Pharmacy Benefits Management and Medical Advisory Panel
Drug Class Review
Selective Serotonin Reuptake Inhibitors

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OBJECTIVES

1. To review the efficacy, safety, and administration of the currently available selective serotonin reuptake inhibitors (SSRIs).

Table 1. Agents Available in U.S.

Generic Name	Trade Name®	Manufacturer
Fluoxetine	Prozac	Lilly
Sertraline	Zoloft	Pfizer
Paroxetine	Paxil	SmithKline Beecham
	Luvox	Solvay

2. To present criteria for determining the formulary status of selective serotonin reupake inhibitors for the Veterans Health Administration National Drug Formulary.

I. INDICATIONS

There are currently three main indications for the use of SSRIs: major depression, obsessive compulsive disorder (OCD) and panic disorder. Recently, fluoxetine was approved for the treatment of bulimia nervosa.

Table 2. FDA Approved Indications

Generic Name	Major depression	Obsessive-compulsive Disorder	Panic disorder
Fluoxetine	Yes	Yes	No
Sertraline	Yes	Yes	Yes
Paroxetine	Yes	Yes	Yes
	No	Yes	No

II. PHARMACOLOGY[1]

The effects of SSRIs in depression, obsessive-compulsive disorder and panic disorder are thought to be through increasing serotonergic activity in the central nervous system by inhibiting serotonin reuptake into the presynaptic terminal. More recently, another mechanism of action has been proposed that involves delayed desensitization of the serotonin autoreceptor. This results in an increase in serotonin release and transmission. Unlike many of the other antidepressants, the SSRIs have minimal or no effect on the reuptake of norepinephrine or dopamine and do not exhibit significant anticholinergic, antihistaminic or α_1-adrenergic blocking activity.

III. PHARMACOKINETICS [2,3]

Table 3. Pharmacokinetic Comparisons of SSRIs

	FLUOXETINE	SERTRALINE	PAROXETINE	
Absorption F (%)	72-90	80-95	>90	94
Tmax (hrs)	6-8	4-9	3-8	3-8
Effect of food on absorption	None	Small ↑ Cmax and AUC	None	None
Volume of distribution (l/kg)	25	25	13	25
Protein binding	>95% (AAG)[a]	>95% (AAG)[a]	>95% (AAG)[a]	77% (albumin)
Active metabolite	Yes	Yes (very weak)	No	No
HALF-LIFE (hrs)	4-6days 4-16days (metabolite)	26	21	15
Effected by patient age	Yes	Yes	Yes	No

[a](AAG) alpha -1-acid glycoprotein

IV. CLINICAL EFFICACY

A. Treatment of major depression [4-23]

Treatment of major depression can be divided into 3 phases: acute, continuation and maintenance. The acute phase lasts about 12 weeks and involves stabilizing the acute symptoms. Once a patient is stabilized, they are said to enter the continuation phase which usually involves an additional 3-6 months of therapy. This phase represents how long a depressive episode would have lasted had there been no treatment and the goal is to prevent relapse. Lastly, the goal of the maintenance phase is to prevent a new depressive episode. Treatment can continue for a year or more. The optimal duration of maintenance therapy has not been determined for any antidepressant.

Several placebo controlled and active comparator controlled trials have shown the SSRIs to be effective in acute treatment of major depression. The focus of this review will be on randomized double-blind trials comparing the SSRIs to each other in **acute** treatment of major depression and is summarized in **Table 4**. These studies generally excluded patients who were on concomitant psychotropics, had other Axis I diagnosis, severe medical diseases, were at high suicide risk, were pregnant or nursing or who had a response during the placebo run-in phase.

There are few randomized double-blind studies with SSRIs looking at the continuation or maintenance phase**.** Most of the studies compared SSRIs to placebo or an active comparator such as imipramine. There are 2 head-to-head trials, one with sertraline vs. fluoxetine and the other with sertraline vs. . These long-term studies are summarized in **Table 5**.

