South Dakota Department of Social Services

Medicaid P&T Committee Meeting

June 11, 2010

DEPARTMENT OF SOCIAL SERVICES
MEDICAL SERVICES
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SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

Friday, June 11, 2010
1:00 – 3:00 PM

Sioux Falls
Sheraton Convention Center
Fontanelle Ballroom
1211 Northwest Avenue

Call to Order

Approval of Minutes of Previous Meeting

Prior Authorization Update

Review of Top 15 Therapeutic Categories/Top 25 Drugs

Old Business
- **Medications used to treat ADD/ADHD**

New Business
- **Drug Product and Utilization Review**
  - **Suboxone/Subutex**
  - **Review of Narcotics**
  - **Prior Authorization of High Cost/Low Utilization Drugs**
  - **Metozolv ODT®**

Oral Presentations and Comments by Manufacturers' Representatives

Next Meeting Date/Adjournment

Minutes of the March 12, 2010
Pharmacy & Therapeutics (P&T) Committee Meeting
SD Department of Social Services, Medical Services Division

Members present
Dana Darger, R.Ph.; Bill Ladwig, R.Ph.; Dennis Hedge, PharmD.; Rick Holm, M.D.; Debra Farver, PharmD.; Verdayne Brandenburg, M.D.; Timothy Soundy, M.D.

Members absent
Willis Sutliff, M.D.; James Engelbrecht, M.D.; Galen Goeden, R.Ph.

DSS staff present
Mike Jockheck, RPh; Larry Iversen, Director of Medical Services

HID staff present
Candace Rieth, Pharm.D.

Administrative Business
The P&T meeting was called to order by D. Darger at approximately 1:02pm. The minutes of the December 11, 2009 meeting were presented. D. Farver made a motion to approve. B. Ladwig seconded the motion. The motion was approved unanimously.

Prior Authorization Statistics
C. Rieth presented an overview of the prior authorization (PA) activity for December 2009. There were a total of 2,294 PAs processed in the month of December, with 99.78% of those requests responded to in less than 8 hours. There were 1,583 (89%) requests received electronically and 195 (11%) requests received by fax. In response to a request from the committee, C. Rieth presented the number of approvals and denials, by form type, for the faxed (manual) PA requests.

Analysis of the Top 15 Therapeutic Classes
C. Rieth reviewed the Top 15 Therapeutic Classes by total cost of claims from 10/01/2009 – 12/22/2009. The top five classes were antipsychotics, cerebral stimulants, amphetamines, beta-adrenergic agonists, and antidepressants. The top 15 therapeutic classes make up 42.90% of total claims.

Antipsychotic Review
C. Rieth reviewed antipsychotic utilization with the P&T committee. At the December meeting, a motion was made to implement a prior authorization on antipsychotics and a request was made that a form and criteria be developed for the committee to review at the next meeting. P. Arends, representing NAMI, spoke against implementation of a prior authorization on antipsychotics. M. Boarne, representing Merck, discussed prescribing information for Saphris. M. McGuire, representing BMS, discussed prescribing information for Abilify. J. Stoffel, representing OMJ, discussed prescribing information for Risperdal Consta and Invega Sustenna. S. Cleft, volunteer with NAMI, spoke about life experiences related to disorders that are treated with antipsychotics. C. Taylor, representing NAMI, spoke about life experiences related to disorders that are treated with antipsychotics. J. Brokars, representing Lilly, discussed prescribing information for Relprevv. Each committee member spoke and gave their credentials as well as the reason they each serve on the SD Medicaid P&T Committee.

Discussion ensued regarding the prior authorization of the antipsychotics. Committee members would prefer that psychiatrists were exempt from the prior authorization process, but there is currently an issue with programming that would prevent this from happening. Concerns were also raised about patients getting their

medications without a lapse in therapy because of the prior authorization. M. Jockheck informed committee members and the public that the current prior authorization system makes decisions within 8 hours, 99% of the time and within 24 hours, 100% of the time; therefore quick turnaround of the prior authorization should not be a problem. He also mentioned that the state allows for a 5 day emergency fill option that will address this concern. Committee members are also concerned about polypharmacy with the antipsychotics. The overall consensus was that polypharmacy is a separate issue that can be addressed at a later date or through the RDUR process. The committee requested that education, through the pharmacy association, providers, and mental health facilities, take place prior to implementation of the prior authorization. R. Holm made a motion to approve the prior authorization form with one amendment; include an additional check box that states 'currently being discharged from an inpatient mental health facility'. V. Brandenburg seconded the motion. The motion was approved unanimously.

Antidepressant Review

C. Rieth reviewed antidepressant utilization with the P&T committee. At the December meeting, a motion was made to implement a prior authorization on antidepressants and a request was made that a form and criteria be developed for the committee to review at the next meeting. The committee reviewed the proposal. P. Arends, representing NAMI, spoke against implementation of a prior authorization on antidepressants. S. Schneider, a practicing physician in South Dakota spoke against implementation of a prior authorization on antidepressants. J. Brokars, representing Lilly, discussed prescribing information for Cymbalta.

The committee discussed duloxetine and the ability of providers to use it for fibromyalgia and neuropathic pain. This problem will be resolved through the electronic PA process by building specific diagnosis codes into the system. B. Ladwig made a motion to approve the form with two changes. The first change states one failed trial for recipients under the age of 18 and two failed trials for those 18 and above. The second change states escitalopram will not require a prior authorization for recipients under the age of 18. R. Holm seconded the motion. The motion was approved unanimously.

The next meeting date is June 11, 2010. The location should remain the same. A motion was made by D. Farver at 3:30pm to adjourn the SD Medicaid P&T meeting. B. Ladwig seconded. Motion passed unanimously and the meeting was adjourned.

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2010 – April 30, 2010

Time Ratio

Total PAs	Response Under 8 Hours	Response Over 8 Hours	% Under 8 Hours	% Over 8 Hours
1,912	1,908	4	99.79%	0.21%

By Form Type

Form Type	Description	Approve	Deny
AFX	Amrix and Fexmid	1	15
ALT	Altabax	1	21
AMB	Ambien CR	8	22
ANF	Anti-Infectives	0	4
ANT	Antihistamines	64	113
ARB	ARBS	22	49
DAW	Dispense As Written	16	30
GRH	Growth Hormone	6	0
HLM	Head Lice Medication	15	34
MAX	Max Units Override	87	1,024
NUC	Nucynta	1	16
PPI	Proton Pump Inhibitors	74	177
STI	Stimulants	15	44
TIM	Targeted Immunomodulators	1	1
ULT	Ultram ER	6	30
VUS	Vusion	0	14
XEN	Xenical	1	0
Totals		318	1,594

By Request Type

04/01/10 - 04/30/10	# of	Electronic Requests		Faxed Requests	
	Requests	#	%	#	%
Amrix and Fexmid	16	13	81%	3	19%
Altabax	22	21	95%	1	5%
Ambien CR	30	26	87%	4	13%
Anti-infectives	4	4	100%	0	0%
Antihistamines	177	143	81%	34	19%
ARBS	71	63	89%	8	11%
Dispense As Written	46	23	50%	23	50%
Growth Hormone	6	0	0%	6	100%
Head Lice Medication	49	31	63%	18	37%
Max Units Override	1,111	1,030	93%	81	7%
Nucynta	17	13	76%	4	24%
Proton Pump Inhibitors	251	193	77%	58	23%
Stimulants	59	46	78%	13	22%

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2010 – April 30, 2010

04/01/10 - 04/30/10	# of Requests	Electronic Requests #	Electronic Requests %	Faxed Requests #	Faxed Requests %
Targeted Immunomodulators	2	1	50%	1	50%
Ultram ER	36	28	78%	8	22%
Vusion	14	13	93%	1	7%
Xenical	1	0	0%	1	100%
Prior Authorization Totals	1,912	1,648	86%	264	14%

Electronic PAs (unique)

04/01/10 - 04/30/10	# Unique Approved	# Unique Denied	# Unique Incomplete	Unique Total	Approval %	Total Transactions
Prior Authorizations:						
Amrix and Fexmid	0	13	0	13	0.00%	13
Altabax	0	21	0	21	0.00%	21
Ambien CR	6	20	0	26	23.10%	26
Anti-infectives	0	4	0	4	0.00%	4
Antihistamines	36	106	0	142	25.40%	143
ARBS	15	45	0	60	25.00%	63
Dispense As Written	0	23	0	23	0.00%	23
Head Lice Medication	0	31	0	31	0.00%	31
Max Units Override	32	968	0	1,000	3.20%	1,030
Nucynta	0	8	0	8	0.00%	13
Proton Pump Inhibitors	31	157	0	188	16.50%	193
Stimulants	9	34	0	43	20.90%	46
Targeted Immunomodulators	1	0	0	1	100.00%	1
Ultram ER	0	28	0	28	0.00%	28
Vusion	0	12	0	12	0.00%	13
Prior Authorization Totals:	130	1,470	0	1,600	8.10%	1,648

Manual PAs (unique)

04/01/10 - 04/30/10	# Requests	# Approved	% Approved	# Denied	% Denied
Prior Authorizations:					
Amrix and Fexmid	3	1	33%	2	67%
Altabax	1	1	100%	0	0%
Ambien CR	4	2	50%	2	50%
Antihistamines	34	28	82%	6	18%
ARBS	8	7	88%	1	13%
Dispense As Written	23	16	70%	7	30%
Growth Hormone	6	6	100%	0	0%
Head Lice Medication	18	15	83%	3	17%
Max Units Override	81	55	68%	26	32%
Nucynta	4	1	25%	3	75%

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2010 – April 30, 2010

04/01/10 - 04/30/10	# Requests	# Approved	% Approved	# Denied	% Denied
Proton Pump Inhibitors	58	43	74%	15	26%
Stimulants	13	6	46%	7	54%
Targeted Immunomodulators	1	0	0%	1	100%
Ultram ER	8	6	75%	2	25%
Vusion	1	0	0%	1	100%
Xenical	1	1	100%	0	0%
Prior Authorization Totals	264	188	71%	76	29%

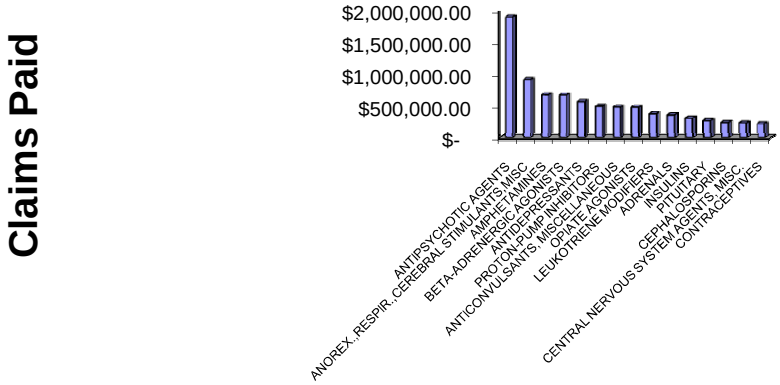
SOUTH DAKOTA MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 01/01/2010 - 03/31/2010

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	7,256	$ 1,897,293.29	$ 261.48	3.37%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,616	$ 913,647.96	$ 138.10	3.07%
AMPHETAMINES	4,859	$ 675,358.25	$ 138.99	2.25%
BETA-ADRENERGIC AGONISTS	11,077	$ 673,503.04	$ 60.80	5.14%
ANTIDEPRESSANTS	15,076	$ 565,819.68	$ 37.53	7.00%
PROTON-PUMP INHIBITORS	6,135	$ 495,281.39	$ 80.73	2.85%
ANTICONVULSANTS, MISCELLANEOUS	7,237	$ 483,513.86	$ 66.81	3.36%
OPIATE AGONISTS	13,932	$ 480,284.28	$ 34.47	6.46%
LEUKOTRIENE MODIFIERS	3,298	$ 376,577.53	$ 114.18	1.53%
ADRENALS	6,140	$ 357,573.32	$ 58.24	2.85%
INSULINS	1,865	$ 308,660.84	$ 165.50	0.87%
PITUITARY	617	$ 269,660.96	$ 437.05	0.29%
CEPHALOSPORINS	7,261	$ 241,070.30	$ 33.20	3.37%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,368	$ 232,539.68	$ 169.99	0.63%
CONTRACEPTIVES	3,599	$ 220,875.90	$ 61.37	1.67%
TOTAL TOP 15	96,336	$ 8,191,660.28	$ 85.03	44.70%

Total Rx Claims From 01/01/2010 - 03/31/2010	215,509

Top 15 Therapeutic Classes
Based on Total Cost of Claims

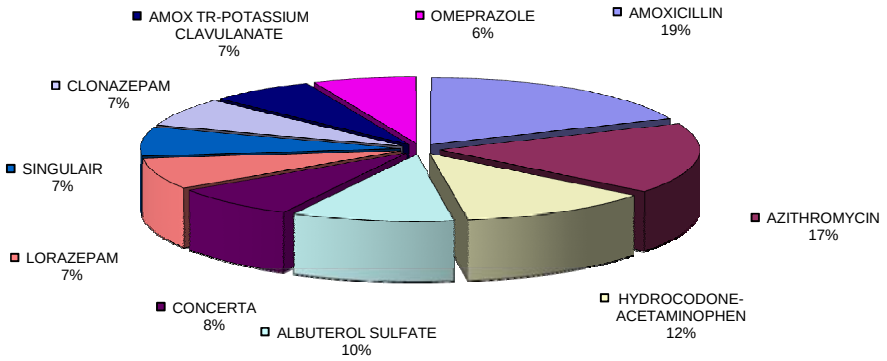


TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 01/01/2010 - 03/31/2010

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AMOXICILLIN	PENICILLINS	8,791	$ 89,846.83	$ 10.22	4.08%
AZITHROMYCIN	MACROLIDES	8,029	$ 165,826.45	$ 20.65	3.73%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	5,679	$ 60,900.80	$ 10.72	2.64%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	4,785	$ 90,920.57	$ 19.00	2.22%
CONCERTA	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,728	$ 551,252.85	$ 147.87	1.73%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	3,520	$ 30,699.04	$ 8.72	1.63%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,287	$ 375,380.73	$ 114.20	1.53%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,262	$ 28,849.75	$ 8.84	1.51%
AMOX TR-POTASSIUM CLAVULANA	PENICILLINS	3,066	$ 86,397.35	$ 28.18	1.42%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,048	$ 58,487.27	$ 19.19	1.41%
CEFDINIR	CEPHALOSPORINS	2,867	$ 137,920.29	$ 48.11	1.33%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,522	$ 21,647.18	$ 8.58	1.17%
SERTRALINE HCL	ANTIDEPRESSANTS	2,341	$ 21,019.71	$ 8.98	1.09%
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	2,257	$ 37,776.43	$ 16.74	1.05%
LEVOTHYROXINE SODIUM	THYROID AGENTS	2,159	$ 19,405.15	$ 8.99	1.00%
CEPHALEXIN	CEPHALOSPORINS	2,114	$ 26,349.86	$ 12.46	0.98%
SULFAMETHOXAZOLE-TRIMETHOP	SULFONAMIDES (SYSTEMIC)	2,113	$ 18,601.45	$ 8.80	0.98%
DEXTROAMPHETAMINE-AMPHETAI	AMPHETAMINES	1,974	$ 337,761.17	$ 171.10	0.92%
LORATADINE	SECOND GENERATION ANTIHISTAMINES	1,927	$ 15,160.91	$ 7.87	0.89%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,865	$ 53,665.85	$ 28.78	0.87%
TRAZODONE HCL	ANTIDEPRESSANTS	1,833	$ 12,778.27	$ 6.97	0.85%
TRAMADOL HCL	OPIATE AGONISTS	1,817	$ 23,849.82	$ 13.13	0.84%
LISINOPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITOR	1,762	$ 12,026.56	$ 6.83	0.82%
PREDNISOLONE SODIUM PHOSPH	ADRENALS	1,756	$ 17,969.39	$ 10.23	0.81%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	1,725	$ 12,793.46	$ 7.42	0.80%
TOTAL TOP 25		78,227	$ 2,307,287.14	$ 29.49	36.30%

