor[a]	
Cimetidine		Monitor[d]
Interacting Drug	**Mirtazapine**	**Venlafaxine**
Ciprofloxacin	Monitor[b]	
Diazepam	Monitor	No significant interaction
Erythromycin	Monitor[b]	

Haloperidol		Monitor[d]
Indinavir		Monitor[c]
Ketoconazole	Monitor[b]	
Lorazepam	Monitor	
MAOIs	Contraindicated	Contraindicated
Phenobarbital	Monitor[a]	
Phenytoin	Monitor[a]	
Risperidone		Monitor[d]
TCAs		Monitor[d]
Temazepam	Monitor	
Triazolam	Monitor	

Clinically Significant Drug Interactions: Bupropion, Nefazodone

Interacting Drug	Buproprion	Nefazodone
Alprazolam		Monitor[d]
Amantadine	Monitor	
Atenolool	Monitor	
Buspirone		Monitor
Carbamazepine	Monitor	Contraindicated
Cimetidine	Monitor[b]	No significant interaction
Cyclosporine		Monitor[d]
Digoxin		Monitor
Flecainide	Monitor	
Haloperidol	Monitor	Monitor[d]
HMG-CoA Red Inh.		Monitor[d]
Ketoconazole	Monitor	
Levodopa	Monitor	
Lithium		Monitor
Lorazepam		No significant interaction
MAOIs	Contraindicated	Contraindicated
Metoprolol	Monitor	
Phenobarbital	Monitor	
Phenytoin	Monitor	Monitor
Pimozide	`	Contraindicated
Propafenone	Monitor	
Propranolol	Monitor	Monitor[b]
Risperidone	Monitor	
Tacrolimus		Monitor[d]
TCAs	Monitor	Monitor
Theophylline	Monitor	Monitor
Thioridazine	Monitor	
Triazolam		Contraindicated

Clinically Significant Drug Interactions: Duloxetine

Affected Drug	Affected By	Mechanism	Reasons/Results
Duloxetine	Cimetidine, fluvoxamine, quinolones antimicrobials, and other CYP1A2 inhibitors	CYP1A2 inhibition	When duloxetine was co-administered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n=14) the AUC was increased over 5-fold,

			the Cmax was increased about 2.5 fold and duloxetine t1/2 was increased approximately 3-fold. Other CYP1A2 inhibitors could have similar results
	TCAs, antipsychotics, cimetidine, and other CYP2D6 inhibitors	CYP2D6 inhibition	Because CYP2D6 is involved in duloxetine metabolism, concomitant use of Duloxetine with potent inhibitors of CYP2D6 would be expected to, and does result in higher concentrations of duloxetine.
CYP2D6 Substrates	Duloxetine	CYP2D6 inhibition	Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and Cmax of drugs metabolized by CYP2D6. Therefore, co-administration of duloxetine with other drugs thar are extensively metabolized by this isoenzyme and that have a narrow therapeutic index should be approached with caution
Highly protein-bound drugs		Drug displacement	Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein-bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

VI. Black Box Warnings[xi]

The Food and Drug Administration (FDA) requires manufacturers to include a black-box warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents. In 2005, the FDA issued a public health advisory cautioning that adults being treated for depression should be watched closely for worsening of depression and for increased suicidal thinking or behavior. In 2007, the FDA notified healthcare professionals of an agency proposal that requires makers of all antidepressant medications update the existing black box warning to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

Paroxetine-The FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations. At the FDA's request, the manufacturer has changed paroxetine's pregnancy category from C to D and added new data and recommendations to the WARNINGS section of paroxetine's prescribing information.