B. Treatment of obsessive-compulsive disorder [24-32]

The overall goals of treatment are to decrease the frequency and severity of obsessions and compulsions and improve the patient's functioning. OCD management can also be divided into 3 treatment phases: acute, continuation and maintenance. There are no studies comparing the SSRIs to each other however they have been studied in a randomized double-blind fashion comparing them to either placebo or clomipramine for **acute** treatment **(Table 6)**. Patients were generally excluded if they had other psychiatric illnesses, significant medical diseases, were receiving concomitant psychotropic medications, were pregnant/nursing, or had a response during the placebo run-in phase. There are 2 studies evaluating continuation therapy, one with sertraline and the other with fluoxetine.

C. Treatment of panic disorder [33-41]

Panic disorder also has an acute, continuation and maintenance treatment phase. The acute phase lasts for about 2-3 months. The continuation phase lasts 2-6 months after the acute phase and is for prolonging the benefits seen in the acute phase. The goal of maintenance phase is to encourage recovery to normal activities and can last for 1 year. The majority of the randomized double-blind studies were done with and paroxetine and compared them to placebo or an active comparator **(Table 7)**. Smaller trials with less than 50 patients are not presented in this review. There is only 1 long-term controlled study that compared paroxetine to placebo or clomipramine. These trials also excluded patients as described for depression and OCD.

D. Treatment of bulimia nervosa [42-45]

Fluoxetine was found to be beneficial for treating bulimia in two 8-week and one 16-week randomized double-blind placebo controlled studies. The two 8-week studies compared fluoxetine 20mg and 60mg to placebo. The 60mg dose was superior to placebo and the 20mg dose had an effect intermediate effect between that of placebo and 60mg. The 16 week study compared fluoxetine 60mg to placebo. Fluoxetine 60mg significantly reduced vomiting and binge-eating episodes when compared to placebo. has been found to be superior to placebo in preventing relapse in patients successfully treated with behavior psychotherapy.

E. Other uses

Posttraumatic stress disorder (PTSD)[46-55]

The SSRIs are used in the treatment of both combat-related and civilian PTSD. All 4 of the SSRIs have been studied in open-label trials and have shown an improved outcome in PTSD symptoms. There is one randomized double-blind study comparing fluoxetine to placebo in a veteran and civilian population. Fluoxetine decreased PTSD symptomatology using the Clinician Administered PTSD Scale. The civilian group and patients without chronic treatment histories had a better response. There is a second, recently completed, placebo controlled trial with fluoxetine, currently under review and a large double-blind multicenter controlled trial with sertraline that is currently ongoing.[54]

Social phobia [56-62]

All of the SSRIs have been studied for use in social phobia either in case reports or small open-label trials. Additionally, and sertraline have been compared to placebo in 2 small trials. The response rates ranged from 62-90% (fluoxetine), 58-80% (sertraline), 77-83% (paroxetine) and 47% (). These studies utilized different outcome measurement scales and included only patients who completed the trials for the efficacy evaluation. The duration of these studies ranged from 6-18 weeks.

Headache [63-66]

, paroxetine and fluoxetine have been studied in randomized controlled trials for the treatment of chronic headache. Additionally, fluoxetine has been studied in migraine headaches. These trials showed a beneficial effect though more trials are needed.

Premenstrual syndrome (PMS) [67-73]

Several small, randomized, placebo-controlled studies evaluated fluoxetine for symptoms associated with PMS. Fluoxetine, sertraline and paroxetine have each been evaluated in a larger trial comparing them to placebo or active comparator (maprotiline). In all these studies, reduction of symptoms was significantly superior with the SSRIs than with placebo.