Total Rx Claims From 01/01/2010 - 03/31/2010	215,509

Top 10 Drugs
Based on Number of Claims

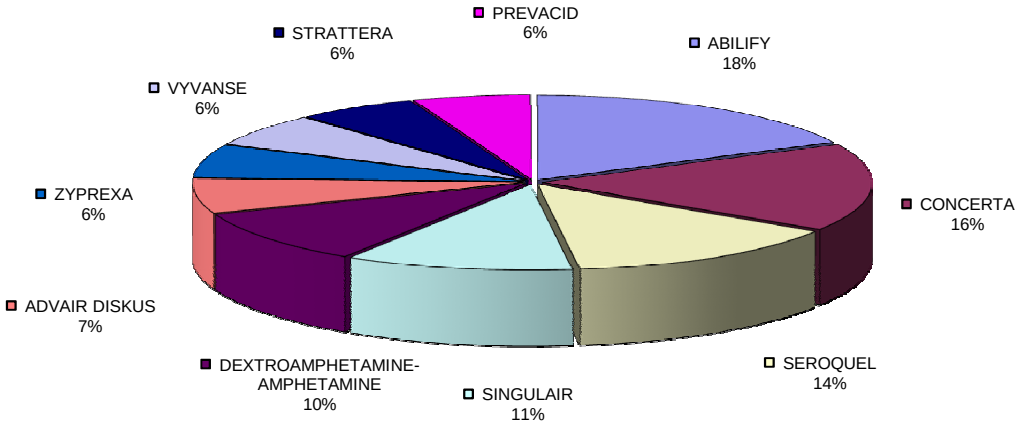


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 01/01/2010 - 03/31/2010

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ABILIFY	ANTIPSYCHOTIC AGENTS	1,498	$ 592,696.48	$ 395.66	0.70%
CONCERTA	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,728	$ 551,252.85	$ 147.87	1.73%
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,596	$ 462,072.18	$ 289.52	0.74%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,287	$ 375,380.73	$ 114.20	1.53%
DEXTROAMPHETAMINE-AMP	AMPHETAMINES	1,974	$ 337,761.17	$ 171.10	0.92%
ADVAIR DISKUS	BETA-ADRENERGIC AGONISTS	1,118	$ 217,826.43	$ 194.84	0.52%
ZYPREXA	ANTIPSYCHOTIC AGENTS	388	$ 210,761.41	$ 543.20	0.18%
VYVANSE	AMPHETAMINES	1,720	$ 210,428.10	$ 122.34	0.80%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,315	$ 197,768.77	$ 150.39	0.61%
PREVACID	PROTON-PUMP INHIBITORS	1,134	$ 193,837.12	$ 170.93	0.53%
FOCALIN XR	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,207	$ 172,599.55	$ 143.00	0.56%
AZITHROMYCIN	MACROLIDES	8,029	$ 165,826.45	$ 20.65	3.73%
OXYCONTIN	OPIATE AGONISTS	433	$ 158,617.60	$ 366.32	0.20%
XOPENEX	BETA-ADRENERGIC AGONISTS	1,140	$ 155,440.49	$ 136.35	0.53%
CYMBALTA	ANTIDEPRESSANTS	900	$ 138,187.91	$ 153.54	0.42%
CEFDINIR	CEPHALOSPORINS	2,867	$ 137,920.29	$ 48.11	1.33%
GEODON	ANTIPSYCHOTIC AGENTS	338	$ 136,676.53	$ 404.37	0.16%
SEROQUEL XR	ANTIPSYCHOTIC AGENTS	362	$ 122,821.10	$ 339.28	0.17%
NEXIUM	PROTON-PUMP INHIBITORS	558	$ 112,243.97	$ 201.15	0.26%
FLOVENT HFA	ADRENALS	938	$ 110,616.81	$ 117.93	0.44%
RISPERDAL CONSTA	ANTIPSYCHOTIC AGENTS	140	$ 109,329.00	$ 780.92	0.06%
LEXAPRO	ANTIDEPRESSANTS	1,166	$ 108,734.42	$ 93.25	0.54%
BUDESONIDE	ADRENALS	490	$ 102,327.23	$ 208.83	0.23%
PULMOZYME	ENZYMES	54	$ 101,535.76	$ 1,880.29	0.03%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	56	$ 101,319.69	$ 1,809.28	0.03%
TOTAL TOP 25		36,436	$ 5,283,982.04	$ 145.02	16.91%

Total Rx Claims From 01/01/2010 - 03/31/2010	215,509

Top 10 Drugs
Based on Total Claims Cost



South Dakota Department of Social Services
Pharmacotherapy Review
Medications for
Attention Deficit Hyperactivity Disorder (ADHD)
June 11, 2010

I. Overview

ADHD is a severe, debilitating condition affecting approximately 7.8% of school age children, based on a recent national survey. Other sources report prevalence as high as 12% in school-aged children with 60%-85% of children continuing to experience ADHD symptoms into their adolescent years and 30%-77% into their adult years. Children with ADHD are usually diagnosed between the ages of 6 to 12. Suboptimal academic performance is often the reason for initial screening. A diagnosis of ADHD is subjective in nature, with the provider looking for symptoms of inattention, hyperactivity, and impulsivity: symptoms that are frequent and severe enough to interfere with the child's, and often the family's, ability to lead a normal life. These children, left undiagnosed or untreated, are at higher risk of self-injury, depression, low self-esteem, delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.

Most medications for Attention Deficit Hyperactivity Disorder (ADHD) are CNS stimulants, which are thought to work by blocking reuptake of norepinephrine and dopamine in the presynaptic neurons and increasing release of these neurotransmitters into the extraneural space. There are two non-stimulant medications for ADHD, atomoxetine (Strattera®) and guanfacine (Intuniv®). Strattera is classified as a norepinephrine reuptake inhibitor and works by selectively inhibiting presynaptic norepinephrine transporters. Intuniv is classified as a selective $alpha_{2A}$-adrenergic receptor agonist that reduces sympathetic nerve impulses to the heart and blood vessels resulting in a decrease in peripheral vascular resistance and a reduction in heart rate.

Pharmacotherapy, along with behavior therapy and counseling, can help those patients diagnosed with ADHD lead a normal and productive life. For many years, CNS stimulants have been considered first-line therapy for the treatment of ADHD. With the approval of atomoxetine in late 2002, patients now have another treatment option.

II. Current Treatment Guidelines

American Academy of Child and Adolescent Psychiatry (AACAP)
Practice Parameter for the Use of Stimulant Medication in the Treatment of Children, Adolescents, and Adults (2007)

1) The first agent tried should have FDA approval for the treatment of ADHD; possible agents would be dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine.
2) Stimulants have been proven in many clinical trials to be highly effective in the treatment of ADHD.
3) The physician may choose either MPH or amphetamines, as data suggests equal efficacy between the two stimulant types.
4) Longer-acting formulations may be used as initial treatment and are associated with greater compliance. Physicians do not need to initiate treatment with the short-acting forms, or use them to titrate to the appropriate dosage of the long-acting forms. Short-acting forms may be used to initiate therapy in low-weight children where long-acting forms may not be available in the necessary smaller doses.
5) Once a medication is initiated, the dose should be titrated up every 1 to 3 weeks until the maximum dose for the stimulant is reached, the symptoms of ADHD remit, or side effects prevent further titration.

6) It is recommended that the patient be in contact with the physician during the titration period and visit the physician after 1 month of therapy to assess effectiveness and determine long-term therapy plans.
7) Patients may show an initial response rate of up to 85% when both stimulant forms are tried versus the response rate of only 65%-75% observed in clinical trials when patients were treated with only one stimulant. Therefore, if a patient fails one stimulant, it is recommended that another be tried.
8) For the treatment of preschoolers, the available evidence suggests that titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of methylphenidate (MPH) in preschoolers.
9) In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants.
10) Atomoxetine may be used as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants.

American Academy of Child and Adolescent Psychiatry (AACAP)
Clinical Practice Guideline: Treatment of the School-Aged Child with Attention-Deficit Hyperactivity Disorder (2001)

1) Identify target behavior symptom(s) and collect previous treatment data.
2) Develop a treatment plan that involves drug and/or behavioral therapy and involves parents, teachers, and caregivers. It is also important to recognize that ADHD is a chronic condition.
3) Define appropriate target outcomes, so that medication effectiveness can be clearly and systemically evaluated. It is important to define clear goals – control of symptoms at school, at home, or both – so that it can be determined whether or not a child needs long-acting, short-acting, or a combination of the two types of medication.
4) Medication selection:
    a. CNS stimulants are still considered to be first-line therapy as 70 to 80% of children respond favorably to this class.
    b. Response to one stimulant medication does not predict response to another.
    c. Children who fail two stimulant medications can be tried on a third stimulant medication.
    d. When the selected regimen has not met targeted outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions.
    e. If a child fails treatment with at least 3 stimulants, second-line treatments may be considered. These include tricyclic antidepressants, bupropion, and clonidine.

III. Drug Treatment for ADHD

Product	Dosage Forms	Dosing Frequency	Duration of Action
Immediate-release (IR) methylphenidate			
Ritalin (Novartis)	5, 10, 20 mg tabs	Adults: Given bid to tid preferably 30 to 45 minutes before meals. Children ≥ 6 yr: Given twice daily before breakfast and lunch.	3 to 4 h
Methylin Tabs (Mallinckrodt)	5, 10, 20 mg tabs	Adults: Given bid to tid preferably 30 to 45 minutes before meals. Children ≥ 6 yr: Given twice	3 to 4 h

Product	Dosage Forms	Dosing Frequency	Duration of Action
		daily before breakfast and lunch.	
Methylin Chewable Tabs(Mallinckrodt)	2.5, 5, 10 mg chewable tabs	Adults: Given bid to tid preferably 30 to 45 minutes before meals. Children ≥ 6 yr: Given twice daily before breakfast and lunch.	3 to 4 h
Methylin Oral Solution (Mallinckrodt)	5 mg/5 mL, 10 mg/5 mL oral solution	Adults: Given bid to tid preferably 30 to 45 minutes before meals. Children ≥ 6 yr: Given twice daily before breakfast and lunch.	3 to 4 h
Immediate-release (IR) dexmethylphenidate			
Focalin (Novartis)	2.5, 5, 10 mg tabs	Given bid at least 4 hr apart without regard to meals.	4 to 5 h
Extended-release (ER) dexmethylphenidate			
Focalin XR (Novartis)	5, 10, 15, 20 mg caps	Given once daily in the morning. May be taken whole or sprinkled over applesauce. If sprinkled over applesauce, should be used immediately and not be stored for future use. Capsule and/or capsule content should not be crushed.	up to 12 h
Extended-(ER)/Sustained release-(SR) methylphenidate			
Ritalin LA (Novartis) Bead-filled capsule (1/2 IR and 1/2 enteric coated, delayed release)	10, 20, 30, 40 mg LA caps	Given once daily in the morning. May be taken whole or sprinkled on applesauce. Applesauce should not be warm. If sprinkled over applesauce, should be used immediately and not stored for future use. Capsule and/or capsule content should not be crushed.	8 to 10 h
Ritalin SR (Novartis) Wax matrix tab	20 mg SR tabs	Given once daily to bid in dose corresponding to q8h dose IR. Must be swallowed whole.	6 to 8 h (Package insert says approx. 8 h)
Metadate ER (UCB)	10, 20 mg ER tabs	Given once daily to bid in dose corresponding to q8h dose IR. Must be swallowed whole.	6 to 8 h (Package insert says approx. 8 h)
Methylin ER (Mallinckrodt)	10, 20 mg ER tabs	Given once daily to bid in dose corresponding to q8h dose IR. Must be swallowed whole.	6 to 8 h (Package insert says approx. 8 h)
Concerta (McNeil Pediatrics) OROS (osmotic system has	18, 27, 36, 54 mg ER tabs	Given once daily in the morning without regard to meals. Must be	12 h

Product	Dosage Forms	Dosing Frequency	Duration of Action
hole for drug release) with IR over-coat.		swallowed whole.	
Metadate CD (UCB) Bead-filled capsule (30% IR and 70% ER)	10, 20, 30, 40, 50, 60 mg ER caps	Given once daily in the morning before breakfast. May be taken whole or sprinkled over applesauce. If sprinkled over applesauce, should be used immediately and not stored for future use. Capsule and/or capsule content should not be crushed.	8 to 9 h
Daytrana (Shire) Transdermal patch	1.1 mg/hr (10 mg/9 hr) 1.6 mg/hr (15 mg/9 hr) 2.2 mg/hr (20 mg/9 hr) 3.3 mg/hr (30 mg/9 hr)	Worn daily for 9 hours (apply 2 hrs before desired effect). Patch to be replaced once a day in the morning. Alternate application site daily.	12 h
Immediate-release (IR) dextroamphetamine and amphetamine salts mixture			
Adderall (Barr)	5, 7.5, 10, 12.5, 15, 20, 30 mg scored tabs	Given once daily or bid without regard to meals. First dose on awakening, additional doses at 4 to 6 h intervals.	4 to 6 h
Extended-release (ER) dextroamphetamine and amphetamine salts mixture			
Adderall XR (Shire)	5, 10, 15, 20, 25, 30 mg ER caps	Given once daily in the morning without regard to meals. May be taken whole or sprinkled on applesauce. Sprinkled applesauce should not be chewed or stored for later.	10 to 12 h
Sustained-release (SR) dextroamphetamine			
Dexedrine Spansule Cap filled with IR and SR beads (GlaxoSmithKline)	5, 10, 15 mg SR caps	Once daily or bid dose without regard to meals. Do not chew beads in cap.	6 to 10 h
Vyvanse (lisdexamfetamine) (Shire) Prodrug of dextroamphetamine.	20, 30, 40, 50, 60, 70 mg caps	Given once daily in the morning without regard to meals. May be taken whole or contents dissolved in glass of water. If solution prepared, it should be used immediately and not stored.	13 h
Nonstimulants			
Atomoxetine			
Strattera (Eli Lilly & Co.) • Response rate is lower compared to	10, 18, 25, 40, 60, 80, 100 mg caps	Given once daily or bid without regard to meals.	24 h

Product	Dosage Forms	Dosing Frequency	Duration of Action
methylphenidate. • Consider atomoxetine for patients with anxiety, insomnia, or substance abuse disorders.			
Guanfacine			
Intuniv (Shire) • May be an alternative or an add-on to stimulants for children who do not receive enough benefit from, or who are intolerant to, stimulants alone (e.g., tics, insomnia, etc). • There are no head-to-head trials comparing *Intuniv* to other ADHD medications. However, the improvements in mean ADHD-RS-IV scores were comparable to atomoxetine at lower doses and comparable to stimulants at higher doses (≥0.13 mg/kg).[37]	1, 2, 3, 4 mg extended-release tabs	Given once daily; avoid high-fat meals. Tablets should not be crushed or chewed or broken before swallowing. Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis due to different pharmacokinetic profiles. Start at 1 mg daily and titrate dose at no more than 1 mg/week increments. Keep dose within 1 mg to 4 mg/day depending on response and tolerability. Consider dosing on a mg/kg basis with starting doses of 0.05 mg/kg to 0.08 mg/kg once daily. Doses up to 0.12 mg/kg once daily may provide additional benefit. When discontinuing, taper the dose in decrements of no more than 1 mg every 3 to 7 days.	About 24 h

IV. ADHD Medication Drug Interactions

Clinically important drug interactions exist for the ADHD medications with certain, important differences among the classes. Each of the medications in this class should be used cautiously with antihypertensives (as stimulants, atomoxetine and guanfacine, may antagonize the effects of antihypertensive medications), tricyclic antidepressants, and MAO inhibitors (can result in hypertensive crisis).

Amphetamines

- GI acidifying agents (ascorbic acid, guanethidine, fruit juice) decrease absorption of amphetamines and urinary acidifiers (aluminum chloride) increase excretion of amphetamines.
- GI alkalinizers (sodium bicarb) increase absorption of amphetamines and urinary alkalinizers (acetazolamide) decrease excretion of amphetamines.
- Chlorpromazine/haloperidol block dopamine/norepinephrine receptors decreasing effects of amphetamines.
- Lithium carbonate inhibits stimulatory effects of amphetamines.
- Meperidine activity is potentiated by amphetamines.
- Co-administration of phenobarbital and phenytoin with amphetamines may lead to a synergistic anticonvulsant action.

Methylphenidate and Dexmethylphenidate

- May decrease metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, phenytoin, and primidone), and antidepressants (TCA's and SSRI's) resulting in the need for dosage adjustments.
- Serious adverse events have been noted with concomitant use of clonidine, although no causality has been established. This combination should be carefully monitored if use is deemed therapeutically necessary.

Atomoxetine

- Paroxetine, fluoxetine, and quinidine are all CYP2D6 inhibitors, dosing of atomoxetine may need to be adjusted when given with any of these medications.
- The effects of albuterol on heart rate and blood pressure may be potentiated by atomoxetine.
- MAOIs-coadministration is contraindicated.
- Pressor agents-administer with caution because of possible effects on blood pressure.
- CYP3A substrates-coadministration resulted in a 15% increase in midazolaum AUC.

Guanfacine

- CYP3A4/5 inhibitors (e.g., ketoconazole)-coadministration may increase rate and extent of guanfacine exposure.
- CYP3A4 inducers (e.g., rifampin)-coadministration may decrease rate and extent of guanfacine exposure.
- Valproic acid-coadministration may increase serum valproic acid concentrations.
- Antihypertensive drugs-use caution
- CNS depressants-use caution

V. Comparative Adverse Effects of ADHD Medications

Black Box Warning for Amphetamines

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events.

Black Box Warning for Methylphenidate and Dexmethylphenidate

ORAL

Methylphenidate and dexmethylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

TRANSDERMAL

Methylphenidate patch should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

In September 2005, the FDA issued an alert and the manufacturer of atomoxetine revised its labeling to include a black box warning about the risks of suicidal ideation. Patients started on atomoxetine should be monitored for suicidal thinking and behavior, clinical worsening of symptoms, and unusual changes in behavior. The risk of suicidal ideation in patients taking atomoxetine was 0.4% (5/1357

patients) versus none (0/851) in the placebo arm. Additionally, there have been postmarketing reports indicating that atomoxetine can cause severe liver damage in rare instances. In clinical trials with over 6,000 patients and postmarketing use in over 2 million patients, there have been rare cases of serious liver injury that were considered probably or possibly related to atomoxetine. Because of this information, atomoxetine should be discontinued and liver function testing should be performed at the first sign of liver injury (e.g., pruritus, jaundice, dark urine, right upper quadrant tenderness or unexplained flu-like symptoms).

On February 21, 2007, the FDA directed all manufacturers of products approved for the treatment of ADHD to develop Patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken. An FDA review of reports of serious cardiovascular adverse events in patients taking usual doses of ADHD products revealed reports of sudden death in patients with underlying serious heart problems or defects, and reports of stroke and heart attack in adults with certain risk factors. FDA recommends that children, adolescents, or adults who are being considered for treatment with ADHD drug products work with their physician or other health care professional to develop a treatment plan that includes a careful health history and evaluation of current status, particularly for cardiovascular and psychiatric problems (including assessment for a family history of such problems).