VII. Outcomes Evidence

Study	Methods	Efficacy variables	Results
Fluoxetine 20mg/d versus 50mg/d versus paroxetine 20mg/d in depression[xii]	Randomized, double-blind, mult-center study N = 284 10-16 weeks	D-17 scores Improvement in insomnia (HAM-D sleep disturbance factor score)	Depression improvement was similar in all patients (p=0.365) Insomnia improvement was similar in all patients (p=0.868)
Paroxetine (10-40mg) versus sertraline (25-100mg) in generalized anxiety disorder[xiii]	Randomized, double-blind, parallel-group, flexible-dose study N = 53 8 weeks	HAM-A CGI-S (response and remission rates)	Both paroxetine and sertraline resulted in significant reduction in HAM-A scores from baseline (p<0.0001) but no significant group effect. HAM-A (paroxetine) = 57% +/- 28% HAM-A (sertraline) = 57% +/- 28% Response (paroxetine) = 68% Response (sertraline) = 61% Remission (paroxetine) = 40% Remission (sertraline) = 46%
Sertraline 50-150mg/d versus paroxetine 40-60mg/d in panic disorder[xiv]	Randomized, double-blind, parallel-group, multi-center study N=225 12 weeks	Clinician-rated PAS	No significant difference in the PAS scores between the two treatment groups across the agoraphobia and non-agoraphobia subtypes (p=0.487)
Sertraline versus paroxetine versus citalopram in depression, posttraumatic stress disorder or social anxiety disorder[xv]	Retrospective cohort study N-14933 Data gathered from 1/1/99-6/30/02	Persistence Switching Discontinuation	Overall, higher rates of switching and discontinuation and lower rates of persistence for paroxetine vs citalopram and sertraline. Paroxetine (23.79%) vs. sertraline (25.96%); p=0.0093 citalopram (26.56%); p=0.0022 Paroxetine (3.55%) vs sertraline (3.32%); p=0.5076 citalopram (2.78%); p=0.0359 Paroxetine (72.66%) vs sertraline (70.72%) ; p=0.0258 citalopram (70.66%); p= 0.0334
Bupropion sustained-release vs. sertraline[xvi]	Randomized, double-blind, parallel-group trial	HAM-D HAM-A CGI-I CGI-S scores	No between-group differences were observed on any of the scales (p>0.05). However, side effect profiles differed

	N=248 16 weeks		significantly; Orgasm dysfunction was more common in sertraline-treated patients ($p<0.001$). Nausea, diarrhea, somnolence, and sweating were also experienced more frequently ($p<0.05$) in sertraline-treated patients.
Bupropion sustained-release vs. paroxetine[xvii]	Randomized, double-blind, multicenter trial N=100 6 weeks	HAM-D HAM-A CGI-I and CGI-S scores	No statistically significant differences between the two groups ($p>0.05$). Somnolence and diarrhea were more common in paroxetine-treated patients ($p<0.05$).
Duloxetine vs. paroxetine vs. placebo[xviii]	Randomized, double-blind, placebo-controlled, and active comparator-controlled study N=353 8 weeks	HAM-D	Duloxetine 80 mg/d was more effective than placebo($p=0.002$). Duloxetine at 40 mg/d was also significantly more effective than placebo ($p=0.034$). Paroxetine was not more effective than placebo ($p=0.150$). Duloxetine 80 mg/d was more effective than placebo for most other measures, including overall pain severity, and was more effective than paroxetine on HAMD17 ($p=0.037$).
Mirtazapine vs. fluoxetine[xix]	Randomized, double-blind trial N=123 6 weeks	HAM-D	The mean HAM-D17 scores were no different at week 6 for the two groups; although at week 3 (the estimated treatment difference -3.4 in favor of mirtazapine; 95% CI -6.1,-0.76; $p=0.006$) and week 4 (the estimated treatment difference -3.8 in favor of mirtazapine: 95% CI -6.61,-1.02, $p=0.009$), statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6.
Mirtazapine vs. venlafaxine[xx]	Randomized, multicenter, double-blind trial N=157 8 weeks	HAM-D MADRS	A statistically significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points ($p \leq 0.03$). A statistically significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events ($p=0.037$).
Venlafaxine vs. fluoxetine vs. placebo[xxi]	Randomized, multicenter, double-blind, placebo-controlled trial N=308	HAM-D	On the HAM-D, overall differences among treatment groups at week 6 did not quite reach statistical significance ($p=0.051$), though the difference between the venlafaxine and placebo groups was statistically significant ($p=0.016$). The