Table 4. Acute treatment of major depression[a]

CLINICAL TRIAL	INCLUSION	DAILY DOSE	MEASURED OUTCOMES	RESULTS
Tignol [4] RDB, multicenter **Fluoxetine vs. paroxetine** N=176 Intention-to-treat 6 weeks	Major depression (DSM-III-R) Inpatients MADRS≥24	3-7 day placebo run-in fluoxetine 20mg and paroxetine 20mg	≥50% ↓ of MADRS from baseline and final score ≤11. CGI 1 or 2 ≥50% ↓ of HAM-A from baseline	Fluoxetine=paroxetine in efficacy Slightly more AE in fluoxetine group(not significant). More wt loss in fluox group(P=0.05)
Schone[5] RDB, multicenter **Fluoxetine vs. paroxetine** N=106 Intention-to–treat 6 weeks	Major depression (DSM-III-R) Geriatric outpatients 17 item HAM-D ≥18	3-7 day placebo run-in fluoxetine 20mg/paroxetine 20mg at week 1 fluoxetine 40mg/paroxetine 30mg at week 2 thereafter, can adjust fluoxetine to 20-60mg and paroxetine to 20-40mg	≥50% ↓ of HAM-D and MADRS score from baseline final HAM-D≤11 CGI≤2 SCAG MMSE	Paroxetine>fluoxetine as measured by ≥50% ↓ in HAM-D and MADRS Paroxetine=fluoxetine (HAM-D≤11 and CGI≤2) Paroxetine=fluoxetine (MMSE and SCAG), but earlier response seen with paroxetine Paroxetine=fluoxetine(AE)
Gagiano[6] RDB **Fluoxetine vs. paroxetine** N=90 Intention-to-treat 6 weeks	Major depression(DSM-III-R) 21 item HAM-D ≥ 18 outpatients	1 week placebo run-in fluoxetine 20mg/paroxetine 20mg at week 1. Fluoxetine 40mg/paroxetine 30mg at week 2. Thereafter can adjust fluoxeetine 20-60mg and paroxetine 20-40mg	≥ 50% ↓ of HAM-D from baseline, total score ≤ 14 MADRS CGI severity of illness 1-2 HAMA psychic and somatic subfactors	Fluoxetine = paroxetine in all efficacy parameters # and nature of AEs similar
DeWilde[7] RDB, multicenter **Fluoxetine vs. paroxetine** N=78 Intention-to-treat 6 weeks	Major depression (DSM-III-R) 21 item HAM-D ≥ 18	1 week placebo run-in paroxetione 20mg/fluoxetine20mg at week 1 paroxetine 30mg/fluoxetine 40mg at week 2 may ↑ to max dose of paroxetine 40mg and fluoxetine 60mg	≥50% ↓ of HAM-D from baseline and total score ≤14 ≥50% ↓ of MADRS from baseline and total ≤12 CGI≤2 SCL-58	Fluoxetine=paroxetine in efficacy however an earlier response was seen with paroxetine. No difference in AE between groups except more sweating seen with fluoxetine.
Ontiveros[8] RDB, 2-centers **Fluoxetine vs. paroxetine** N= 121 Intention-to-treat 6 weeks	Major depression (DSM-III-R) 21 item HAM-D ≥ 18 outpatients	3-7 day placebo run-in fluoxetine20mg/paroxetine 20mg once daily	≥ 50% ↓ in HAM-D from baseline CGI-severity and improvement	Fluoxetine=paroxetine in all efficacy parameters except subfactor score for sleep disturbance better with paroxetine. 93% paroxetine vs 76% fluoxetine patients rated their tx as successful
Aguglia[9] Double-blind, multicenter **Sertraline vs. fluoxetine** N=88 8 weeks	Major depression (DSM-III-R) 17 item HAM-D≥18	1 week placebo run-in sertraline 50mg/fluoxetine 20mg x 2 weeks. Thereafter, can ↑ to max dose of sertraline 150mg and fluoxetine 60mg	HAM-D, HAM-A, MADRS CGI-improvement and severity Zung Self Rating for Anxiety Change from baseline for above scales	Sertraline=fluoxetine in all efficacy parameters. Incidence of AE same in both groups however sertraline>fluoxetine were described as mild.
Bennie[10] RDB, multicenter **Sertraline vs. fluoxetine** N=248 Intention-to-treat 6 weeks	Major depression (DSM-III-R) single or recurrent 17 item Ham-D≥ 18	1-2 week placebo run-in sertraline 50mg/fluoxetine 20mg for 2 weeks. Thereafter , may ↑ to sertraline 100mg and fluoxetine 40mg.	≥50% ↓ in HAM-D and HAM-A score from baseline CGI score ≤2	Sertraline=fluoxetine in efficacy and AE's Majority of patients were treated with starting dose in both groups.
Van Moffaert [11] RDB, multicenter **Sertraline vs. fluoxetine** N=165 Intention-to-treat 8 weeks	Major depression(DSM-III-R) Single or recurrent Inpatient and outpatient 17 item HAM-D ≥ 18 CGI ≥3	1-2 week placebo run-in sertraline 50mg/fluoxetine 20mg. May ↑ to sertaline 100mg or fluoxetine 40mg if no significant improvement after 4 weeks	≥50% ↓in HAM-D or MADRS score from baseline or ≤ to 10 on HAM-D CGI-improvement and severity of 1-2	Sertraline = fluoxetine in efficacy an in incidence of AE