Rare reports of neuroleptic malignant syndrome (NMS) have occurred with dexmethylphenidate and methylphenidate. In most cases, patients were receiving therapies associated with NMS. It is not known whether this is a drug/drug interaction, a reaction to one drug alone, or due to some other cause. In regard to other adverse reactions, many similarities exist between the drugs used to treat ADHD. Tachycardia, increased blood pressure, anorexia, weight loss, and sleep pattern disturbances are of major concern, especially in this population of patients. Dry mouth, restlessness, visual disturbances and urticaria are also commonly seen. With the exception of atomoxetine, all medications carry the risk of lowering the seizure threshold, exacerbating tics, and Tourettes syndrome. One consideration to note, it has been clearly demonstrated that patients who do not respond well to one stimulant medication may respond to another. However, there have been reports of psychiatric adverse effects such as exacerbation of pre-existing psychosis, induction of mixed/manic episodes, hallucinations, delusions, paranoia, and aggression that could be cause for concern.

One final consideration is that CNS stimulants have reported suppression of growth (weight gain and/or height) with long-term use. Although it appears that this a temporary delay and that the patients will normalize in late adolescence, children should be monitored for height and weight changes while taking a CNS stimulant.

VI. Conclusion

Medication treatment for ADHD has increased dramatically over the past 10 years with stimulants becoming the most prescribed psychotropic drug for children. Scientific evidence shows that stimulants are an effective short-term treatment for ADHD, with medication resulting in better symptomatic relief than treatment with behavioral therapy, alone. However, the evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely lacking in measuring functional or long-term outcomes. More rigorous studies are needed to establish the comparative effectiveness of medications used to treat ADHD

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SD Medicaid
Utilization of Medications Used for ADD/ADHD
12/23/2008 - 12/22/2009

Label Name	Rx Num	Total Reimb Amt	Cost per Script
ADDERALL 10 MG TABLET	3	$50.70	$16.90
ADDERALL 20 MG TABLET	15	$4,712.81	$314.19
ADDERALL XR 10 MG CAPSULE	768	$139,255.53	$181.32
ADDERALL XR 15 MG CAPSULE	566	$106,276.88	$187.77
ADDERALL XR 20 MG CAPSULE	1579	$350,247.16	$221.82
ADDERALL XR 25 MG CAPSULE	505	$100,657.77	$199.32
ADDERALL XR 30 MG CAPSULE	1077	$207,551.79	$192.71
ADDERALL XR 5 MG CAPSULE	335	$62,112.46	$185.41
AMPHETAMINE SALTS 10 MG TAB	645	$9,789.71	$15.18
AMPHETAMINE SALTS 12.5 MG TB	18	$1,189.94	$66.11
AMPHETAMINE SALTS 15 MG TAB	82	$2,541.03	$30.99
AMPHETAMINE SALTS 20 MG TABLET	372	$7,607.66	$20.45
AMPHETAMINE SALTS 30 MG TAB	211	$4,071.41	$19.30
AMPHETAMINE SALTS 5 MG TAB	502	$7,087.49	$14.12
CONCERTA 18 MG TABLET SA	2090	$259,942.13	$124.37
CONCERTA 27 MG TABLET SA	2132	$287,442.62	$134.82
CONCERTA 36 MG TABLET SA	5608	$939,178.87	$167.47
CONCERTA 54 MG TABLET SA	3840	$558,426.20	$145.42
D-AMPHETAMINE ER 10 MG CAPSULE	182	$12,829.27	$70.49
D-AMPHETAMINE ER 15 MG CAPSULE	145	$14,640.12	$100.97
D-AMPHETAMINE ER 5 MG CAPSULE	73	$3,315.89	$45.42
DAYTRANA 10 MG/9 HR PATCH	173	$27,967.81	$161.66
DAYTRANA 15 MG/9 HR PATCH	196	$30,616.65	$156.21
DAYTRANA 20 MG/9 HOUR PATCH	196	$31,360.95	$160.00
DAYTRANA 30 MG/9 HOUR PATCH	263	$42,112.98	$160.13
DESOXYN 5 MG TABLET	18	$18,154.08	$1,008.56
DEXEDRINE SPANSULE 10 MG	6	$467.49	$77.92
DEXEDRINE SPANSULE 15 MG	8	$782.37	$97.80
DEXEDRINE SPANSULE 5 MG	1	$202.89	$202.89
DEXMETHYLPHENIDATE 10 MG TAB	102	$4,478.77	$43.91
DEXMETHYLPHENIDATE 2.5 MG TAB	67	$1,293.63	$19.31
DEXMETHYLPHENIDATE 5 MG TAB	117	$3,539.69	$30.25
DEXTROAMPHETAMINE 10 MG TAB	158	$3,618.57	$22.90
DEXTROAMPHETAMINE 5 MG TAB	54	$1,354.56	$25.08
DEXTROSTAT 5 MG TABLET	2	$11.57	$5.79
FOCALIN 10 MG TABLET	113	$5,919.46	$52.38
FOCALIN 2.5 MG TABLET	16	$463.64	$28.98
FOCALIN 5 MG TABLET	183	$7,138.54	$39.01
FOCALIN XR 10 MG CAPSULE	1402	$186,886.21	$133.30
FOCALIN XR 15 MG CAPSULE	887	$130,081.08	$146.65
FOCALIN XR 20 MG CAPSULE	1480	$229,370.35	$154.98
FOCALIN XR 5 MG CAPSULE	613	$92,608.36	$151.07

SD Medicaid
Utilization of Medications Used for ADD/ADHD
12/23/2008 - 12/22/2009

Label Name	Rx Num	Total Reimb Amt	Cost per Script
METADATE CD 10 MG CAPSULE	109	$14,551.19	$133.50
METADATE CD 20 MG CAPSULE	289	$34,530.36	$119.48
METADATE CD 30 MG CAPSULE	111	$14,124.52	$127.25
METADATE CD 40 MG CAPSULE	79	$11,814.22	$149.55
METADATE CD 50 MG CAPSULE	12	$2,437.53	$203.13
METADATE CD 60 MG CAPSULE	24	$4,873.14	$203.05
METADATE ER 20 MG TABLET	1	$12.13	$12.13
METHYLIN 10 MG CHEWABLE TABLET	15	$2,807.64	$187.18
METHYLIN 10 MG TABLET	583	$7,910.71	$13.57
METHYLIN 10 MG/5 ML SOLUTION	42	$9,701.22	$230.98
METHYLIN 2.5 MG CHEWABLE TAB	38	$4,458.52	$117.33
METHYLIN 20 MG TABLET	222	$4,837.11	$21.79
METHYLIN 5 MG CHEWABLE TABLET	38	$4,100.08	$107.90
METHYLIN 5 MG TABLET	587	$5,775.52	$9.84
METHYLIN 5 MG/5 ML SOLUTION	35	$4,706.34	$134.47
METHYLIN ER 10 MG TABLET	69	$1,987.45	$28.80
METHYLIN ER 20 MG TABLET	139	$2,193.68	$15.78
METHYLPHENIDATE 10 MG TABLET	311	$3,840.15	$12.35
METHYLPHENIDATE 20 MG TABLET	97	$2,098.31	$21.63
METHYLPHENIDATE 5 MG TABLET	245	$2,327.86	$9.50
METHYLPHENIDATE ER 20 MG TAB	127	$1,876.85	$14.78
PROVIGIL 100 MG TABLET	93	$27,581.68	$296.58
PROVIGIL 200 MG TABLET	531	$206,123.30	$388.18
RITALIN 20 MG TABLET	12	$1,564.76	$130.40
RITALIN LA 10 MG CAPSULE	110	$15,190.11	$138.09
RITALIN LA 20 MG CAPSULE	303	$40,046.35	$132.17
RITALIN LA 30 MG CAPSULE	289	$37,567.63	$129.99
RITALIN LA 40 MG CAPSULE	172	$24,162.21	$140.48
STRATTERA 10 MG CAPSULE	368	$63,931.86	$173.73
STRATTERA 100 MG CAPSULE	108	$18,447.39	$170.81
STRATTERA 18 MG CAPSULE	495	$75,437.83	$152.40
STRATTERA 25 MG CAPSULE	1208	$172,019.25	$142.40
STRATTERA 40 MG CAPSULE	1433	$221,745.00	$154.74
STRATTERA 60 MG CAPSULE	1022	$151,276.05	$148.02
STRATTERA 80 MG CAPSULE	498	$80,045.30	$160.73
VYVANSE 20 MG CAPSULE	540	$71,875.20	$133.10
VYVANSE 30 MG CAPSULE	1415	$185,901.72	$131.38
VYVANSE 40 MG CAPSULE	651	$86,038.08	$132.16
VYVANSE 50 MG CAPSULE	1344	$179,527.00	$133.58
VYVANSE 60 MG CAPSULE	501	$65,540.91	$130.82
VYVANSE 70 MG CAPSULE	1069	$139,261.89	$130.27
Totals	**42,138**	**$5,901,605.14**	**5,538 recipients**

Medications Used to Treat ADD/ADHD
Summary by Age

Age	Recip Count	Rx Count	Total Dollars
3	11	47	$2,369.75
4	41	215	$22,851.48
5	106	648	$73,147.86
6	227	1612	$192,923.87
7	335	2547	$340,733.46
8	404	3318	$417,517.82
9	460	3976	$520,721.10
10	477	3970	$517,521.48
11	434	3666	$501,541.63
12	411	3640	$519,081.67
13	395	3050	$432,672.35
14	401	3200	$489,700.61
15	358	2613	$376,216.83
16	313	2068	$314,417.93
17	295	2051	$311,501.76
18	195	1195	$187,178.32
19	114	529	$82,595.34
20	57	324	$46,659.60
21	41	293	$51,338.28
22	14	81	$10,438.25
23	23	147	$19,195.55
24	23	155	$30,486.96
25	26	196	$23,076.03
26	20	79	$12,467.84
27	34	173	$24,706.04
28	26	152	$19,870.97
29	18	124	$24,169.91
30	16	69	$8,126.78
31	17	153	$11,579.06
32	19	114	$18,473.79
33	9	52	$5,852.71
34	19	141	$14,022.94
35	17	112	$22,390.43
36	17	122	$15,334.99
37	14	59	$8,612.82
38	10	85	$22,950.78
39	14	94	$10,980.76
40	10	64	$18,360.51
41	7	56	$5,633.90
42	12	70	$10,266.36
43	4	43	$2,313.56
44	10	105	$20,799.11
45	7	33	$6,368.58
46	12	102	$27,894.03
47	4	28	$2,317.29
48	8	34	$4,078.14

Age	Recip Count	Rx Count	Total Dollars
49	6	43	$10,030.71
50	6	52	$13,580.15
51	4	43	$4,267.62
52	5	36	$937.78
53	2	18	$1,135.18
54	2	7	$955.81
55	2	19	$6,535.43
56	7	81	$29,597.03
57	6	96	$12,544.97
58	4	31	$9,549.79
59	1	8	$1,928.40
60	2	13	$465.91
61	2	33	$541.79
62	2	38	$607.90
64	2	17	$7,499.66

Consecutive Duplication for Medications used to treat ADD/ADHD
12/23/2008 - 12/22/2009
Overlap of 90 days

Unique Recipients = 47, Unique Providers = 72	Occurences
ADDERALL XR , AMPHETAMINE SALT COMBO , CONCERTA , METHYLPHENIDATE HCL	4
ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE SULFATE	7
ADDERALL XR , AMPHETAMINE SALT COMBO , STRATTERA	3
ADDERALL XR , AMPHETAMINE SALT COMBO , STRATTERA	2
ADDERALL XR , AMPHETAMINE SALT COMBO , STRATTERA , VYVANSE	2
ADDERALL XR , CONCERTA , STRATTERA	3
ADDERALL XR , FOCALIN XR , STRATTERA	2
AMPHETAMINE SALT COMBO , CONCERTA , FOCALIN XR , STRATTERA	4
AMPHETAMINE SALT COMBO , METHYLIN , VYVANSE	5
AMPHETAMINE SALT COMBO , METHYLPHENIDATE HCL , VYVANSE	1
CONCERTA , DEXTROAMPHETAMINE SULFATE , STRATTERA , VYVANSE	1
CONCERTA , FOCALIN , FOCALIN XR , METHYLIN	2
CONCERTA , FOCALIN , METHYLIN	1
CONCERTA , FOCALIN XR , METHYLPHENIDATE HCL	1
CONCERTA , METHYLIN , METHYLPHENIDATE HCL	2
CONCERTA , METHYLIN , METHYLPHENIDATE HCL	1
CONCERTA , METHYLIN , STRATTERA	2
CONCERTA , METHYLIN , STRATTERA	4
CONCERTA , METHYLIN , STRATTERA	4
CONCERTA , METHYLIN , STRATTERA	1
CONCERTA , METHYLIN , STRATTERA	1
CONCERTA , METHYLIN , STRATTERA	1
CONCERTA , METHYLIN , STRATTERA	1
CONCERTA , METHYLPHENIDATE HCL , STRATTERA	2
DAYTRANA , FOCALIN XR , STRATTERA , VYVANSE	1
DAYTRANA , METADATE CD , METHYLIN	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	1
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	3
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	4
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR	4
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR , STRATTERA	2
DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR , STRATTERA	1
DEXMETHYLPHENIDATE HCL , FOCALIN , RITALIN LA	1
DEXMETHYLPHENIDATE HCL , FOCALIN XR , STRATTERA	1
DEXMETHYLPHENIDATE HCL , FOCALIN XR , STRATTERA	2
DEXTROAMPHETAMINE SULFATE , STRATTERA , VYVANSE	2
FOCALIN , FOCALIN XR , STRATTERA	2
METADATE CD , METHYLIN , METHYLPHENIDATE HCL	2
METADATE CD , METHYLIN , METHYLPHENIDATE HCL	1
METHYLIN , METHYLIN ER , METHYLPHENIDATE SR	2
METHYLIN , METHYLIN ER , METHYLPHENIDATE SR , STRATTERA	2
METHYLIN , METHYLPHENIDATE HCL , RITALIN LA	2
METHYLIN , METHYLPHENIDATE HCL , RITALIN LA	4

South Dakota Department of Social Services
Pharmacotherapy Review
Suboxone® and Subutex® Review

I. Overview

Suboxone and Subutex are both schedule III narcotic medications currently approved for the treatment of opioid dependence under the federal Drug Addiction Treatment Act of 2000 (DATA) . Both contain buprenorphine, an opioid agonist-antagonist that produces the same opioid agonist effects as other opioids but produces less psychomimetic effects (e.g., delusions, euphoria, hallucinations, etc.), and less withdrawal symptoms in opioid-dependent patients. Suboxone also contains naloxone, an agent that is included to discourage the diversion and misuse of the buprenorphine component. When taken orally, naloxone has limited bioavailability; when crushed and injected, it will precipitate opioid withdrawal symptoms. Therefore, Suboxone is the preferred agent when being used in an outpatient setting; Subutex should only be administered in a supervised setting, due to the absence of naloxone.

II. Pharmacology

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

III. Pharmacokinetics

Pharmacokinetic parameters of buprenorphine after the administration of 4mg, 8mg, and 16mg Suboxone doses and 16mg Subutex dose				
Parameter	**Suboxone 4mg**	**Suboxone 8mg**	**Suboxone 16mg**	**Subutex 16mg**
C_{max} ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC (hour.ng/mL)	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

IV. Warnings/Precautions

Respiratory Depression – significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with Subutex or Suboxone.

CNS Depression – Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered.

Dependence – Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

Hepatitis, hepatic events – Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. A measurement of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended.

Allergic Reactions – Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported.

Use in Ambulatory Patients – Suboxone and Subutex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery

Head Injury and Increased Intracranial Pressure – Suboxone and Subutex, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased.

Opioid Withdrawal effects – Suboxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, Suboxone may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

V. Drug Interactions

CYP3A4 Inhibitors – subjects receiving Subutex and Suboxone should be closely monitored and may require dose-reduction if inhibitors of CYP3A4 (e.g., azole antifungal agents, macrolide antibiotics, HIV protease inhibitors) are co-administered.

CYP3A4 Inducers – the interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving Subutex or Suboxone should be closely monitored if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampin) are co-administered.

Benzodiazepines – based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports of coma and death associated with concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. Patients should be warned of the potential danger.

VI. Adverse Events ≥ 2% in short term studies

Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study			
Adverse Event	**Suboxone 16mg/day n=107**	**Subutex 16mg/day n=103**	**Placebo n=107**
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

VII. Dosage and Administration

Suboxone or Subutex is administered sublingually as a single daily dose in the range of 12 to 16mg/day. When taken sublingually, Suboxone and Subutex have similar clinical effects and are interchangeable. Subutex contains no naloxone and is preferred for use during induction. Following induction, Suboxone, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of Subutex for unsupervised administration should be limited to those patients who cannot tolerate Suboxone, for example, those patients who have been shown to be hypersensitive to naloxone.

VIII. Conclusion

Sublingual buprenorphine (Suboxone, Subutex), like methadone, is approved for the treatment of opioid detoxification. Injectable buprenorphine is indicated for the treatment of moderate to severe pain, and although not indicated, sublingual buprenorphine has been studied for treatment of both acute and chronic pain. There is very little data on buprenorphine use for cancer pain compared to other opioids. Treatment of cancer pain usually requires high doses of opioids, whereas buprenorphine appears to have an analgesic ceiling at higher doses.

Since buprenorphine has a lower abuse potential and is less dangerous in an overdose, some clinicians prefer to use it for pain management. Because Suboxone and Subutex are considerably more expensive than traditional generically available opioids, these agents might best be reserved for their FDA approved indication.