	6 weeks		differences between fluoxetine and placebo (p=0.358) and between venlafaxine and fluoxetine (p=0.130) were not statistically significant. The difference on the HAM-D depressed mood item was statistically significant among treatment groups at week 6 (p<0.001); both active treatments were significantly more effective than placebo (venlafaxine, p<0.001; fluoxetine, p=0.024). The difference between the active treatments was not statistically significant (p=0.117).
Venlafaxine extended-release vs. fluoxetine vs. placebo[xxii]	Randomized, multicenter, double-blind, parallel-group, placebo-controlled trial N=301 8 weeks	HAM-D	The percentages of patients who achieved full remission of their depression (HAM D total score ≤7) at the end of treatment were 37%, 22% and 18% for the venlafaxine XR, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine XR and the other groups were statistically significant (p<0.05).
Venlafaxine extended-release 225 mg/day vs. escitalopram 20 mg/day[xxiii]	Randomized, double-blind N=100 venlafaxine extended-release N=98 escitalopram 8 weeks	MADRS	There were no significant differences in efficacy, remission rates or response rates between venlafaxine ER and escitalopram. More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0% vs. 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16% vs. 4.1%; p<.01).

VIII. Conclusions

Clinical studies support that antidepressants are of equivalent efficacy when administered in comparable doses. Choice of antidepressant is influenced by diagnosis, medical history, potential for drug-drug interactions and adverse events. Treatment failure with one antidepressant does not predict treatment failure to another drug class or antidepressant.

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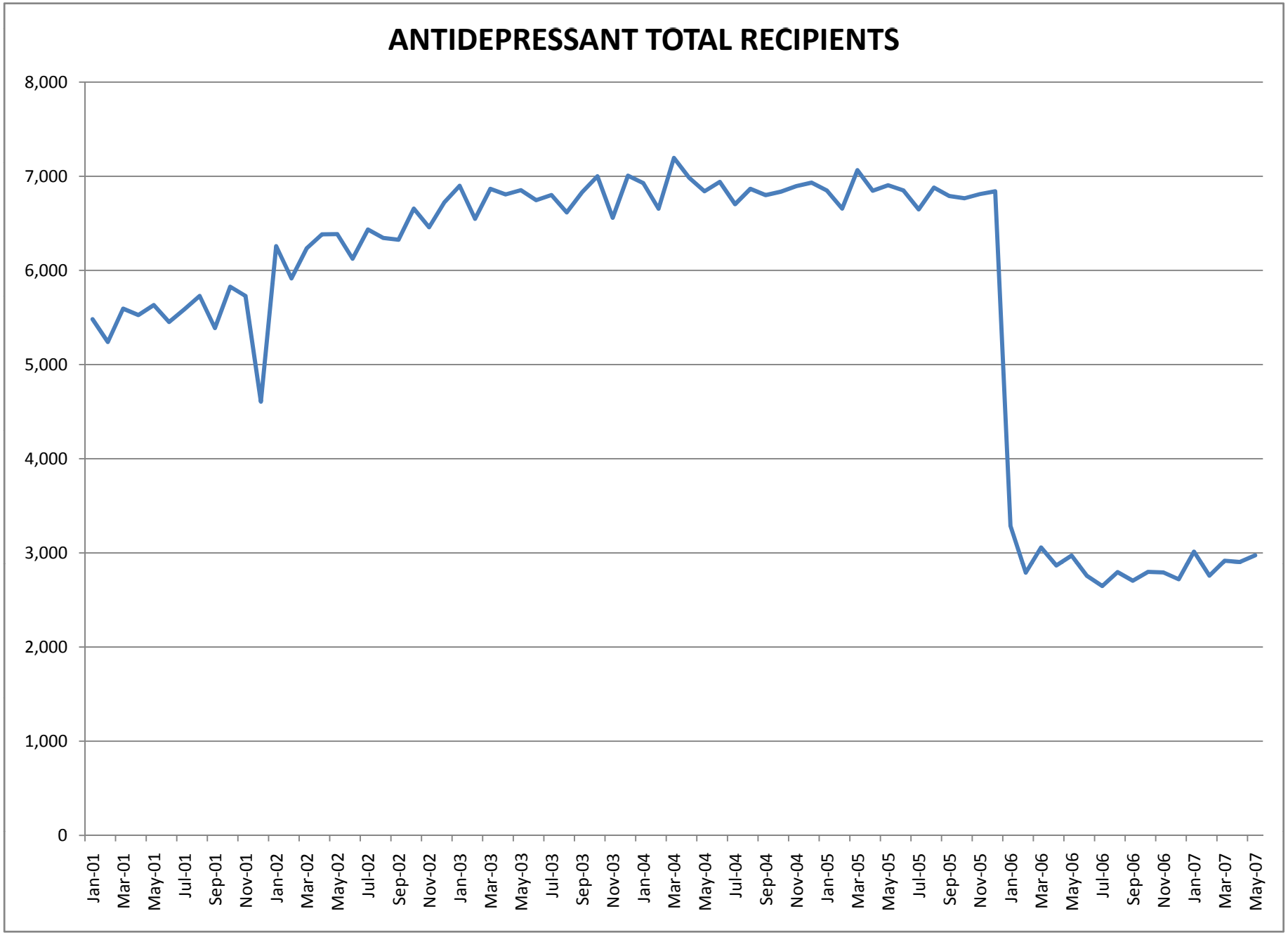
North Dakota Medicaid Statistics