Zanardi[12] RDB **Sertraline vs. paroxetine** N=46 6 weeks	Major depression with mood-congruent or mood-incongruent psychotic features (DSM-III-R)	7 day placebo run-in sertraline 50mg/paroxetine 20mg on days 1-3 sertraline 100mg/paroxetine 40mg on days 4-7 Sertaline 150mg/paroxetine 50mg after day 8	HAM-D <8 Dimensions of delusional experience rating scale=0	46% drop-out rate with paroxetine vs. 0% with sertraline. Paroxetine=sertraline in efficacy among those completing study. Sertraline>paroxetine in efficacy(intent-to-treat data)
Ansseau[13] DB, multicenter **vs. paroxetine** N=120 Intention-to-treat 6 weeks	Major depression(DSM-III-R) 21 item HAM-D $\geq$ 18 inpatients and outpatients	1 week placebo run-in 50mg x 1 week. Then $\uparrow$ 100mg. May $\uparrow$ to 200mg if no response. Paroxetine 20mg x 2 weeks. May $\uparrow$ to 30mg if no response	$\geq$50% in HAM-D from baseline HAM-A CGI- severity and improvement	=paroxetine in all efficacy parameters. No difference seen between inpatients and outpatients. Overall incidence of AE similar in both groups, however more drop-outs due to AE with
Rapaport[14] RDB **vs. fluoxetine** N=100 Intention-to-treat 7 weeks	Major depression (DSM-III-R) 21 item HAM-D$\geq$21 $\geq$2 on depressed mood item of HAM-D	2 week placebo run-in 50mg, 100mg at week 1 and 2 respectively can $\uparrow$ up to 150mg. Fluoxetine 20mg at week 1 and 2. May $\uparrow$ to max of 80mg.	Change in scores from baseline for HAM-D, CGI-severity and improvement HAM-A	=fluoxetine in efficacy More reports of AE in fluoxetine vs. (not significant)
Kiev[15] RDB, 2 centers **vs. paroxetine** N=58 Intention-to-treat 7 weeks	Major depression (DSM-III-R) Outpatients 21 item HAM-D $\geq$20 "depressed mood" item of HAM-D $\geq$2	1 week placebo run-in 50mg, can $\uparrow$ to 100mg at week 1 visit and 150mg at week 2 visit paroxetine 20mg, can $\uparrow$ to 30mg at week 1 visit, 40mg at week 2 visit and 50mg at week 3 visit	HAM-D HAM-A CGI-severity SCL-56 Change from baseline for above scales	=paroxetine in efficacy Incidence of AE same in both groups, however AE profile differed.