References

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South Dakota Department of Social Services
Pharmacotherapy Review
Opiate Agonists
AHFS Class 280808
June 11, 2010

I. Overview

There are numerous pharmacologic agents available to help manage pain. Opioids, the most potent analgesics, are generally reserved for the treatment of chronic, moderate-to-severe pain that has not responded to non-opioid therapy. Pain management may incorporate both pharmacologic and nonpharmacologic treatments. Successful pain management requires frequent reassessment of patient's pain level and response to therapy.

Opioid receptors are found in inhibitory pain circuits that descend from the midbrain to the spinal cord dorsal horn and also exist in the peripheral nervous system. There are several opioid receptors including mu, delta, kappa, and sigma. Most opioid agonists, like morphine, are selective for the mu receptor. Binding and activation of the mu receptor causes analgesia, euphoria, nausea/vomiting, respiratory depression, sedation, constipation, and over time tolerance and dependence. Opiate agonists have no ceiling to their analgesic effect, but dosing is typically limited by drug-induced adverse effects.

Table 1 lists the agents included in this review.

Table 1. Opiate Agonists Included in this Review

Generic Name	Brand Name	Dosage Form
Alfentanil	Alfenta®	Injection
Codeine	N/A	Tablet, injection
Codeine/APAP	Capital w/Codeine®, Tylenol w/Codeine #3®, Tylenol w/Codeine #4®	Elixir, suspension, tablet
Codeine/ASA	N/A	Tablet
Codeine/APAP/butalbital/caffeine	Fioricet w/codeine®	Capsule
Codeine/ASA/butalbital/caffeine	Fiorinal w/codeine#3®	Capsule
Dihydrocodeine/APAP/caffeine	Panlor DC®, Panlor SS®	Capsule, tablet
Fentanyl	Duragesic®, Actiq®, Fentora®, Sublimaze®, Onsolis®	Buccal tablet, buccal soluble film, extended-release transdermal patch, transmucosal lozenge, injection
Hydrocodone/APAP	Lortab®, Hycet®, Maxidone®, Norco®, Vicodin®, Xodol®, Zamicet®, Zydone®	Capsule, tablet, solution
Hydrocodone/ibuprofen	Ibudone®, Reprexain®, Vicoprofen®	Tablet
Hydromorphone	Dilaudid®	Liquid, tablet, rectal suppository, injection
Levorphanol	Levo-Dromoran®	Tablet, injection

Generic Name	Brand Name	Dosage Form
Meperidine	Demerol®	Solution, tablet, injection
Methadone	Dolophine, Methadose	Oral concentrate, solution, tablet
Morphine	MS Contin®, Oramorph SR®, Avinza®, Kadian®, Roxanol®, Depodur®, Duramorph®, Astramorph®, Infumorph®	Injection, intravenous, epidural, tablet, solution, rectal suppository
Morphine sulfate/naltrexone	Embeda®	Capsule
Opium/belladonna	N/A	Rectal suppository
Oxycodone	Oxy IR®, Dazidox®, Roxicodone®, Oxycontin®	Capsule, oral concentrate, solution, tablet
Oxycodone/APAP	Percocet®, Magnacet®, Primalev®, Tylox®	Capsule, solution, tablet
Oxycodone/ASA	Percodan®	Tablet
Oxycodone/ibuprofen	Combunox®	Tablet
Oxymorphone	Opana®, Numorphan®	Tablet, injection
Propoxyphene HCL	Darvon®	Capsule
Propoxyphene HCL/APAP	N/A	Tablet
Propoxyphene napsylate	Darvon-N®	Tablet
Propoxyphene napsylate/APAP	Darvocet-N 50®, Darvocet-N 100®, Darvocet A500®	Tablet
Remifentanil	Ultiva®	Intravenous
Sufentanil	Sufenta®	Intravenous
Tapentadol	Nucynta®	Tablet
Tramadol	Ultram®, Ultram ER®, Ryzolt®, Rybix® ODT	Tablets, orally disintegrating tablets, sustained-release tablet
Tramadol/APAP	Ultracet®	Tablet

II. Current Treatment Guidelines

Table 2. Treatment Guidelines for the agents included in this review

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Assessment and Management of Chronic Pain (2009)**	• A thorough medication history is critical to the development of an effective treatment plan. • Define the goals of therapy before prescribing, and tailor medications to meet the individual goals of each patient. • Identify and treat specific source(s) of pain, and base the initial choice of medication on the severity and type of pain. • Patients need to know that whether prescribed or non-prescribed, all drugs have risks and benefits. Watch for and manage side effects. • For opioid therapy: o Use caution before starting a patient on long-term opioid therapy. o Follow the 4 A's (Analgesia,

Clinical Guideline	Recommendation(s)
	Adverse drug reactions, Activity, Adherence) o Use a written opioid agreement for patients anticipated to be on long-term therapy. • Medications are not the sole focus of treatment in managing pain. They should be used when needed to meet overall goals of therapy in conjunction with other treatment modalities: psychosocial and spiritual management, rehab and functional management, non-pharmacologic and complementary medicine, and intervention management. • Use of medication should be directed not just toward pain relief, but for increasing function and restoring quality of life.
Annals of Oncology: **Management of Cancer Pain: ESMO Clinical Recommendations (2008)**	• Step-wise escalation of analgesic therapy should usually follow the 'pain ladder' as described by the WHO: o Step I, Mild Pain: non-opiate analgesics (e.g., APAP, NSAIDs) +/- adjuvant pain meds o Step II, Mild-Moderate Pain: mild opiate (e.g., codeine) +/- non-opiate analgesics +/- adjuvant pain meds o Step III, Moderate-Severe Pain: strong opiate (e.g., morphine) +/- non-opiate analgesics +/- adjuvant pain meds • Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by IV or SC • Opioid doses should be titrated to effect as rapidly as possible, with around-the-clock dosing and an as-needed 'breakthrough dose' (usually = 10% of total daily dose) to manage transient pain exacerbations. If more than 4 'breakthrough doses' per day are necessary, opioid treatment with a slow-release formulation should be initiated. • Reduction in opioid dose may be achieved

Clinical Guideline	Recommendation(s)
	by using a co-analgesic, such as an antidepressant, neuroleptic psychoactive drug or anticonvulsant. Such combinations may also alleviate refractory side effects such as constipation, nausea, vomiting, and central nervous system toxicity. Other strategies include the continued use of antiemetics, laxatives, major tranquilizers, and psychostimulants; also, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. • Neuropathic pain may not be adequately controlled by opioids alone; combination with co-analgesics may improve pain control. Steroids should be considered in case of nerve compression.
American Society of Interventional Pain Physicians: **Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines (2008)**	• Comprehensive initial evaluation • Establish diagnosis • Establish medical necessity • Assess risk-benefit ratio • Establish treatment goals • Obtain informed consent and agreement • Initial dose adjustment phase (up to 8-12 weeks)-start low dose and utilize opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvants • Stable phase (stable-moderate doses)-assess for four As • Adherence monitoring through random drug screens or pill counts.
Veterans Health Administration, Department of Defense: **VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2003)**	• The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions. • The ethical imperative to relieve pain should be considered when evaluating therapeutic options.

Clinical Guideline	Recommendation(s)
WHO Three-Step Analgesic Ladder for Cancer Pain Management (1990)	• Mild Pain-prompt oral administration of nonopioid analgesics (e.g. acetaminophen, NSAIDs) +/- adjuvant pain medications • Mild-Moderate Pain-Mild opiate (e.g. codeine) +/- non-opiate analgesic +/- adjuvant pain medications • Moderate-Severe Pain-Strong opiate (e.g. morphine) +/- non-opiate analgesic- (e.g. acetaminophen, NSAIDS) +/- adjuvant pain medications

III. Indications

Table 3. FDA-Approved Indications for the Opiate Agonists

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
Alfentanil	√	√			
Codeine	√		√[a]		
Codeine/APAP	√				
Codeine/ASA	√				
Codeine/APAP/butalbital/ caffeine					√
Codeine/ASA/butalbital/ caffeine					√
Dihydrocodeine/APAP/ caffeine	√				
Fentanyl injection	√	√			
Fentanyl transdermal/ transmucosal	√				
Hydrocodone			√[a]		
Hydrocodone/APAP	√				
Hydrocodone/ibuprofen	√				
Hydromorphone	√				
Levorphanol	√				
Meperidine	√	√			
Methadone	√			√	
Morphine sulfate	√	√			
Morphine sulfate/naltrexone	√				
Oxycodone	√				
Oxycodone/APAP	√				
Oxycodone/ASA	√				
Oxycodone/ibuprofen	√				
Oxymorphone	√	√			
Propoxyphene HCL	√				
Propoxyphene HCL/APAP	√				
Propoxyphene napsylate	√				
Propoxyphene napsylate/	√				

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
APAP					
Remifentanil	√	√			
Sufentanil	√	√			
Tapentadol	√				
Tramadol	√				
Tramadol ER	√				
Tramadol/APAP	√				

[a]Currently only available for this indication when part of a multi-ingredient product.

IV. Pharmacokinetics

Table 4. Pharmacokinetic Parameters of the Long-Acting Oral Opiates Included in this Review

Generic Name	Onset	Peak	$t_{1/2}$ (hours)	Metabolism
Alfentanil	Immediate	1.5-2 min	1.5-1.85 hours	Hepatic
Codeine	Oral: 10-30 min Parenteral: 15 min	0.5-1 hour	2.5-3.0	Hepatic CYP2D6 CYP3A4
Dihydrocodeine/APAP/ caffeine		1.6-1.8 hours	3.3-4.5 hours	
Fentanyl	Parenteral: IV-immediate IM-7-8 min Transdermal: 12-24 hours Buccal: 5-15 min	Transdermal: 24-72 hours Buccal: 20-40 min	Parenteral: 3.65 hours Transdermal: 17 hours Buccal: 7 hours	Hepatic CYP3A4
Hydrocodone	1 hour	1.3 hour	3.8-4.5 hours	Hepatic CYP2D6
Hydromorphone	Oral: 30 min Parenteral: 15 min	48-60 min	IR: 2.3 hours ER: 18.6 hours IM/Subcutaneous: 2.6 hours	Hepatic Glucuronidation
Levorphanol	Parenteral: 15-30 min Oral: 10-60 min	Parenteral: 20-90 min Oral: 60 min	11-16 hours	Hepatic
Meperidine	Parenteral: 5-30 min	IM: 25 min	3-6 hours	Hepatic
Methadone	Oral: 30-60 min	2-4 hours	8-59 hours	Hepatic CYP3A4 CYP2D6

Generic Name	Onset	Peak	$t_{1/2}$ (hours)	Metabolism
	Parenteral: 10-20 min			
Morphine	Parenteral: 10-30 min Rectal: 20-60 min	Epidural: 10-15 min Oral: 1 hour Oral: 60 min	1.5-2 hours	Hepatic Glucuronidation
Oxycodone	Oral: 1 hour	1.6 hours	IR: 3.2 hours CR: 4.5 hours	Hepatic CYP2D6
Oxymorphone	Oral: 1 hour Parenteral: 5-10 min	Oral: 1-2 hours	Oral: 7-9 hours Parenteral: 1.3 hours	Hepatic Glucuronic acid conjugation
Propoxyphene	0.25-1 hour	2-2.5 hours	6-12 hours(parent), 30-36 hours (norpropoxyphene)	Hepatic, 25% conversion to norpropoxyphene
Remifentanil	Rapid	3-10 min	10-20 min	Hydrolysis by esterases
Sufentanil	IV: immediate Epidural: 10 min	20 min	2.7 hours	Hepatic + small intestines
Tapentadol		1.25 hours		Conjugation with glucoronic acid: CYP2C9 CYP3A4
Tramadol	IR: 30-60 min	IR: 30-60 min ODT: 2.3 hours ER: 12 hours	IR: 6.3 hours ODT: 6.7 hours ER: 7.9 hours	Hepatic CYP2D6 CYP3A4

V. Drug Interactions

Table 5. Significant Drug Interactions with the Opiate Agonists

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
Acyclovir	Opioid analgesics	↑	Plasma concentrations of meperidine and normeperidine may be increased; use with caution
Amiodarone	Opioid analgesics	↑	Profound bradycardia, sinus arrest, and hypotension have occurred with concomitant administration. Monitor hemodynamic function and administer inotropic, chronotropic, and pressor support as necessary. The bradycardia is usually

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
			unresponsive to atropine; large doses of vasopressors have been used.
Anticholinergics	Methadone	↑	Coadministration may result in increased risk of urinary retention and/or severe constipation which may lead to paralytic ileus.
Azole antifungals	Opioid analgesics	↑	Coadministration may lead to increased pharmacological and adverse effects of the narcotic. Use with caution, and monitor for prolonged or recurrent respiratory depression. A lower dose of the narcotic may be necessary.
Barbiturate anesthetics	Opioid analgesics	↑	Barbiturate anesthetics may increase the respiratory and CNS-depressant effects of the narcotics because of additive pharmacologic activity.
Barbiturates	Methadone	↓	Coadministration may reduce methadone actions. Patients receiving chronic methadone treatment may experience withdrawal symptoms. A higher dose of methadone may be required during coadministration of barbiturates.
Benzodiazepines	Opioid analgesics Sufentanil	↑	Coadministration may result in decreased mean arterial pressure and systemic vascular resistance (also see CNS depressant interaction)
Benzodiazepines Diazepam	Opioid analgesics Alfentanil Fentanyl	↑	Diazepam may produce cardiovascular depression when given with high doses of fentanyl and alfentanil. Administration prior to or following high doses of alfentanil decreases blood pressure secondary to vasodilation; recovery may be prolonged.
Beta-blockers Calcium channel blockers	Opioid analgesics Sufentanil	↑	Increased incidence and degree of bradycardia and hypotension during induction of sufentanil in patients on long-term calcium channel or beta-blocker therapy.
Carbamazepine	Opioid analgesics Tramadol	↓	Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, coadministration is not recommended.
Cigarette smoking	Opioid analgesics Propoxyphene	↓	Cigarette smoking may induce liver enzymes responsible for the metabolism of propoxyphene; efficacy is reportedly decreased in smokers. Patients may increase the dosage to obtain adequate pain relief.
Cimetidine	Opioid analgesics	↑	The actions of opioid analgesics may be enhanced, resulting in toxicity. Alfentanil clearance may be reduced; therefore, smaller alfentanil doses may be needed.
CNS depressants (e.g. barbiturates, tranquilizers, inhalation anesthetics, ethanol)	Opioid analgesics	↑	Both the magnitude and duration of CNS and cardiovascular effects may be enhanced. Reduce the dose of one or both agents during concomitant use.
CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine, amitriptyline)	Opioid analgesics Oxycodone Tramadol	↑	Inhibition of the metabolism of tramadol or oxycodone may occur.
CYP3A4 inducers (e.g., phenytoin, rifampin)	Opioid analgesics Fentanyl Tramadol	↓	May produce increased clearance of fentanyl and tramadol; use with caution.

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
CYP3A4 inhibitors (e.g., certain protease inhibitors, erythromycin, ketoconazole)	Opioid analgesics Fentanyl Tramadol	↑	Coadministration may produce increased fentanyl and tramadol concentrations. Carefully monitor patients receiving fentanyl and potent CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir) for an extended period of time and adjust the dosage as needed.
Droperidol	Opioid analgesics Fentanyl	↑	Pulmonary arterial pressure may be depressed and hypotension may occur.
Erythromycin	Opioid analgesics Alfentanil Fentanyl Methadone	↑	Erythromycin may inhibit the metabolism of the narcotic. Coadministration may result in increased pharmacologic effects of the narcotic. Monitor for prolonged or recurrent respiratory depression and sedation. Consider a lower dose of the narcotic or an alternate narcotic.
Ethanol	Opioid analgesics Alfentanil	↓	Chronic ethanol consumption may produce a pharmacodynamic tolerance to alfentanil. Chronic ethanol consumers may need higher doses of alfentanil.
Hydantoins (e.g. phenytoin)	Opioid analgesics Meperidine Methadone	↓	Hydantoins may decrease the pharmacologic effects of meperidine and methadone, possibly because of increased hepatic metabolism of the narcotic.
Lidocaine	Opioid analgesics Morphine	↑	Respiratory depression and loss of consciousness may occur.
MAOIs	Opioid analgesics	↑	Severe and unpredictable potentiation by MAOIs has been reported with certain opioid analgesics. Opioids are not recommended for use in patients who have received MAOIs within 14 days.
Neostigmine	Opioid analgesics Morphine	↑	Increases the intensity and duration of the analgesic action.
Nitrous oxide	Opioid analgesics Fentanyl Sufentanil	↑	Nitrous oxide may cause cardiovascular depression with high-dose sufentanil and fentanyl.
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. nevirapine, efavirenz)	Opioid analgesics Methadone	↓	Concomitant administration may result in reduced methadone action and opiate withdrawal symptoms. Anticipate an increase in the methadone dose when starting an NNRTI and monitor for withdrawal symptoms. Monitor for methadone overdose signs when an NNRTI is discontinued and adjust the methadone dose accordingly.
Nucleoside reverse transcriptase inhibitors (Abacavir, Didanosine, Stavudine, Zidovudine)	Opioid analgesics Methadone	↓	When coadministered with abacavir, methadone clearance increased by 22%. Methadone dose adjustment may be needed in a small number of patients. Coadministration may decrease AUC and C_{max} of didanosine and stavudine; however, coadministration may increase zidovudine concentration. Monitor zidovudine effects closely; a lower dose may be needed
Opioid agonist/antagonist analgesics, opioid partial agonist analgesics	Opioid analgesics	↓	Do not administer opioid agonist/antagonist analgesics (e.g. pentazocine, nalbuphine, butorphanol) or partial agonists (e.g. buprenorphine) to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic. In opioid-dependent patients, mixed agonist/antagonist analgesics and partial agonists may precipitate withdrawal symptoms.
Phenothiazines	Opioid analgesics	↑	Although the analgesic effect of narcotics may be potentiated, a higher incidence of toxic effects may occur.