Antidepressants

Drug Usage from 06/01/06 to 05/31/07		
Generic Name	**Rx Num**	**Total Reimb Amt**
BUPROPION HCL	6045	$579,151.36
VENLAFAXINE HCL	3835	$400,032.17
SERTRALINE HCL	6538	$388,569.93
DULOXETINE HCL	2830	$300,892.98
ESCITALOPRAM OXALATE	3865	$274,434.62
PAROXETINE HCL	3064	$159,475.59
FLUOXETINE HCL	5713	$100,147.73
MIRTAZAPINE	1971	$55,338.67
CITALOPRAM HYDROBROMIDE	1971	$30,122.08
FLUVOXAMINE MALEATE	238	$13,650.09
NEFAZODONE HCL	19	$471.26
TOTAL	36089	$2,302,286.48


ANTIDEPRESSANT TOTAL RECIPIENTS
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
Jan-01
Mar-01
May-01
Jul-01
Sep-01
Nov-01
Jan-02
Mar-02
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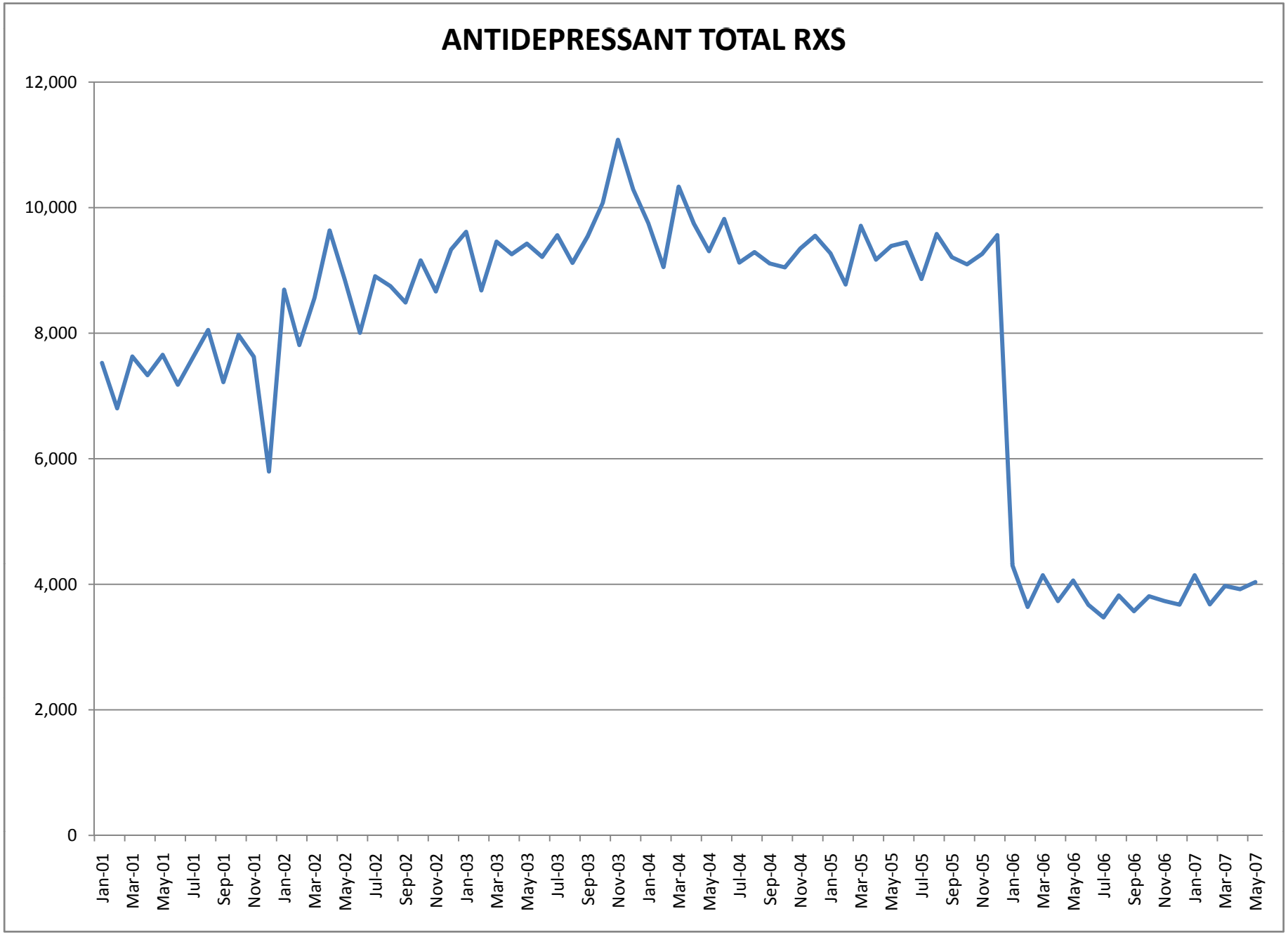
ANTIDEPRESSANT TOTAL RXS
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10,000
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4,000
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Nov-01