[a]RDB=randomized double-blind; MADRS=Montgomery-Ashberg Depression Scale; CGI=Clinical global Impression; HAM-D=Hamilton Rating Scale for Depression; HAM-A=Hamilton Rating Scale for Anxiety; SCL-56=Hopkins symptoms checklist; SCAG=Sandoz Clinical Assessment Geriatric Scale; MMSE=Mini-mental. AE=adverse event

Table 5. Long-term treatment of major depression[a]

CLINICAL TRIAL	INCLUSION	DURATION	ASSESSMENTS	RESULTS
Montgomery[16] RDB, multicenter **Fluoxetine vs placebo** N=182	Patients who had no relapses and HAM-D ≤8 at end of 18 weeks open continuation trial with fluoxetine	1 year trial evaluating maintenance therapy	HAM-D>18 CGI	Recurrence occurred in 26% of fluoxetine vs. 57% of placebo patients. Recurrence occurred later in fluoxetine group
Doogan[17] RDB, multicenter **Sertraline vs. placebo** N=300 Intention-to-treat	Patients who responded to open label acute treatment with sertraline with CGI improvement score of 1-2	44 week trial evaluating continuation and maintenance	CGI severity score>3 HAM-D≥17	Relapse occurred in 13% of setraline vs 46% of placebo patients AE similar in both groups
Ohrberg[18] DB **Paroxetine vs. imipramine** N=96 Intention-to-treat	Patients responding to acute treatment in trial with paroxetine vs imipramine	7 month trial evaluating continuation	HAM-D≥15	Relapse occurred in 10% of paroxetine vs. 14% of imipramine patients. AE improved over time in paroxetine group and not in imipramine group
Montgomery[19] RDB, multicenter **Paroxetine vs. placebo** N=135	Patients responding to 8 week acute treatment with paroxetine. HAM-D≤8 Pts. had ≥ 3 depressive episodes in the 4 years prior to entering acute study.	1 year trial evaluating continuation and maintenance	CGI severity ≥4 Deterioration of CGI≥2 points since previous visit Depressive symptoms for ≥7days DSM-III-R criteria for depression for > 2 weeks.	3% paroxetine vs. 19.4% placebo patients relapsed. 13.6% vs. 29.6% of patients had a recurrence. Incidence of AEs similar in both groups.
Claghorn[20] Double-blind, multicenter **Paroxetine vs. imipramine vs. placebo** N=219 Intention-to-treat	HAM-D score≤10 after 6 weeks of acute therapy with paroxetine, imipramine or placebo	1 year trial evaluating continuation and maintenance	HAM-D≥18 HAM-D depressed mood item and retardation item CGI	15% of paroxetine vs. 4% of imipramine vs. 25% of placebo initial responders relapsed. 35% (imipramine) and 15% (paroxetine) and 10% (placebo) dropped out due to AE
Van Moffaert[11] RDB, multicenter **Sertaline vs fluoxetine** N=105	Patients who responded (see table 4) or had a partial response (25-50%↓ in HAM-D or MADRS from baseline, and CGI-severity ≤ 4 and CGI-improvement of at least 3) in the acute phase trial.	24 week trial evaluating continuation. Patients remained on final dose from the acute phase trial	Relapse - ≥ 50% ↓ of lowest HAM-D or MADRS for ≥ 2 weeks HAM-D ≥ 18 for ≥ 2 weeks CGI-severity > 4	10% sertraline and 13% fluoxetine pts. relapsed. Both groups continued to show similar improvement with continued therapy. Overall incidence of AE similar and decreased with time.
Franchini[21] RDB **Sertraline vs.** N=64	Unipolar patients with recurrence who had HAM-D<8 and absence of depressive sx's (DSM-IV) at the end of 4 month continuation therapy.	2 year trial evaluating maintenance. Sertraline 100mg vs. 200mg. Max daily dose for sertraline 200mg and for 300mg.	HAM-D>15 Signs of clinical worsening and impairment	21.9% vs. 18.7% of sertraline vs. patients had a single new recurrence (not significant) Recurrences were less severe and of shorter duration than index episode. Incidence of AE similar in both groups.