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
Propofol	Opiate analgesics Oxycodone	↑	Increased risk of bradycardia with concomitant use.
Protease inhibitors (e.g. ritonavir, saquinavir, nelfinavir)	Opioid analgesics Fentanyl Meperidine Methadone Propoxyphene	↓↑	Plasma concentrations of propoxyphene and fentanyl may be increased, possible causing toxicity. The pharmacologic effects of methadone may be decreased. Meperidine levels may decrease and normeperidine levels may increase, possible decreasing efficacy but increasing neurologic toxicity. Concurrent use of propoxyphene or meperidine with a protease inhibitor is contraindicated.
Quinidine	Opioid analgesics Codeine	↓	The analgesic effects of codeine may be decreased. It may be necessary to use an alternative analgesic.
Reserpine	Opioid analgesics Morphine	↓	Inhibits analgesic action.
Rifamycins (e.g. rifampin)	Opioid analgesics Methadone Morphine	↓	Rifampin appears to stimulate methadone metabolism. Coadministration may result in reduced methadone action and opiate withdrawal symptoms. A higher dose of methadone may be required during coadministration of rifampin. The analgesic effects of morphine may be decreased with concurrent administration. May be necessary to administer an alternative analgesic.
Sibutramine	Opioid analgesics Meperidine	↑	Serotonergic effects of these agents may be additive, resulting in serotonin syndrome. Coadministration is not recommended.
SSRIs Nefazodone Venlafaxine	Opioid analgesics Methadone Tapentadol Tramadol	↑	Fluvoxamine may inhibit methadone metabolism and therefore increase toxicity. Use with caution. The serotonergic effects of tapentadol and tramadol, and serotonin reuptake effects of tapentadol, tramadol and serotonin reuptake inhibitors may be additive, increasing the risk for adverse effects (e.g., seizures, serotonin syndrome)
Tricyclic antidepressants Amitriptyline Clomipramine Nortriptyline	Opioid analgesics Morphine Tapentadol	↑	Monitor for increased CNS and respiratory depression when administered with morphine. A serotonin syndrome may occur when tricyclic antidepressants are used with tapentadol.
Urinary acidifiers	Opioid analgesics Methadone	↓	Urinary acidifiers increase the renal clearance of methadone.
Opioid analgesics Propoxyphene	Carbamazepine	↑	Propoxyphene may inhibit the metabolism of carbamazepine, thereby increasing the carbamazepine serum concentrations and toxicity.
Opioid analgesics Methadone	Desipramine	↑	Desipramine blood levels have increased with concurrent methadone therapy.
Opioid analgesics Tramadol	Digoxin	↑	Rare reports of digoxin toxicity have been reported in postmarketing surveillance.
Opioid analgesics Morphine	Diuretics	↓	Reduces efficacy by inducing the release of antidiuretic hormone.
Opioid analgesics Remifentanil	Opioid analgesics Morphine	↓	The analgesic effect of morphine may be decreased with coadministration. It may be necessary to titrate morphine to higher levels than expected.
Opioid analgesics Morphine Propoxyphene Tramadol	Warfarin	↑	The oral anticoagulant effect of warfarin may be increased. Monitor coagulation tests and adjust dose as needed.
Opioid analgesics	Skeletal muscle relaxants	↑	Coadministration may enhance the neuromuscular blocking action and produce an increased degree of respiratory dep.

VI. Adverse Drug Events of the Opiate Agonists

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Cardiovascular															
Abnormal ECG	-	-	-	-	-	-	√	-	-	-	-	-	-	-	PM
Arrhythmia	14	-	-	-	√	-	√	-	-	-	-	-	0.3-1	-	-
Atrial fibrillation	-	-	-	-	-	-	-	√	-	-	-	<1	-	-	-
Bradycardia	14	√	√	√	√	√	√	√	-	√	-	1-7	3-9	≤1	-
Cardiac arrest	-	√	√	√	√	√	√	√	√	-	-	-	-	-	PM
Chest pain	-	-	<1	-	-	-	-	√	-	-	-	<1	-	-	-
CHF/heart failure	-	-	-	√	-	-	-	-	-	-	-	-	-	-	-
Circulatory depression/ collapse	-	√	√	√	-	√	√	√	√	-	-	-	-	-	-
Deep thrombophlebitis	-	-	√	√	-	-	-	-	√	-	-	-	-	-	-
Extrasystoles	-	-	-	-	√	-	-	-	-	-	-	-	-	-	-
Faintness	-	√	-	√	-	-	√	√	-	-	-	-	-	-	-
Flushing	-	√	√	√	√	√	√	√	-	√	-	1	-	-	-
Hypertension	18	-	√	√	-	-	√	√	-	-	-	1-2	3-9	-	PM
Hypotension	10	√ (ortho static)	√	√	√	√	√	√	√	√	-	4-19	3-9	≤1	<1

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Palpitation	-	√	√	√	√	√	-	√	√	√	-	-	-	-	PM
Pallor	-	-	-	≥ 1 (ER)	√	-	-	√	-	-	-	-	-	-	-
Phlebitis	-	-	-	-	-	√	√	√ (IV)	-	-	-	-	-	-	-
Syncope	-	√	√	√	√	√	√	√	√	-	-	<1	-	≤1	<1
Tachycardia	12	√	√	√	√	√	√	√	√	√	-	<1	0.3-1	≤1	<1
Vasodilation	-	-	≤4	-	-	-	-	√	√	-	-	-	-	-	1-5
CNS															
Abnormal gait	-	-	1-5	-	-	-	-	√	<1	-	-	-	-	-	<1
Abnormal thinking	-	-	0-2 (trans-mucosal)	-	-	-	-	√	1-5	-	-	-	-	≤1	<1
Agitation	-	√	√	-	-	√	√	√	√	-	-	<1	-	≤1	-
Anxiety	-	-	3-15	√	-	-	-	√	√	-	-	<1	-	1	1-5
Asthenia	-	-	0-38	-	-	-	-	-	6	-	-	-	-	-	6-12
Coma	-	-	-	-	√	-	-	√	<3	-	-	<1	-	-	-
Confusion	-	-	10-13	-	√	-	√	√	<1	√	-	<1	-	1	1-5
Convulsion/ Seizure	-	√	0-2	-	√	√	√	√	-	-	-	-	-	-	<1

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Depression	-	-	2-10	-	√	-	-	√	<1	√	-	-	-	-	<1
Disorientation	-	√	-	√	√	√	√	√	13	-	-	<1	-	≤1	-
Dizziness	3-9	√	3-17	√	-	-	√	√	-	-	<1	<5	-	24	26-33
Drowsiness	-	-	-	-	√	-	-	√	-	√	-	-	-	-	-
Dysphoria	-	√	-	√	-	√	√	-	-	√	<1	<1	-	-	-
Euphoria	0.3-1	√	3-10	√	-	√	√	√	1-5	√	<1	-	-	≤1	1-5
Fear	-	√	-	√	-	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	-	3-10	√	-	√	-	√	<1	√	<1	<1	-	-	<1
Headache	0.3-1	√	3-20	√	-	√	√	√	7	√	<1	≤18	-	-	18-32
Insomnia	-	√	1-10	√	√	-	√	√	1-5	√	-	-	-	2	-
Lethargy	-	√	-	√	√	√	-	√	-	-	-	-	-	≤1	-
Light-headedness	-	√	-	√	-	-	√	√	-	√	<1	-	-	-	-
Mental clouding	-	√	-	√	-	-	-	√	-	√	-	-	-	-	-
Mood changes	-	√	-	√	-	-	-	√	-	-	-	-	-	-	-
Myoclonic movement	PM	-	1-4	-	-	√	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Nervousness	-	-	1-10	-	√	-	-	√	1-5	√	-	-	-	≤1	1-5
Postoperative confusion	0.3-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shivering	0.3-1	-	√	-	-	-	-	-	-	-	-	1-5	-	-	-
Sleepiness/sedation	1-3	√	3-20	√	-	√	√	√	23	√	<1	-	3-9	≤1	16-25
Somnolence	-	-	-	-	-	-	-	-	-	-	-	-	-	15	-
Stupor	-	-	1-4	-	-	-	-	-	√	-	-	-	-	-	-
Tremor	-	-	1-2	√	-	√	-	√	√	-	-	<1	-	1	<1
Weakness	-	√	-	√	-	√	√	√	-	√	<1	-	-	-	-
Vertigo	-	-	0-4 (trans-mucosal)	-	-	-	-	√	<1	-	-	-	-	-	26-33
GI															
Abdominal pain	-	-	1-10	-	√	-	√	-	1-5	√	<1	-	-	-	-
Anorexia	-	√	-	-	-	-	√	√	1-5	√	-	-	-	-	1-5
Biliary tract spasm	-	√	-	-	√	√	√	√	-	√	-	-	-	-	-
Constipation	-	√	3-20	√	-	√	√	√	23	√	<1	<1	-	8	24-36
Diarrhea	-	-	3-10	√	-	-	-	√	1-5	-	-	<1	-	-	5-10

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Dry mouth	-	√	1-10	√	√	√	√	√	6	√	-	-	-	4	5-10
Dyspepsia	-	-	3-10	-	√	-	-	√	1-5	√	-	-	-	2	5-13
Nausea	28	√	10-45	√	√	√	√	√	23	-	<1	1.4-4	3-9	30	24-40
Vomiting	18	√	6-31	-	√	√	√	√	12	√	<1	≤22	3-9	18	9-17
GU															
Antidiuretic effect	-	√	-	√	-	√	√	√	<1	√	-	-	-	-	-
Decreased libido/potency	-	√	√	-	-	-	√	√	<1	-	-	-	-	-	-
Spasm of vesical sphincters	-	√	-	-	-	-	-	√	-	-	-	-	-	-	-
Ureteral spasm	-	√	-	-	-	-	-	√	-	√	-	-	-	-	-
Urinary hesitancy	-	√	-	√	-	-	√	√	-	√	-	-	-	≤1	-
Urinary retention	-	√	1-10	√	-	√	√	√	<1	√	-	<1	√	-	1-5
Miscellaneous															
Accidental injury	-	-	0-9	-	-	-	-	√	√	-	-	-	-	-	<1
Anaphylaxis/ anaphylactoid	PM	-	-	-	-	-	√	√	√	-	-	-	PM	-	<1
Application site reactions	-	-	1-10	-	-	-	-	-	-	-	-	1	-	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Blurred vision	1-3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest wall rigidity	17	-	√	-	-	-	-	-	-	-	-	-	3-9	-	-
Edema	-	-	√	-	-	-	√	√	√	-	-	-	-	≤1	-
Itching/pruritus	<1	-	1-10	√	√	-	√	√	13	√	-	≤18	25	5	8-11
Injection site pain/reaction	0.3-1	-	-	√	-	√	-	-	-	-	-	<1	√	-	-
Muscle rigidity	-	-	√	√	-	-	-	√	-	-	-	2-11	-	-	-
Rash	-	-	1-8	√	√	-	-	√	1-5	-	-	<1	-	1	1-5
Shock	-	√	-	-	-	√	√	-	√	-	-	-	-	-	-
Skeletal muscle movement	3-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweating	-	-	-	√	√	√	√	√	5	√	-	6	-	-	-
Visual disturbances	-	√	-	√	-	√	-	-	-	-	-	-	-	-	-
Respiratory															
Apnea	1-3	-	3-10	√	√	-	-	√	-	-	-	≤30	0.3-1	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Bronchospasm	<1	-	-	-	-	-	-	-	-	-	-	<1	0.3-1	-	-
Dyspnea	-	-	2-22	-	-	-	-	√	-	1-5	-	-	-	≤1	≤1
Hypercarbia	0.3-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laryngospasm	0.3-1	-	-	√	-	-	√	√	-	-	-	<1	-	-	-
Pharyngitis	-	-	3-10	-	-	-	-	-	-	√	-	<1	-	-	-
Respiratory arrest	-	√	-	√	-	√	√	√	-	√	-	-	-	-	-
Respiratory depression	3-9 (post op)	√	-	√	-	√	√	√	-	√	-	<1	0.3-1	≤1	-

PM=Postmarketing

VII. Dosing, Administration and Warnings

The FDA-approved dosing guidelines for the Opiate Agonists are summarized in Table 7.