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Sep-02
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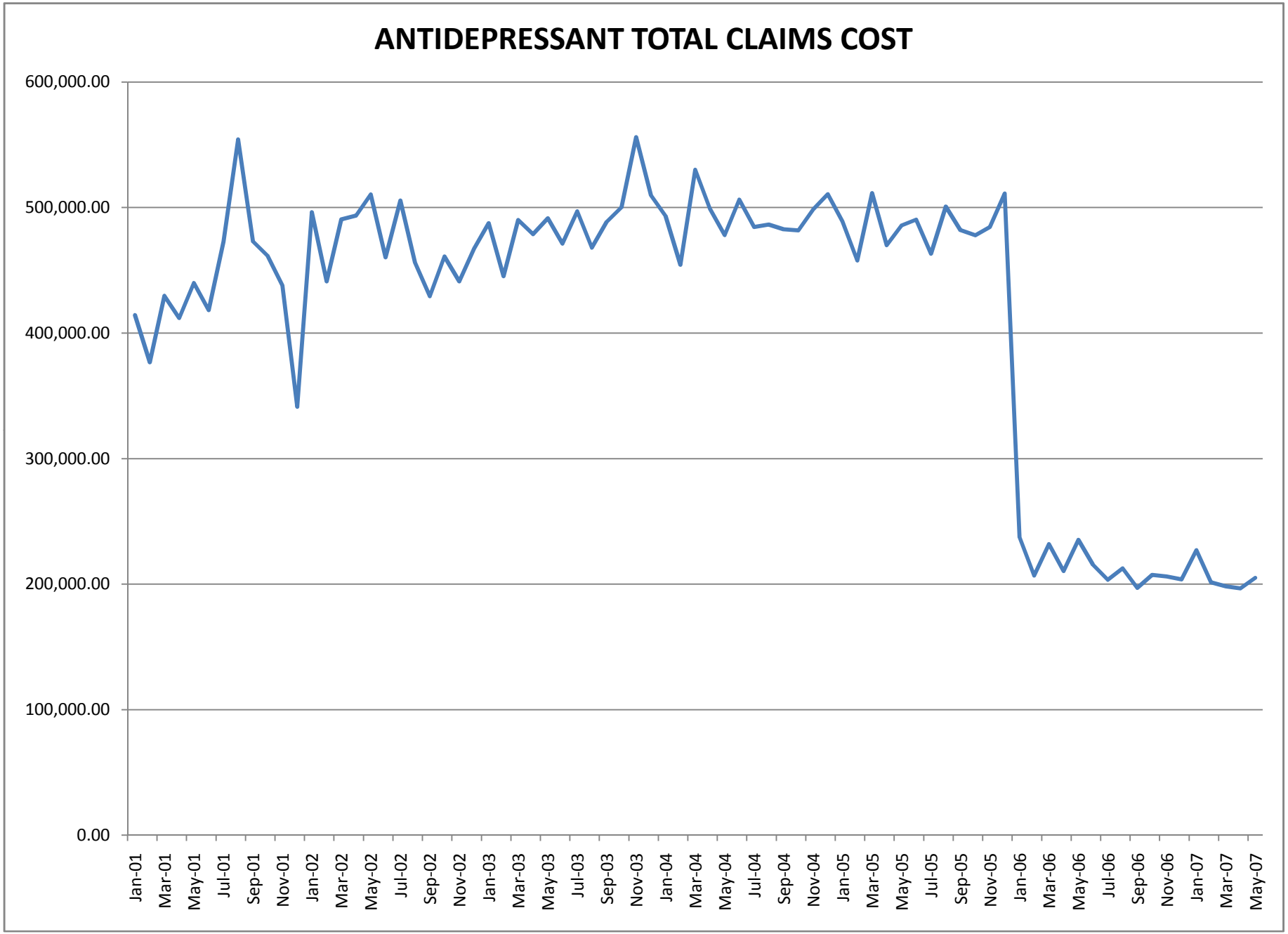
ANTIDEPRESSANT TOTAL CLAIMS COST
600,000.00
500,000.00
400,000.00
300,000.00
200,000.00
100,000.00
0.00
Jan-01
Mar-01
May-01
Jul-01
Sep-01
Nov-01
Jan-02
Mar-02
May-02
Jul-02
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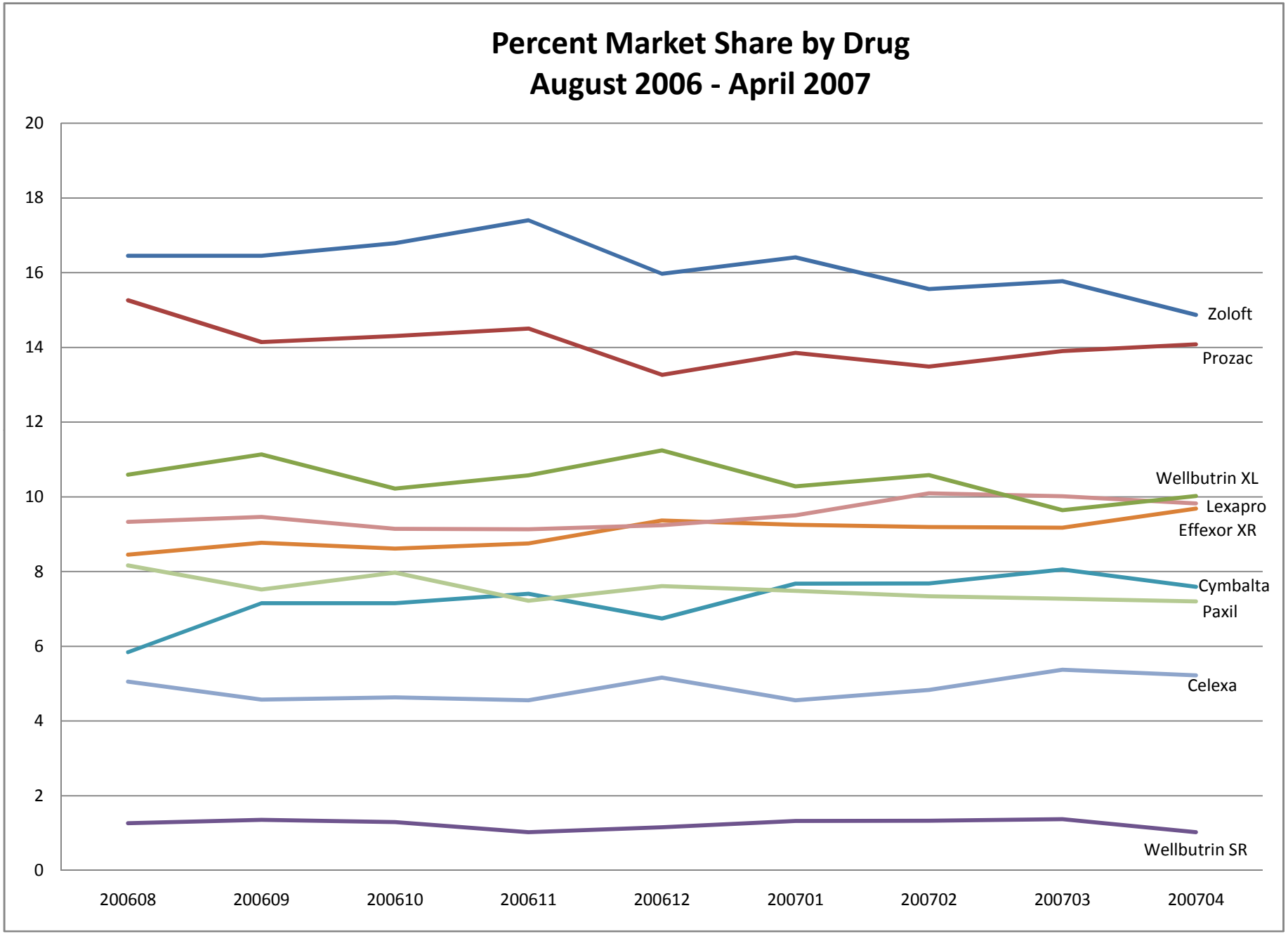
Mar-07
May-07