[a]RDB=randomized double-blind, HAM-D=Hamilton Rating Scale for Depression, CGI=Clinical Global Impression, AE=adverse event

Table 6. Treatment of obsessive-compulsive disorders[a]

CLINICAL TRIAL	INCLUSION	DAILY DOSE	MEASURED OUTCOMES	RESULTS
Tollefson[24] RDB, multicenter **Fluoxetine vs. placebo** N=355 13 weeks	OCD (DSM-III-R)≥1 year CGI-severity of OCD of at least moderate Y-BOCS ≥16 (both O and C present) or ≥10 if only O or C present.	1 week placebo run-in fixed dose of fluoxetine 20mg/40mg/60mg vs placebo	≥35% dec of Y-BOCS from baseline Y-BOCS compulsion and obsession subscores HAM-D CGI severity/improve PGI	Response rate for 20mg/40mg/60mg/placeb 32.1%/32.4%/35.1%/8.5% respectively. All doses of fluoxetine significantly better than placebo in all other measures.
Montgomery[25] RDB, multicenter **Fluoxetine vs placebo** N=214 Intention-to-treat 8 weeks	OCD(DSM-III-R)≥ 1 year CGI-severity ≥ moderate Y-BOCS≥16 (if both O and C present) or ≥10 if only O or C present.	7 day placebo run-in fixed dose of fluoxetine 20mg/40mg/60mg vs placebo pts. in 60mg group initially received 40mg x 1 week.	≥25%↓ Y-BOCS score from baseline. CGI of 1-2 PGI NIMH HAM-D	Response rates 36% (20mg), 48% (40mg), 47% (60mg), 26% (placebo) based on Y-BOCS and CGI. Fluoxetine>placebo for PGI No difference between groups on other efficacy measures and incidence of AEs.
Chouinard[26] RDB, multicenter **Sertraline vs. placebo** N=87 Intention-to-treat 8 weeks	OCD (DSM-III) HAM-D≤15	1 week placebo run-in sertraline titrated from 50mg to 200mg over 2 week period. Dose maintained through week 8 unless AE.	change from baseline for : Y-BOCS NIMH CGI (severity and improvement)	Sertraline>placebo 25% sert. vs. 11% placebo had CGI-I of 1-2 82% sert vs. 62% placebo patties had AE.
Greist[27] RDB, multicenter **Sertraline vs. placebo** N=325 Intention-to-treat 12 weeks	OCD (DSM-III-R) NIMH≥7 HAM-D≤17	1 week placebo run-in fixed dose of sertraline 50mg/100mg/200mg vs. placebo	Y-BOCS change from baseline HIMH≤6 CGI-severity CGI-improvement of 1- 2	Mean drop in Y-BOCS score 23.4% for sertraline and 14.6% for placebo. 35.4% (sertraline) vs. 24% (placebo) had NIMH≤6. Sertraline>placebo for all other efficacy measures.
Zohar[28] RDB, multicenter **Paroxetine vs. clomipramine vs. placebo** N=399 Intention-to-treat 12 weeks	OCD (DSM-III-R)≥6 months. NIMH≥7 Y-BOCS≥16	2 week placebo run-in paroxetine 10mg/ clomipramine 25mg x3 days paroxetine 20mg/ clomipramine 50mg x 11 days. Thereafter can be adjusted to max of paroxetine 60mg/clomipramine 250mg	≥25% ↓ of Y-BOCS score from baseline NIMH change from baseline	Resp. rate 55.1% (paroxetine) vs. 55.3% (clomipramine) vs. 35.4% (placebo) Paroxetine=clomipramine> placebo in mean change from baseline score for Y-BOCS and NIMH scores
Freeman[29] RDB, multicenter **vs clomipramine** N=64 Intention-to-treat 10 weeks	OCD (DSM-III-R). NIMH≥7 Y-BOCS≥16 HAM-D<20	No placebo run-in For and clomipramine 50mg initially, 100mg after week 1, 150mg after week 2. Can be ↑ to max of 250mg	Y-BOCS NIMH CGI-Improvement of 1-2	59% () vs. 53% (clomipramine) responded based on CGI-I of 1-2 =clomipramine on all other efficacy measures. Incidence of AE, = clomipramine, however AE profiles differed.
Goodman[30] RDB, multicenter **vs. placebo** N=156 Intention-to-treat 10 weeks	2-4 week placebo run-in OCD (DSM-III-R)≥ 1 yr. NIMH≥7 17 item HAM-D≤19	50mg x 4days, 100mg x 4 days, 150mg thereafter. May adjust to 100-300mg.	Y-BOCS NIMH CGI-Improvement of 1-2	43.4% vs. 8.6%placebo pts responded based on CGI of 1-2. >placebo on other efficacy measures. Patients with lower baseline values more likely to respond to treatment with . AE-95% (Fuvoxamine) and 83.7% (Placebo)