Table 7. Dosage Guidelines for the Opiate Agonists Included in this Review

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Alfentanil	Individualized dosing based on body weight, physical status, underlying pathological conditions, use of other drugs, and type and duration of surgical procedure and anesthesia.	≥ 12 years: Individualized dosing based on body weight, physical status, underlying pathological conditions, use of other drugs, and type and duration of surgical procedure and anesthesia	Injection: 500mcg/ml
Belladonna/Opium	1 or 2 suppositories/day	Safety and efficacy in children have not been established.	Rectal suppositories: 30/16.2mg, 60/16.2mg
Codeine	Oral: 15 to 60mg every 4-6 hours 30mg SC or IM every 4 hours as needed	Oral: 0.5 to 1mg/kg every 4-6 hours ≥3 years: 500mcg/kg or 15mg/m^2 SC or IM every 4 hours as necessary	Tablet: 15mg, 30mg, 60mg Solution, oral: 15mg/5ml Injection: 15mg/ml, 30mg/ml
Codeine/APAP	½ -2 tablets every 4 hours	½-1 mg codeine/kg/dose every 4-6 hours (10-15mg APAP/kg/dose every 4 hours) Liquid: >12 years: 15ml every 4 hours as needed 7-12 years: 10ml 3-4 times daily as needed 3-6 years: 5ml 3-4 times daily as needed	Tablet: 15/300mg, 30/300mg, 30/650mg, 60/300mg Elixir and Suspension: 12/120mg per 5ml
Codeine/ASA	30mg tablets: 1-2 tablets every 4 hours as needed. 60mg tablets: 1 tablet every 4 hours as needed.	Safety and efficacy in children have not been established	Tablet: 30/325mg, 50/325mg
Codeine/butalbital/ APAP/caffeine	1 or 2 capsules every 4 hours	≥12 years: 1 or 2 every 4 hours < 12 yrs: Safety and efficacy in children have not been established	Capsules: 30/50/325/40mg
Dihydrocodeine/ APAP/caffeine	2 every 4 hours	Safety and efficacy in children have not been established	Capsule: 16/356/30mg Tablet: 32/713/60mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Fentanyl	Buccal tablet: Initial dose is 100mcg. Take one additional dose using the same strength for that episode. Patients should take a maximum of two doses for any episode of breakthrough pain. Patients must wait at least 4 hours before treating another episode of breakthrough pain. Lozenge: Initial dose is 200mcg. Titrate as necessary to provide adequate analgesia and minimize adverse reactions. Maximum of 4 units/day. Buccal film: Only prescribers enrolled in the FOCUS program may prescribe fentanyl buccal soluble film. Injection: 50-100mcg IM or slow IV Transdermal: Dose based on previous opioid, potency estimates, opioid tolerance and general condition of the patient. The majority of patients are adequately maintained with fentanyl administered every 72 hours, however, some may require application every 48 hours.	Buccal tablet: The safety and efficacy in pediatric patients below the age of 16 years have not been established. Lozenge: Safety and efficacy in children have not been established. Buccal film: The appropriate dosing and safety of fentanyl in opioid-tolerant children with breakthrough cancer pain have not been established in children younger than 18 years of age. Injection: 2-12 years of age a dose as low as 2-3mcg/kg is recommended. Transdermal: Administer to children only if they are opioid tolerant receiving at least oral morphine 60mg/day and 2 years of age and older with chronic pain.	Buccal tablet: 100mcg, 200mcg, 300mcg 400mcg, 600mcg, 800mcg Lozenge on stick: 200mcg, 400mcg, 600mcg, 800mcg, 1200mcg, 1600mcg Film, buccal: 200mcg per film, 400mcg per film, 800mcg per film, 1200mcg per film Injection: 50mcg/ml Transdermal: 12.5mcg/h, 25mcg/h, 50mcg/h, 75mcg/h, 100mcg/h
Hydrocodone	1-2 tablets/capsules or 15ml every 4-6 hours as needed	≥15 years: 1-2 tablets/capsules or 15ml every 4-6 hours as needed. 2-14 years: 0.27ml/kg every 4-6 hours as needed.	Tablet: 2.5/500mg, 5/300mg, 5/325mg, 5/400mg, 5/500mg, 7.5/300mg, 7.5/325mg, 7.5/400mg, 7.5/500mg, 7.5/650mg, 7.5/750mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg, 10/660mg Solution: 2.5/167mg/5ml, 3.33/167mg/5ml, 5/333mg/10ml, 7.5/325mg/15ml, 10/325mg/15ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Hydrocodone/ ibuprofen	1 tablet every 4-6 hours	≥16 years: 1 tablet every 4-6 hours <16 years: Safety and efficacy in children have not been established.	Tablet: 10/200mg, 5/200mg, 7.5/200mg
Hydromorphone	Tablets: 2-4mg every 4-6 hours as necessary Oral solution: 2.5-10mg (2.5 to 10mL) every 3-6 hours as directed. Injection: 1-2mg SC or IM every 4-6 hours as needed. If given IV, inject slowly over at least 2-3 minutes Rectal: 1 suppository inserted rectally every 6-8 hours or as directed by health care provider	Safety and efficacy in children have not been established.	Tablets: 2mg, 4mg, 8mg Injection: 1mg/ml, 2mg/ml, 4mg/ml Injection, concentrate: 10mg/ml, 250mg (10mg/ml after reconstitution) Oral solution: 1mg/ml Rectal suppository: 3mg
Levorphanol	1 tablet every 6-8 hours (Levo-Dromoran) or 3-6 hours (levorphanol) as needed.	Safety and efficacy in children have not been established.	Tablets: 2mg Injection: 2mg/mL
Meperidine	Oral: 50-150mg every 3-4 hours as necessary Injection: 50-150mg IM or SC every 3-4 hours as necessary Preoperative: 50-100mg IM or SC 30-90 minutes before beginning anesthesia.	Oral: 1.1-75mg/kg (0.5-0.8mg/lb) up to the adult dose, every 3-4 hours as necessary Injection: 1.1 to 1.75mg/kg (0.5 to 0.8mg/lb) IM or SC up to the adult dose every 3-4 hours as necessary. Preoperative: 1.1-2.2mg/kg (0.5 to 1mg/lb) IM or SC up to the adult dose to 90 minutes before beginning anesthesia.	Tablet: 50mg, 100mg Oral liquid: 50mg/5ml Injection (vial, cartridge, ampule, syringe): 10mg/ml, 25mg/ml, 50mg/ml, 75mg/ml, 100mg/ml
Meperidine	Oral: 50-150mg every 3-4 hours as necessary Injection: 50-150mg IM or SC every 3-4 hours as necessary Preoperative: 50-100mg IM or SC 30-90 minutes before beginning anesthesia	Oral: 1.1 -1.75mg/kg (0.5 to 0.8mg/lb) up to the adult dose, every 3-4 hours as necessary Injection: 1.1-1.75mg/kg (0.5 to 0.8mg/lb) IM or SC up to the adult dose every 3-4 hours as necessary Preoperative: 1.1- 2.2mg/kg (0.5 to 1mg/lb) IM or SC up to the adult dose 30 to 90 minutes before beginning anesthesia.	Tablets: 50mg, 100mg Syrup: 50mg/5ml Injection: 10mg/ml, 25mg/ml, 50mg/ml, 75mg/ml, 100mg/ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Methadone	Pain: 2.5-10mg every 8-12 hours Detoxification: A single dose of 20-30mg will often be sufficient to suppress withdrawal	Off-label dosing for children: Opiate withdrawal: 0.05-0.2mg/kg every 12-24 hours Pain: 0.7mg/kg day in divided doses every 4-6 hours as needed	Tablets: 5mg, 10mg, 40mg Solution: 5mg/5ml Liquid concentrate 10mg/ml Injection: 10mg/ml
Morphine	IR: 5-30mg every 4 hours as directed. CR/ER: Begin treatment using an IR morphine formulation. CR/ER conversion-administer ½ of the patient's 24-hour requirement as ER morphine on an every 12 hour schedule or administer 1/3 of the patient's daily requirement on an every 8 hour schedule. Injection: 5-20mg SC or IM every 4 hours as needed IV injection: 2-10mg per 70kg of body weight given over 4-5 minutes. Can be given every 4 hours Rectal suppository: 10-20mg every 4 hours	Oral: Safety and efficacy in children have not been established. IM or SC injection: 0.1-0.2mg/kg every 4 hours as needed IV injection: 50-100mcg IV per kg of body weight, not to exceed 10mg/dose Rectal suppository: Safety and efficacy in children have not been established.	IR Tablets: 15mg, 30mg SR Tablets: 15mg, 30mg, 60mg, 100mg, 200mg, Tablets for solution: 10mg, 15mg, 30mg Capsules, extended-release pellets: 10mg, 20mg, 30mg, 45mg, 50mg, 60mg, 75mg, 80mg, 90mg, 100mg, 120mg, 200mg Solution, oral: 10mg/5ml, 20mg/5ml Solution, concentrate: 20mg/ml, 100mg/5ml Injection: 0.5mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml, 10mg/ml, 15mg/ml Injection, extended-release liposomal: 10mg/ml Injection, solution: 25mg/ml, 50mg/ml Suppositories: 5mg, 10mg, 20mg, 30mg
Oxycodone	IR tablets: 10-30mg every 4 hours as needed IR capsules: 5mg every 6 hours as needed Oral solution: 10-30mg every 4 hours as needed Oral concentrate: 5mg every 6 hours as needed	Not recommended for use in children	IR Tablets: 5mg, 10mg, 15mg, 20mg, 30mg CR: 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg Capsules: 5mg Solution, oral: 5mg/5ml Solution, concentrate: 20mg/ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Oxycodone/APAP	5mg/7.5mg/10mg oxycodone strength: 1 tablet, caplet or teaspoonful every 6 hours as needed 2.5mg oxycodone strength: 1-2 tablets every 6 hours as needed	Safety and efficacy in children have not been established	Tablet: 2.5/300mg, 2.5/325mg, 2.5/400mg, 5/300mg, 5/325mg, 5/400mg, 7.5/300mg, 7.5/325mg, 7.5/400mg, 7.5/500mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg Capsule 5/500mg Solution, oral 5/325mg/5ml
Oxycodone/ASA	1 tablet every 6 hours as needed for pain. Maximum 12 tablets every 24 hours	Safety and efficacy have not been established. Reye syndrome has been associated with aspirin administration to children (including teenagers) with acute febrile illness.	Tablets: 4.5mg oxycodone, 0.38mg oxycodone terephthalate/325mg
Oxycodone/ ibuprofen	1 tablet given orally not to exceed 4 tablets in a 24 hour period	Safety and effectiveness in pediatric patients below the age of 14 have not been established.	Tablets: 5/400mg
Oxymorphone	IR: 10-20mg every 4-6 hours ER: 5mg every 12 hours	Safety and efficacy of oxymorphone in children younger than 18 years of age have not been established.	IR Tablets: 5mg, 10mg ER Tablets: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg, 40mg Injection, solution: 1mg/ml
Propoxyphene HCL	65mg every 4 hours as needed	Safety and efficacy in children have not been established.	Capsule: 65mg
Propoxyphene HCL/APAP	65mg (with 650mg acetaminophen) every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 65/650mg
Propoxyphene napsylate	100mg every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 100mg
Propoxyphene napsylate/APAP	100mg (with 325, 500, or 625mg acetaminophen) every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 50/325mg, 100/325mg, 100/500mg, 100/650mg
Remifentanil	Individualize dose given as IV only	≥1 year. Individualize dose	IV: 1mg, 2mg, 5mg
Sufentanil	Individualize dose given as slow IV or IV infusion	2-12 years: 10-25mcg/kg given with 100% oxygen	IV: 50mcg/ml
Tapentadol	50-100mg every 4-6 hours. Daily doses greater than 700mg on the first day of therapy and 600mg on subsequent days have not been studied.	Not recommended for use in children younger than 18 years of age.	Tablets: 50mg, 75mg, 100mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Tramadol	IR tablets: 25mg/day in the morning. After titration, administer 50-100mg every 4-6 hours as needed for pain relief. ODT tablets: 50-100mg every 4-6 hours as needed for pain relief. ER tablets: 100-300mg once daily.	Safety and efficacy in children have not been established.	Tablets: 50mg Tablets ODT: 50mg Tablets, extended release: 100mg, 200mg, 300mg
Tramadol/APAP	2 tablets every 4-6 hours as needed	Safety and efficacy in children have not been established.	Tablets: 37.5mg/325mg

SC=Subcutaneous; IM=Intramuscular; IV=Intravenous

Table 8. Equianalgesic Dosing of Opioid Analgesics

Approximate Equianalgesic Dosing of Opioid Analgesics in Adults			
Opioid	**Oral**	**Parenteral (IM, SC, IV)**	**Rectal**
Codeine	200mg	120-130mg	NA
Fentanyl	NA	0.1mg	NA
Hydrocodone	30mg	NA	NA
Hydromorphone	7.5mg	1.5mg	3mg
Levorphanol	4mg	2mg	NA
Meperidine	300mg	75mg	NA
Methadone	10-20mg	5-10mg	NA
Morphine	60mg single dose, 30mg repeated doses	10mg	-
Oxycodone	20-30mg	NA	NA
Oxymorphone	NA	1mg	10mg

BLACK BOX WARNINGS:

Fentanyl transmucosal:
Oral transmucosal fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and tolerant of opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking morphine 60 mg/day or more, transdermal fentanyl 50 mcg/h, or an equianalgesic dose of another opioid for a week or longer. It is contraindicated in the management of acute or postoperative pain. Because life-threatening hypoventilation could occur at any dose in patients not taking long-term opiate therapy, do not use in nonopioid-tolerant patients. Use only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of schedule II opioids to treat cancer pain. Instruct patients and their caregivers that this drug contains medicine in an amount that can be fatal to a child. Keep all units out of the reach of children, and discard opened units properly.

Fentanyl transdermal system:
Fentanyl transdermal systems contain a high concentration of the potent schedule II opioid agonist, fentanyl. Schedule II opioid substances have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches may be a particular target for abuse and diversion.

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that requires continuous around-the-clock opioid administration for an extended period of time, and cannot be managed by other means, such as nonsteroidal analgesics, opioid combination products, or immediate-release (IR) opioids.

Use fentanyl transdermal system only in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/h. Patients who are considered opioid tolerant are those who have been taking, for a week or longer, morphine 60 mg/day or more, oral oxycodone 30 mg/day or more, oral hydromorphone 8 mg/day or more, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated:

- in patients who are not opioid tolerant,
- in the management of acute pain or in patients who require opioid analgesia for a short period of time,
- in the management of postoperative pain, including use after outpatient or day surgeries (eg, tonsillectomies),
- in the management of mild pain, and
- in the management of intermittent pain (eg, use on an as-needed basis).

Because peak fentanyl levels occur between 24 and 72 hours of treatment, serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period. The concomitant use of fentanyl transdermal system with potent CYP3A4 inhibitors (clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, troleandomycin) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors for an extended period of time and make dosage adjustments if warranted.

Do not administer fentanyl transdermal system to children younger than 2 years of age. Administer to children only if they are opioid tolerant and 2 years of age and older.

Fentanyl transdermal system is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in nonopioid-tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Because of the 17-hour mean elimination half-life of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

Fentanyl transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this risk when administering, prescribing, or dispensing fentanyl transdermal system in situations in which there is concern about increased risk of misuse, abuse, or diversion.

Fentanyl transdermal patches are intended for transdermal use (on intact skin) only. Using damaged or cut fentanyl transdermal patches can lead to the rapid release of the contents of the fentanyl transdermal patch and absorption of a potentially fatal dose of fentanyl.

Hydromorphone:
High-potency injection: High-potency injection is a highly concentrated solution of hydromorphone intended for use in opioid-tolerant patients. Do not confuse high potency injection with standard parenteral formulations of injection or other opioids. Overdose and death could result.

Extended-release capsules: Hydromorphone extended-release (ER) capsules are indicated for the management of persistent moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high-potency opioid for an extended period of time (weeks to months) or longer. Use ER capsules only in patients who are already receiving opioid therapy, have demonstrated opioid tolerance, and require a minimum total daily dose of opiate medication equivalent to oral hydromorphone 12 mg. Patients considered opioid tolerant are those taking, for a week or longer, oral morphine 60 mg/day or more, oral oxycodone 30 mg/day or more, oral hydromorphone 8 mg/day or more, or an equianalgesic dose of another opioid. Administer ER capsules once every 24 hours.

Appropriate patients for treatment with ER capsules include patients who require high doses of potent opioids on an around-the-clock basis to improve pain control, and patients who have difficulty attaining adequate analgesia with IR opioid formulations. ER capsules are contraindicated for use on an as-needed basis.

ER capsules are not intended to be used as the first opioid product prescribed for a patient or in patients who require opioid analgesia for a short period of time.

ER capsules are for opioid-tolerant patients only. Use in nonopioid-tolerant patients may lead to fatal respiratory depression. Overestimating the ER capsule dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Because of the mean apparent 18-hour elimination half-life of ER capsules, patients who receive an overdose will require an extended period of monitoring and treatment that may go beyond 18 hours. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects.

Schedule II opioid agonists (eg, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone) have the highest risk of fatal overdoses because of respiratory depression, as well as the highest potential for abuse. ER capsules can be abused in a manner similar to other opioid agonists, legal or illicit. Consider these risks when administering, prescribing, or dispensing ER capsules in situations in which there is concern about increased risk of misuse, abuse, or diversion.

People at increased risk for opioid abuse include those with a personal or family history of substance abuse (ie, drug or alcohol abuse or addiction) or mental illness (eg, major depression). Assess patients for clinical risks for opioid abuse or addiction prior to prescribing opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

ER capsules are to be swallowed whole and not broken, chewed, opened, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed ER capsules or capsule contents can lead to the rapid release and absorption of a potentially fatal dose of hydromorphone. Overestimating the ER capsule dose when converting the patient from another opioid medication can result in fatal overdose with the first dose. With the long half-life of ER capsules (18 hours), patients who receive the wrong dose will require an extended period of monitoring and treatment that may go beyond 18 hours. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects.

Methadone:
To treat narcotic addiction in detoxification or maintenance programs, methadone should be dispensed only by hospitals, community pharmacies, and maintenance programs approved by the Food and Drug Administration (FDA) and designated state authorities. Approved maintenance programs shall dispense and use methadone in oral form only and according to treatment requirements stipulated in Federal Methadone Regulations. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of drug supply, revocation of program approval, and injunction precluding program operation.

Methadone, used as an analgesic, may be dispensed in any licensed pharmacy.

Methadone dispersible tablets are for oral administration only. This preparation contains insoluble excipients and therefore must not be injected. It is recommended that methadone dispersible tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Cardiac conduction effects: Laboratory studies, in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (more than 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Morphine:
Avinza: Avinza capsules are a modified-release formulation of morphine sulfate indicated for once-daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. Avinza capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The capsule beads are not to be chewed, crushed, or dissolved because of the risk of rapid release and absorption of a potentially fatal dose of morphine.

Astramorph PF, Duramorph, Infumorph: Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.

Infumorph: Infumorph is not recommended for single-dose intravenous (IV), intramuscular (IM), or subcutaneous administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Oxycodone:
Controlled-release (CR) oxycodone is an opioid agonist and a schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this when prescribing or dispensing oxycodone CR tablets in situations in which there is concern about an increased risk of misuse, abuse, or diversion.

Oxycodone CR tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone CR tablets are not intended for use as an as-needed analgesic.

Oxycodone 80 and 160 mg CR tablets are for use in opioid-tolerant patients only. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone CR tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed oxycodone CR tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

Propoxyphene:
Fatalities: Do not prescribe propoxyphene for patients who are suicidal or addiction-prone. Prescribe propoxyphene with caution to patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. Tell patients not to exceed the recommended dose and to limit alcohol intake.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In 1975, a survey was conducted of deaths due to overdosage; in approximately 20% of fatal cases, death occurred within the first hour (5% within 15 minutes). Propoxyphene should not be taken in higher doses than those recommended by the health care provider. Judicious prescribing of propoxyphene is essential for safety. Consider nonnarcotic analgesics for depressed or suicidal patients. Do not prescribe propoxyphene for suicidal or addiction-prone patients. Caution patients about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of added CNS depressant effects, cautiously prescribe with concomitant sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Advise patients of the additive depressant effects of these combinations. Many propoxyphene-related deaths have occurred in patients with histories of emotional disturbances, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs. Deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Do not exceed the recommended dosage.

VIII. Conclusion

Opioids are a class of medications that act on common receptors and are natural derivatives of morphine. Opioids are the most potent medications available for treatment of most types of severe pain. Opioids are also associated with many adverse effects, including abuse and addiction. It is estimated that one in five adult Americans experience chronic pain. Chronic non-cancer pain causes personal suffering, reduced productivity, and substantial health care costs.

The efficacy of opiates for non-cancer pain has been demonstrated in short-term trials but is highly variable for the long-term treatment of non-cancer pain. Guidelines for the management of non-cancer pain recommend opiates for moderate to severe pain. Guidelines for the management of cancer pain recommend

mild opiates for mild to moderate pain, and strong opiates for moderate to severe pain. Current guidelines for cancer and non-cancer pain do not give preference to one opiate over another.