Health Information Designs, Inc.

North Dakota Medicaid
Market Share
June 2006-April 2007

AntiDepressants	200606	200607	200608	200609	200610	200611	200612	200701	200702	200703	200704
SERTRALINE HCL	0	0	4.19	14.73	15.79	16.65	15.46	16.01	15.29	15.57	14.73
FLUOXETINE HCL	13.96	13.76	14.7	13.57	13.71	13.93	12.99	13.34	13.15	13.5	13.66
TRAZODONE HCL	10.4	8.99	11	10.69	10.69	10.6	11.39	10.65	10.76	10.68	11.83
LEXAPRO	9.49	8.8	9.33	9.46	9.14	9.13	9.24	9.5	10.09	10.01	9.82
WELLBUTRIN XL	11.25	10.85	10.59	11.13	10.22	10.57	11.21	8.56	8.43	6.54	9.77
EFFEXOR XR	9.67	9.82	8.45	8.77	8.61	8.75	9.36	9.25	9.19	9.17	9.68
CYMBALTA	5.56	6.62	5.84	7.15	7.15	7.4	6.74	7.67	7.68	8.05	7.59
PAROXETINE HCL	5.75	6.78	6.31	5.92	6.33	5.72	6.22	6.4	5.98	5.9	5.93
CITALOPRAM HBR	4.2	4.54	4.87	4.48	4.39	4.37	4.95	4.44	4.56	5.09	5.11
MIRTAZAPINE	4.53	4.22	4.52	5.01	4.77	5	4.62	5.11	5.14	4.97	4.69
BUPROPION HCL	3.44	3.39	2.96	2.79	3.37	2.82	3.2	2.82	2.87	2.93	2.94
PAXIL CR	1.76	1.92	1.76	1.47	1.55	1.41	1.24	1	1.27	1.31	1.19
BUDEPRION SR	1.03	1.02	1.23	1.35	1.26	1.02	1.15	1.24	1.27	1.31	1.02
FLUVOXAMINE MALEATE	0.52	0.48	0.5	0.47	0.64	0.6	0.6	0.7	0.7	0.5	0.62
PROZAC WEEKLY	0.36	0.22	0.44	0.44	0.47	0.39	0.21	0.32	0.24	0.2	0.31
BUDEPRION XL	0	0	0	0	0	0	0.03	1.72	2.15	3.1	0.25
VENLAFAXINE HCL	0	0	0	0.19	0.21	0.3	0.27	0.24	0.24	0.22	0.23
ZOLOFT	17	17.5	12.26	1.72	1	0.75	0.51	0.4	0.27	0.2	0.14
PROZAC	0.18	0.19	0.12	0.13	0.12	0.18	0.06	0.19	0.09	0.2	0.11
CITALOPRAM	0.12	0.13	0.12	0.06	0.21	0.09	0.15	0.03	0.15	0.2	0.08
PAXIL	0.18	0.16	0.09	0.13	0.09	0.09	0.15	0.08	0.09	0.06	0.08
NEFAZODONE HCL	0.06	0.06	0.03	0.06	0.03	0.06	0.06	0.05	0.03	0.03	0.06
REMERON	0.03	0.03	0.03	0	0	0.03	0	0.05	0.06	0.03	0.06
TRAZODONE	0	0.03	0.06	0	0	0	0.03	0.03	0.03	0.11	0.06
CELEXA	0.06	0.1	0.06	0.03	0.03	0.09	0.06	0.08	0.12	0.08	0.03
EFFEXOR	0.36	0.32	0.47	0.25	0.21	0.06	0.09	0.03	0.09	0	0.03
DESYREL	0.03	0	0.06	0	0	0	0	0	0	0	0
WELLBUTRIN SR	0.06	0.03	0.03	0	0.03	0	0	0.08	0.06	0.06	0


Percent Market Share by Drug
August 2006 - April 2007
20
18
16
14
12
10
8
6
4
2
0
200608
200609
200610
200611
200612
200701
200702
200703
200704
Zoloft
Prozac
Wellbutrin XL
Lexapro
Effexor XR
Cymbalta
Paxil
Celexa
Wellbutrin SR

HEALTH INFORMATION DESIGNS

Antidepressant PA Form

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND Medicaid

ND Medicaid requires the use of one of the following products as first line antidepressant therapy: Bupropion, Citalopram, Fluoxetine, Paroxetine, Sertraline or Venlafaxine.

****Note:***

- **Cymbalta, Effexor XR, Lexapro, Paxil CR, Prozac Weekly, Wellbutrin SR, and Wellbutrin XL all require a Prior Authorization.**

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth: / /	
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone: ( )
City:	FAX: ( )
State: Zip:	

REQUESTED DRUG:	**Requested Dosage:** (must be completed)

Qualifications for coverage:

❑ First line antidepressant therapy tried: Start: Dose:
End: Frequency:

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Services
Antidepressant Authorization Algorithm