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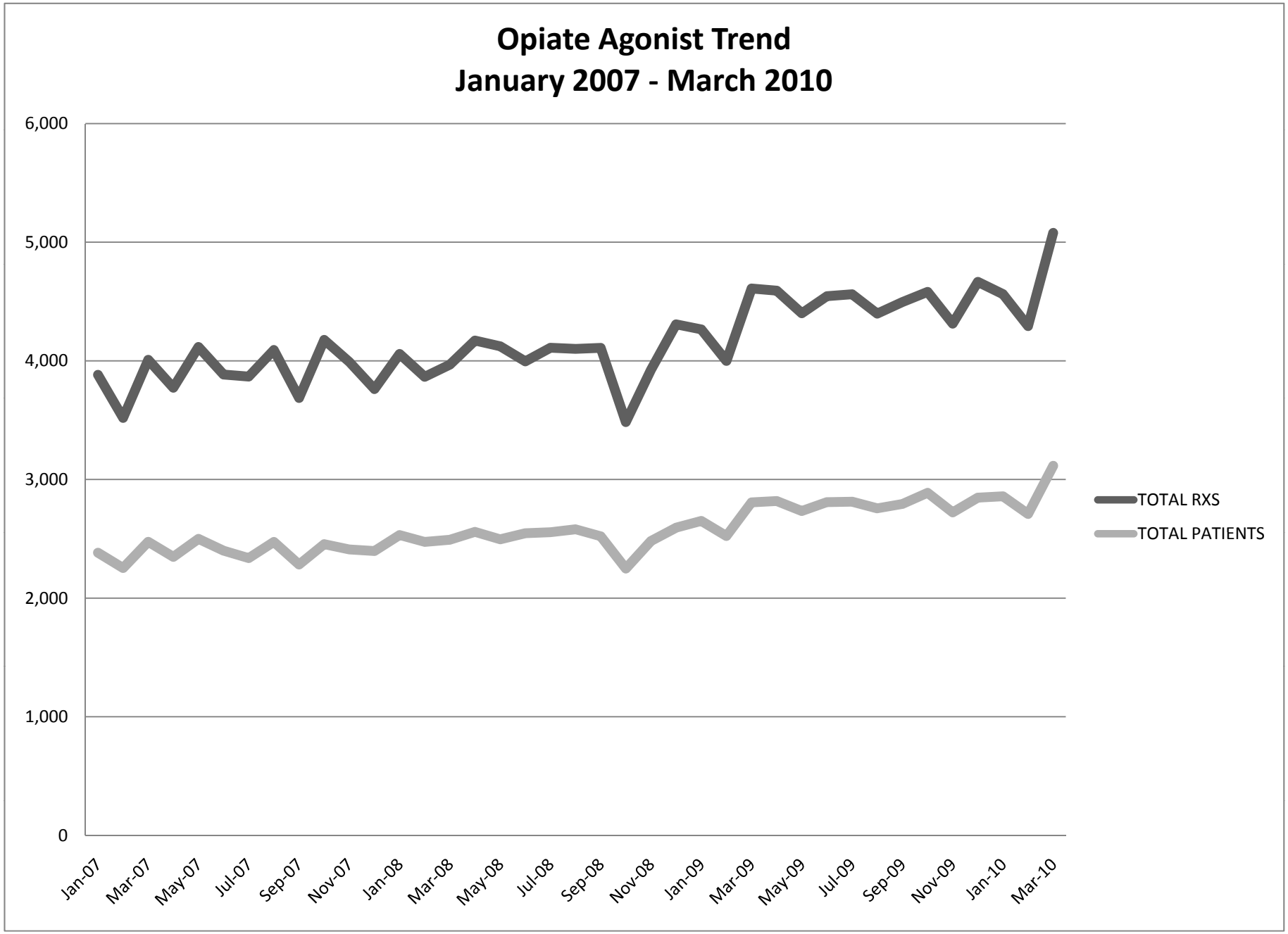
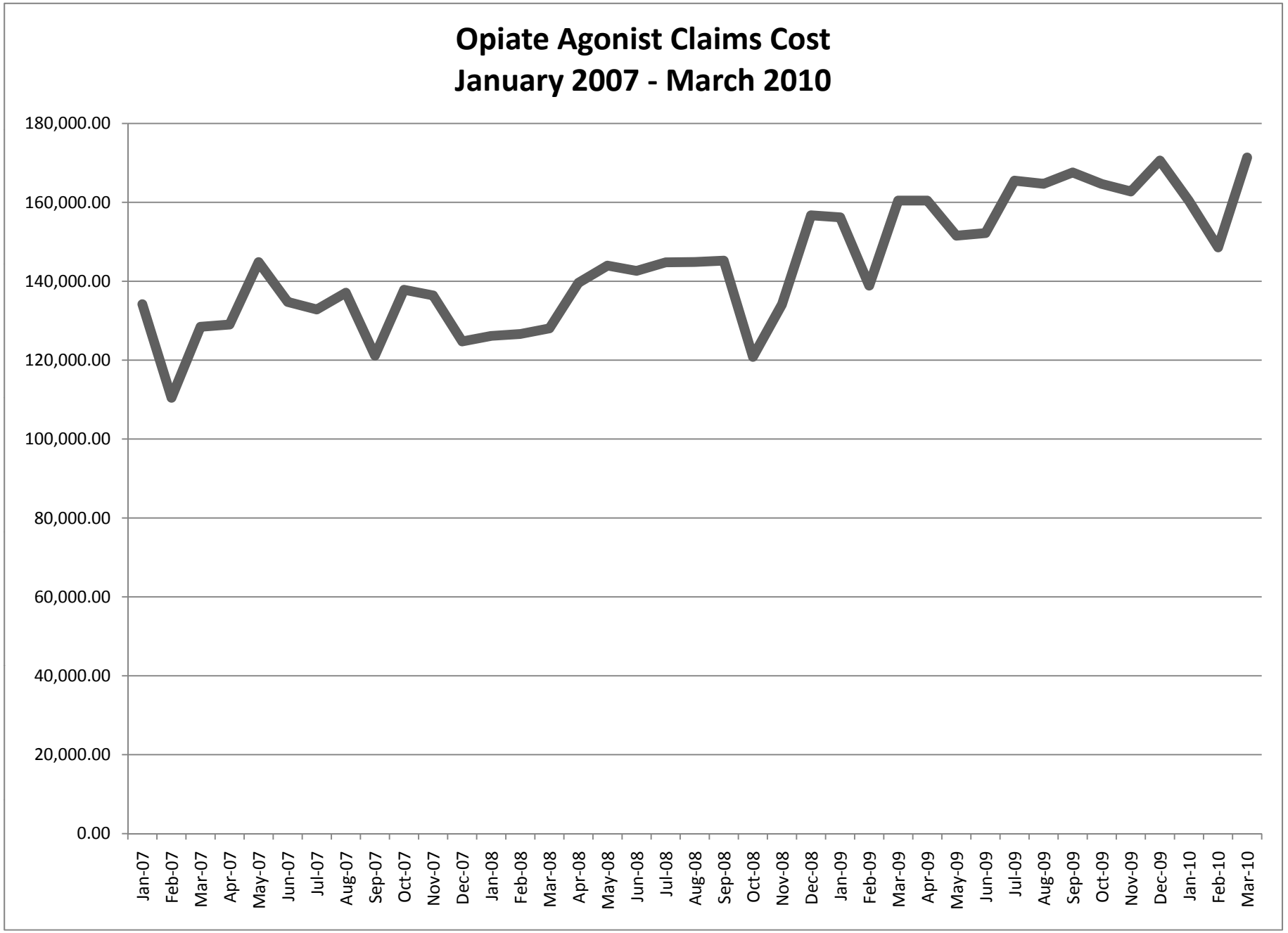
Opiate Agonist Utilization 04/08/09 to 04/07/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per script**
ACETAMINOPHEN-COD #2 TABLET	29	$220.11	$7.59
ACETAMINOPHEN-COD #3 TABLET	3928	$34,731.74	$8.84
ACETAMINOPHEN-COD #4 TABLET	16	$248.19	$15.51
ACETAMINOPHEN-CODEINE ELIXIR	1760	$14,990.41	$8.52
AVINZA 120 MG CAPSULE	9	$3,389.06	$376.56
AVINZA 30 MG CAPSULE	18	$2,219.15	$123.29
BELLADONNA-OPIUM 16.2-30 SUPP	6	$639.15	$106.53
BUTALBITAL COMP/COD #3 CAP	50	$2,252.78	$45.06
BUTALBITAL-CAFF-APAP-COD CAP	133	$3,033.14	$22.81
CODEINE SULFATE 30 MG TABLET	28	$997.12	$35.61
CODEINE SULFATE 60 MG TABLET	3	$335.35	$111.78
DARVON-N 100 MG TABLET	33	$5,683.58	$172.23
DEMEROL 50 MG/ML SYRINGE	2	$14.28	$7.14
DEMEROL 75 MG/ML SYRINGE	3	$19.47	$6.49
DILAUDID 2 MG TABLET	2	$23.50	$11.75
DURAGESIC 75 MCG/HR PATCH	1	$217.75	$217.75
EMBEDA 100-4 MG CAPSULE	8	$6,580.39	$822.55
EMBEDA 20-0.8 MG CAPSULE	20	$3,306.03	$165.30
EMBEDA 30-1.2 MG CAPSULE	6	$1,665.14	$277.52
EMBEDA 50-2 MG CAPSULE	4	$1,357.49	$339.37
EMBEDA 60-2.4 MG CAPSULE	7	$944.49	$134.93
EMBEDA 80-3.2 MG CAPSULE	2	$366.98	$183.49
ENDOCET 10-325 MG TABLET	135	$6,252.39	$46.31
ENDOCET 10-650 MG TABLET	33	$1,646.07	$49.88
ENDOCET 5-325 TABLET	97	$723.55	$7.46
ENDOCET 7.5-325 MG TABLET	27	$2,029.53	$75.17
ENDOCET 7.5-500 MG TABLET	15	$559.45	$37.30
ENDODAN 4.83-325 MG TABLET	16	$663.42	$41.46
FENTANYL 100 MCG/HR PATCH	224	$70,442.27	$314.47
FENTANYL 12 MCG/HR PATCH	77	$5,990.01	$77.79
FENTANYL 25 MCG/HR PATCH	323	$21,630.43	$66.97
FENTANYL 50 MCG/HR PATCH	252	$28,474.74	$113.00
FENTANYL 75 MCG/HR PATCH	194	$32,082.73	$165.37
FENTANYL CITRATE OTFC 200 MCG	2	$496.90	$248.45
HYDROCODONE BT-IBUPROFEN TAB	623	$19,726.55	$31.66
HYDROCODONE-APAP 10-325 TABLET	1978	$47,038.85	$23.78
HYDROCODONE-APAP 10-500 TABLET	1121	$16,930.69	$15.10
HYDROCODONE-APAP 10-650 TABLET	893	$9,059.33	$10.14
HYDROCODONE-APAP 10-660 TABLET	7	$163.20	$23.31
HYDROCODONE-APAP 10-750 TABLET	28	$697.00	$24.89
HYDROCODONE-APAP 2.5-500 TAB	52	$617.03	$11.87
HYDROCODONE-APAP 5-325 TABLET	3961	$52,164.92	$13.17
HYDROCODONE-APAP 5-500 TABLET	10562	$68,354.07	$6.47

Opiate Agonist Utilization 04/08/09 to 04/07/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per script**
HYDROCODONE-APAP 7.5-325 TAB	438	$9,328.39	$21.30
HYDROCODONE-APAP 7.5-500 MG/15	2347	$23,381.32	$9.96
HYDROCODONE-APAP 7.5-650 TAB	32	$537.68	$16.80
HYDROCODONE-APAP 7.5-750 TAB	198	$1,654.06	$8.35
HYDROMORPHONE 2 MG TABLET	146	$2,400.96	$16.44
HYDROMORPHONE 2 MG/ML VIAL	2	$24.50	$12.25
HYDROMORPHONE 3 MG SUPPOS	1	$82.02	$82.02
HYDROMORPHONE 4 MG TABLET	113	$2,749.37	$24.33
HYDROMORPHONE 8 MG TABLET	11	$900.25	$81.84
KADIAN 100 MG CAPSULE SR	1	$875.00	$875.00
KADIAN 80 MG CAPSULE SR	13	$4,900.40	$376.95
KADIAN ER 10 MG CAPSULE	3	$755.54	$251.85
KADIAN ER 20 MG CAPSULE	18	$4,666.38	$259.24
KADIAN ER 30 MG CAPSULE	21	$5,636.01	$268.38
KADIAN ER 50 MG CAPSULE	11	$4,983.63	$453.06
KADIAN ER 60 MG CAPSULE	3	$1,216.01	$405.34
KADIAN ER 80 MG CAPSULE	4	$1,584.04	$396.01
LORCET 10-650 TABLET	2	$197.20	$98.60
MAGNACET 10 MG-400 MG TABLET	1	$307.72	$307.72
MEPERIDINE 50 MG TABLET	61	$846.98	$13.88
MEPERITAB 100 MG TABLET	2	$18.51	$9.26
METHADONE 5 MG/5 ML SOLUTION	9	$497.41	$55.27
METHADONE HCL 10 MG TABLET	413	$9,803.94	$23.74
METHADONE HCL 5 MG TABLET	121	$1,167.93	$9.65
MORPHINE 10 MG/ML SYRINGE	22	$231.68	$10.53
MORPHINE 15 MG/ML VIAL	2	$30.98	$15.49
MORPHINE 2 MG/ML SYRINGE	2	$33.80	$16.90
MORPHINE 4 MG/ML SYRINGE	1	$8.29	$8.29
MORPHINE SULF 10 MG/5 ML SOLN	31	$598.17	$19.30
MORPHINE SULF 20 MG/5 ML SOLN	7	$111.25	$15.89
MORPHINE SULF ER 100 MG TABLET	52	$4,122.90	$79.29
MORPHINE SULF ER 15 MG TABLET	192	$4,977.35	$25.92
MORPHINE SULF ER 30 MG TABLET	328	$10,287.24	$31.36
MORPHINE SULF ER 60 MG TABLET	86	$4,440.65	$51.64
MORPHINE SULFATE 20 MG/ML SOLN	27	$650.93	$24.11
MORPHINE SULFATE 50 MG/ML VIAL	1	$48.75	$48.75
MORPHINE SULFATE IR 15 MG TAB	155	$1,700.54	$10.97
MORPHINE SULFATE IR 30 MG TAB	94	$2,600.31	$27.66
NUCYNTA 100 MG TABLET	13	$4,523.13	$347.93
NUCYNTA 50 MG TABLET	81	$12,612.59	$155.71
NUCYNTA 75 MG TABLET	34	$7,433.30	$218.63
OPANA 10 MG TABLET	51	$31,041.90	$608.66
OPANA 5 MG TABLET	16	$2,752.49	$172.03

Opiate Agonist Utilization 04/08/09 to 04/07/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per script**
OPANA ER 10 MG TABLET	97	$19,349.60	$199.48
OPANA ER 15 MG TABLET	14	$4,105.47	$293.25
OPANA ER 20 MG TABLET	78	$28,646.55	$367.26
OPANA ER 30 MG TABLET	15	$7,430.27	$495.35
OPANA ER 40 MG TABLET	69	$46,355.01	$671.81
OPANA ER 5 MG TABLET	9	$962.70	$106.97
OPANA ER 7.5 MG TABLET	2	$311.55	$155.78
ORAMORPH SR 60 MG TABLET	1	$39.55	$39.55
OXYCODONE HCL 10 MG TABLET	9	$514.55	$57.17
OXYCODONE HCL 15 MG TABLET	275	$13,324.33	$48.45
OXYCODONE HCL 20 MG ER TABLET	7	$489.61	$69.94
OXYCODONE HCL 20 MG/ML SOLN	2	$26.65	$13.33
OXYCODONE HCL 30 MG TABLET	39	$3,654.09	$93.69
OXYCODONE HCL 40 MG ER TABLET	3	$495.44	$165.15
OXYCODONE HCL 5 MG CAPSULE	435	$9,755.73	$22.43
OXYCODONE HCL 5 MG TABLET	1024	$23,667.59	$23.11
OXYCODONE HCL 5 MG/5 ML SOL	13	$207.57	$15.97
OXYCODONE HCL CR 10 MG TABLET	76	$5,619.92	$73.95
OXYCODONE HCL CR 20 MG TABLET	238	$35,279.57	$148.23
OXYCODONE HCL CR 40 MG TABLET	126	$31,467.70	$249.74
OXYCODONE HCL CR 80 MG TABLET	109	$40,351.20	$370.19
OXYCODONE-APAP 10-325 MG TAB	355	$18,341.39	$51.67
OXYCODONE-APAP 10-650 MG TAB	42	$1,692.60	$40.30
OXYCODONE-APAP 5-325 MG TAB	4017	$28,441.98	$7.08
OXYCODONE-APAP 5-500 MG CAP	279	$1,738.54	$6.23
OXYCODONE-APAP 7.5-325 MG TAB	73	$3,012.19	$41.26
OXYCODONE-APAP 7.5-500 MG TAB	25	$589.63	$23.59
OXYCODONE-ASA 4.5-0.38-325 TAB	1	$23.59	$23.59
OXYCONTIN 10 MG TABLET	399	$41,817.92	$104.81
OXYCONTIN 15 MG TABLET	50	$6,105.20	$122.10
OXYCONTIN 20 MG TABLET	643	$148,611.30	$231.12
OXYCONTIN 30 MG TABLET	186	$55,657.91	$299.24
OXYCONTIN 40 MG TABLET	482	$200,489.49	$415.95
OXYCONTIN 60 MG TABLET	125	$81,264.25	$650.11
OXYCONTIN 80 MG TABLET	167	$198,497.21	$1,188.61
OXYIR 5 MG CAPSULE	25	$763.24	$30.53
PANLOR DC CAPSULE	22	$1,203.85	$54.72
PERCOCET 2.5-325 MG TABLET	3	$325.13	$108.38
PERCOCET 5-325 MG TABLET	1	$43.73	$43.73
PROPOXYPHEN-APAP 100-650 MG TB	5168	$42,100.91	$8.15
PROPOXYPHENE HCL 65 MG CAP	379	$6,378.18	$16.83
PROPOXYPHENE-APAP 50-325 MG TB	10	$214.28	$21.43
ROXANOL 20 MG/ML SOLUTION	1	$19.75	$19.75

Opiate Agonist Utilization 04/08/09 to 04/07/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per script**
ROXICET 5-325 ORAL SOLUTION	13	$325.05	$25.00
ROXICET 5-325 TABLET	88	$598.55	$6.80
ROXICODONE 15 MG TABLET	1	$11.95	$11.95
ROXICODONE 30 MG TABLET	1	$4.57	$4.57
ROXICODONE 5 MG TABLET	3	$62.81	$20.94
RYZOLT ER 100 MG TABLET	1	$110.31	$110.31
RYZOLT ER 200 MG TABLET	2	$362.58	$181.29
TRAMADOL HCL 50 MG TABLET	6424	$59,633.53	$9.28
TRAMADOL HCL ER 100 MG TABLET	16	$1,426.11	$89.13
TRAMADOL HCL ER 200 MG TABLET	49	$8,169.11	$166.72
TRAMADOL-APAP 37.5-325 MG TAB	323	$10,237.85	$31.70
TYLENOL WITH CODEINE #3 TABLET	2	$14.00	$7.00
TYLOX 5-500 CAPSULE	10	$4,381.79	$438.18
ULTRAM 50 MG TABLET	2	$13.27	$6.64
ULTRAM ER 100 MG TABLET	110	$14,503.08	$131.85
ULTRAM ER 200 MG TABLET	159	$30,146.58	$189.60
ULTRAM ER 300 MG TABLET	236	$60,243.50	$255.27
VICODIN 5-500 TABLET	7	$33.65	$4.81
ZAMICET SOLUTION	40	$2,235.74	$55.89
Totals 14,588 recipients	**54,435**	**$1,937,600.88**	**2,402 prescribers**


Opiate Agonist Trend
January 2007 - March 2010
6,000
5,000
4,000
3,000
2,000
1,000
0
Jan-07
Mar-07
May-07
Jul-07
Sep-07
Nov-07
Jan-08
Mar-08
May-08
Jul-08
Sep-08
Nov-08
Jan-09
Mar-09
May-09
Jul-09
Sep-09
Nov-09
Jan-10
Mar-10
TOTAL RXS
TOTAL PATIENTS


Opiate Agonist Claims Cost
January 2007 - March 2010
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160,000.00
140,000.00
120,000.00
100,000.00
80,000.00
60,000.00
40,000.00
20,000.00
0.00
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
Sep-07
Oct-07
Nov-07
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Jan-10
Feb-10
Mar-10

Top Drugs by Dollar Total 2009
Reimbursed Amount > $1,000/Rx

Description	Rx Count	Dollar Total	Dollar/Rx
FEIBA VH IMMU 1,750-3,250 UNIT	10	$428,134.84	$42,813.48
NUTROPIN AQ PEN CARTRIDGE	146	$364,550.18	$2,496.92
PULMOZYME 1 MG/ML AMPUL	155	$304,166.97	$1,962.37
TOBI 300 MG/5 ML SOLUTION	101	$256,568.42	$2,540.28
ARCALYST 220 MG INJECTION	10	$222,007.50	$22,200.75
REMODULIN 10 MG/ML VIAL	11	$216,731.75	$19,702.89
OXYCONTIN 80 MG TABLET	168	$210,283.52	$1,251.69
LIORESAL IT 40 MG/20 ML KIT	145	$168,745.14	$1,163.76
ENBREL 50 MG/ML SURECLICK SYR	89	$165,714.67	$1,861.96
ATRIPLA TABLET	106	$164,244.67	$1,549.48
HUMIRA 40 MG/0.8 ML PEN	88	$156,790.20	$1,781.71
HELIXATE FS 1,000 UNIT VIAL	10	$156,348.82	$15,634.88
COPAXONE 20 MG INJECTION KIT	59	$154,162.84	$2,612.93
HUMATROPE 24 MG CARTRIDGE	29	$148,955.50	$5,136.40
REBIF 44 MCG/0.5 ML SYRINGE	57	$140,048.06	$2,456.98
BETASERON 0.3 MG KIT	54	$135,668.86	$2,512.39
HELIXATE FS 2,000 UNIT VIAL	2	$133,301.06	$66,650.53
XOLAIR 150 MG VIAL	57	$129,563.17	$2,273.04
HUMIRA 40 MG/0.8 ML SYRINGE	72	$124,001.39	$1,722.24
XENAZINE 25 MG TABLET	21	$119,577.80	$5,694.18
AVONEX PREFILLED SYR 30 MCG	44	$106,393.22	$2,418.03
RECOMBINATE 801-1,240 UNIT VL	5	$88,835.71	$17,767.14
GENOTROPIN 12 MG CARTRIDGE	31	$80,092.69	$2,583.64
ENBREL 50 MG/ML SYRINGE	46	$78,742.46	$1,711.79
VENTAVIS 10 MCG/1 ML SOLUTION	8	$72,699.65	$9,087.46
NUTROPIN AQ 5 MG/ML VIAL	24	$70,020.27	$2,917.51
SUPPRELIN LA 50 MG KIT	7	$69,696.75	$9,956.68
XELODA 500 MG TABLET	46	$67,862.30	$1,475.27
REVATIO 20 MG TABLET	35	$62,860.07	$1,796.00
NUTROPIN AQ 20 MG/2ML PEN CART	25	$61,988.84	$2,479.55
ZYVOX 600 MG TABLET	40	$61,596.40	$1,539.91
GLEEVEC 100 MG TABLET	10	$58,289.67	$5,828.97
KUVAN 100 MG TABLET	25	$56,704.56	$2,268.18
TRACLEER 125 MG TABLET	10	$54,039.70	$5,403.97
HUMATE-P 2,400 UNITS KIT	3	$53,369.95	$17,789.98
GENOTROPIN MINIQUICK 1 MG	40	$53,076.01	$1,326.90
GENOTROPIN 5 MG CARTRIDGE	44	$52,420.52	$1,191.38
TEV-TROPIN 5 MG VIAL	6	$49,999.62	$8,333.27
GENOTROPIN MINIQUICK 2 MG	14	$47,815.96	$3,415.43
ENBREL 25 MG KIT	30	$46,251.37	$1,541.71
RECOMBINATE 401-800 UNIT VIAL	5	$44,038.81	$8,807.76
PEGASYS 180 MCG/0.5 ML CONV.PK	23	$43,428.34	$1,888.19
HUMATROPE 12 MG CARTRIDGE	16	$38,235.09	$2,389.69
VALCYTE 450 MG TABLET	17	$33,756.20	$1,985.66

Top Drugs by Dollar Total 2009
Reimbursed Amount > $1,000/Rx

Description	Rx Count	Dollar Total	Dollar/Rx
XYREM 500 MG/ML ORAL SOLUTION	21	$33,444.30	$1,592.59
NEUPOGEN 300 MCG/ML VIAL	18	$26,627.68	$1,479.32
GLEEVEC 400 MG TABLET	8	$25,056.01	$3,132.00
REMODULIN 5 MG/ML VIAL	4	$24,082.48	$6,020.62
SIMPONI 50 MG/0.5 ML PEN INJEC	13	$23,460.95	$1,804.69
HUMIRA CROHN'S STARTER PACK	5	$22,800.36	$4,560.07
NEXAVAR 200 MG TABLET	4	$22,662.48	$5,665.62
MEPRON 750 MG/5 ML SUSPENSION	18	$21,234.79	$1,179.71
NORDITROPIN NORDIFLX 15 MG/1.5	7	$21,211.90	$3,030.27
VENTAVIS 10 MCG/1 ML SOLUTION	2	$20,342.37	$10,171.19
PANCRECARB MS-16 CAPSULE EC	13	$20,259.24	$1,558.40
TOBI 300 MG/5 ML SOLUTION	5	$19,066.32	$3,813.26
DESOXYN 5 MG TABLET	18	$18,154.08	$1,008.56
CAFFEINE CIT 20 MG/ML ORAL SOL	18	$18,052.12	$1,002.90
TRIZIVIR TABLET	13	$17,618.62	$1,355.28
LUPRON DEPOT 11.25 MG 3MO KIT	9	$17,269.54	$1,918.84
GENOTROPIN MINIQUICK 1.6 MG	6	$16,897.11	$2,816.19
LUPRON DEPOT-PED 11.25 MG KIT	12	$16,744.23	$1,395.35
LOVENOX 150 MG PREFILLED SYR	6	$16,168.65	$2,694.78
ZYVOX 600 MG TABLET	6	$15,828.01	$2,638.00
KINERET 100 MG/0.67 ML SYR	11	$15,386.29	$1,398.75
VFEND 40 MG/ML SUSPENSION	11	$15,375.95	$1,397.81
GENOTROPIN MINIQUICK 0.8 MG	10	$14,153.24	$1,415.32
ORENCIA 250 MG VIAL	8	$14,097.66	$1,762.21
SENSIPAR 90 MG TABLET	13	$13,882.92	$1,067.92
GENOTROPIN MINIQUICK 1.8 MG	4	$12,931.56	$3,232.89
HUMATROPE 5 MG VIAL	10	$12,899.26	$1,289.93
APTIVUS 250 MG CAPSULE	12	$12,709.04	$1,059.09
PROCRIT 20,000 UNITS/ML VIAL	5	$12,332.90	$2,466.58
REBIF TITRATION PACK	5	$12,271.43	$2,454.29
REMODULIN 2.5 MG/ML VIAL	3	$12,043.00	$4,014.33
ARANESP 300 MCG/0.6 ML SYRINGE	5	$11,614.68	$2,322.94
CUBICIN 500 MG VIAL	5	$11,424.50	$2,284.90
CIMZIA KIT	5	$10,900.21	$2,180.04
HUMATE-P 1,200 UNITS KIT	1	$10,715.31	$10,715.31
PROGRAF 5 MG CAPSULE	4	$10,555.88	$2,638.97
VFEND 200 MG TABLET	6	$10,390.13	$1,731.69
GENOTROPIN MINIQUICK 1.4 MG	2	$9,948.86	$4,974.43
DRONABINOL 10 MG CAPSULE	8	$9,803.00	$1,225.38
TEMODAR 140 MG CAPSULE	9	$9,737.28	$1,081.92
TEMODAR 180 MG CAPSULE	4	$9,384.36	$2,346.09
ARANESP 60 MCG/ML VIAL	7	$9,246.68	$1,320.95
TEMODAR 250 MG CAPSULE	7	$9,152.13	$1,307.45
PEGINTRON REDIPEN 120 MCG	5	$9,105.12	$1,821.02
PEGINTRON REDIPEN 150 MCG	4	$8,919.58	$2,229.90

Top Drugs by Dollar Total 2009
Reimbursed Amount > $1,000/Rx

Description	Rx Count	Dollar Total	Dollar/Rx
ULTRASE MT 20 CAPSULE EC	6	$7,875.47	$1,312.58
TEMODAR 140 MG CAPSULE	1	$7,751.57	$7,751.57
ARANESP 200 MCG/0.4 ML SYRINGE	7	$7,724.98	$1,103.57
SUTENT 50 MG CAPSULE	1	$7,656.81	$7,656.81
TARCEVA 100 MG TABLET	2	$6,976.72	$3,488.36
VANCOCIN HCL 250 MG PULVULE	4	$6,963.51	$1,740.88
SPRYCEL 50 MG TABLET	1	$6,799.62	$6,799.62
NEULASTA 6 MG/0.6 ML SYRINGE	2	$6,743.48	$3,371.74
SPRYCEL 70 MG TABLET	1	$6,739.25	$6,739.25
NEUMEGA 5 MG VIAL	2	$6,582.38	$3,291.19
HUMIRA PSORIASIS STARTER PACK	2	$6,527.61	$3,263.81
PANCRECARB MS-16 CAPSULE EC	5	$6,454.45	$1,290.89
INVEGA SUSTENNA 234 MG PREF SY	4	$6,375.12	$1,593.78
LUPRON DEPOT-PED 15 MG KIT	4	$6,121.18	$1,530.30
SUCRAID 8,500 UNITS/ML SOLN	1	$6,073.96	$6,073.96
EXJADE 500 MG TABLET	1	$6,003.34	$6,003.34
CANCIDAS IV 50 MG VIAL	2	$5,298.92	$2,649.46
BENEFIX 500 UNIT VIAL	2	$4,811.00	$2,405.50
BOTOX 100 UNITS VIAL	4	$4,697.15	$1,174.29
BETASERON 0.3 MG KIT	2	$4,448.56	$2,224.28
INVEGA SUSTENNA 156 MG PREF SY	4	$4,255.36	$1,063.84
LUPRON DEPOT-PED 11.25 MG KIT	3	$4,131.24	$1,377.08
HUMATE-P 600 UNITS KIT	1	$4,107.35	$4,107.35
LUPRON DEPOT 11.25 MG 3MO KIT	3	$4,017.09	$1,339.03
NEUPOGEN 480 MCG/1.6 ML VIAL	1	$3,857.50	$3,857.50
ARIXTRA 10 MG SYRINGE	1	$3,811.04	$3,811.04
TEMODAR 100 MG CAPSULE	1	$3,622.00	$3,622.00
CAFCIT 20 MG/ML ORAL SOLN	3	$3,524.25	$1,174.75
THALOMID 50 MG CAPSULE	1	$3,399.15	$3,399.15
GENOTROPIN MINIQUICK 0.6 MG	3	$3,206.81	$1,068.94
NEUPOGEN 300 MCG/0.5 ML SYR	3	$3,154.44	$1,051.48
FEIBA VH IMMUNO 651-1,200 UNIT	1	$3,032.21	$3,032.21
NAGLAZYME 5 MG/5 ML VIAL	1	$2,992.18	$2,992.18
NEUPOGEN 300 MCG/ML VIAL	2	$2,820.26	$1,410.13
COLISTIMETHATE 150 MG VIAL	2	$2,769.50	$1,384.75
NEUMEGA 5 MG VIAL	1	$2,743.45	$2,743.45
ELAPRASE 6 MG/3 ML VIAL	2	$2,706.56	$1,353.28
TARCEVA 25 MG TABLET	2	$2,434.55	$1,217.28
PEGINTRON 150 MCG KIT	1	$2,298.82	$2,298.82
EPOGEN 10,000 UNITS/ML VIAL	2	$2,156.65	$1,078.33
TEMODAR 250 MG CAPSULE	1	$2,090.94	$2,090.94
PULMOZYME 1 MG/ML AMPUL	1	$1,861.11	$1,861.11
OCTREOTIDE ACET 200 MCG/ML VL	1	$1,355.09	$1,355.09
PROGRAF 1 MG CAPSULE	1	$1,332.16	$1,332.16
ARANESP 60 MCG/0.3 ML SYRINGE	1	$1,298.49	$1,298.49

Top Drugs by Dollar Total 2009
Reimbursed Amount > $1,000/Rx

Description	Rx Count	Dollar Total	Dollar/Rx
VFEND 50 MG TABLET	1	$1,251.66	$1,251.66
RABAVERT RABIES VACCINE KIT	1	$1,112.31	$1,112.31
AZACTAM 1 GM VIAL	1	$1,095.96	$1,095.96
Totals	**2,414**	**$6,262,804.94**	**$2,594.37**

South Dakota Department of Social Services
Pharmacotherapy Review
Metozolv® ODT
June 11, 2010

I. Overview

Metozolv is a dopamine receptor antagonist indicated for the short-term (4-12 weeks) relief of symptomatic gastroesophageal reflux in patients who fail to respond to conventional therapy. Metozolv is also indicated for the relief of symptoms in adults associated with acute and recurrent diabetic gastroparesis (gastric stasis).

II. Pharmacology

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. While its mode of action is unclear, it appears to sensitize tissues to the action of acetylcholine. Metoclopramide increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter.

The onset of pharmacological action of metoclopramide is 30 to 60 minutes following an oral dose; pharmacological effects persist for 1-2 hours. In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure) single oral doses of metoclopramide produce dose-related increases in LESP. The increase in LESP from a 5mg dose lasts about 45 minutes and that of a 20mg dose lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10mg.

III. Pharmacokinetics

In a randomized, two-arm, two-way crossover study in 44 healthy adult fasted subjects, Metozolv ODT was bioequivalent to Reglan Tablets.

In a food-effect study with 28 subjects, Metozolv ODT taken immediately after a high-fat meal had a 17% lower peak blood level than when taken after an overnight fast. The time to peak blood levels increased from about 1.75 hours under fasted conditions to 3 hours when taken immediately after a high-fat meal. The extent of metoclopramide absorbed was comparable whether taken with or without food.

Adult Pharmacokinetic Data

Parameter	Value
VD (L/kg)	~3.5
Plasma Protein Binding	~30%
T ½	5-6 hours
Oral Bioavailability	80%±15.5%

IV. Contraindications

- Intestinal obstruction, hemorrhage, or perforation
- Pheochromocytoma
- Known sensitivity or intolerance
- Epilepsy
- Concomitant medication with extrapyramidal reactions

V. Warnings/Precautions

- Tardive dyskinesia
- Acute dystonic reactions, drug-induced parkinsonism, and other extrapyramidal symptoms
- Neuroleptic Malignant Syndrome (NMS)
- Depression
- Hypertension
- Congestive Heart Failure and Ventricular Arrhythmia
- Withdrawal from metoclopramide

Warning: Tardive Dyskinesia
Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

VI. Drug Interactions

- Anticholinergic drugs-antagonize effects of metoclopramide
- Narcotic analgesic drugs-may increase sedation
- Monoamine oxidase inhibitors-may cause hypertensive crisis (due to catecholamine release)
- Altered drug absorption-may decrease absorption of drugs from the stomach and increase absorption of drugs from the small bowel
- Insulin-changes in food transit time may require adjustment of insulin dose or timing to avoid hypoglycemia
- Antidepressants, Antipsychotics, and Neuroleptics-concomitant use with metoclopramide is associated with increased risk of tardive dyskinesia and NMS

VII. Adverse Reactions

The most common adverse reactions (>2%) are headache, nausea, vomiting, fatigue, and somnolence.

VIII. Dosage and Administration

Gastroesophageal Reflux Disease: 10-15mg dose up to four times daily at least 30 minutes before eating and at bedtime.

Diabetic Gastroparesis (Diabetic Gastric Stasis): 10mg dose four times daily at least 30 minutes before eating and at bedtime for two to eight weeks.

IX. Conclusion

Metozolv is indicated for the short-term (4-12 weeks) relief of symptomatic gastroesophageal reflux who fail to respond to conventional therapy and for the relief of symptoms in adults associated with acute and recurrent diabetic gastroparesis (gastric stasis). The estimated acquisition cost of Metozolv for a month's supply is approximately 142 dollars compared to 14 dollars for metoclopramide.

References

1. Metozolv® Prescribing Information, September 2009, Salix Pharmaceuticals, Inc.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.