Table 6. (cont'd)

CLINICAL TRIAL	INCLUSION	DAILY DOSE	OUTCOME MEASUREMENT	RESULTS
Koran[31] RDB, multicenter **vs. clomipramine(clomip)** N=73 Intention-to-treat 10 weeks	OCD (DSM-III-R)>1yr. NIMH≥7 Y-BOCS≥16 HAM-D<21	2 week placebo run-in 50mg/clomip 25mg x 4days 100mg/clomip 50mg x 4days then ↑ to 150mg and 100mg clomip. Max dose for 300mg and clomip 250mg.	≥25% ↓ Y-BOCS score and ≥35% ↓ from baseline NIMH CGI-Improvement 1-2 PGI	56% () vs. 54% (clomip) had 25% ↓ in Y-BOCS. 44% () vs. 38% (clomip) had ≥35% ↓ in Y-BOCS. 50% () vs. 48.7% (clomip) had CGI-I 1-2
Greist[32] RDB, multicenter **Sertraline vs. placebo** N=118 Intention-to-treat 40 weeks	Treatment responders from the 12 week acute study as defined by CGI-Efficacy of 1-2	Patient continued on same dose or placebo as from acute study.	Y-BOCS NIMH CGI-improvement, efficacy	Trend towards continued improvement in sertraline group. AE-94%sertraline vs 79% placebo and improved over time.
Montgomery[25] RDB, multicenter **Fluoxetine vs. placebo** N=95 16 weeks	1. completed 8 week acute trial, had ≥25% ↓ Y-BOCS and CGI 1-2 2. nonresponders	1. continuation with same treatment as in acute phase. 2. Open-label, 40mg x 1wk, thereafter 60mg	Y-BOCS	1. response maintained in all treatment groups 2. significant ↓ in Y-BOCS score during open-label trial

[a]RDB=randomized double-blind; CGI=Clinical Global Impression; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale;HAM-D=Hamilton Rating Scale for Depression; PGI=Patient Global Improvement; NIMH=National Institute of Mental Health Global Obsessive-compulsive Scale; AE=adverse event

Table 7. Treatment of Panic Disorder[a]

CLINICAL TRIAL	INCLUSION	DAILY DOSE	OUTCOME MEASUREMENT	RESULTS

Oehrberg[33] RDB, multicenter **Paroxetine vs. placebo** N=120 Intention-to-treat 12 weeks	Panic disorder ± agoraphobia (DSM-III-R) ≥3 full attacks during the 4 weeks prior to entry HAM-D≤ 14	3 week placebo run-in 10mg⇒↑ 20mg over 2 weeks. At week 3, can ↑ to 40mg and at week 4 can ↑ to max of 60mg if indicated. **All patients received standard cognitive therapy.**	≥50% ↓ in #panic attacks from baseline(patient diary). % pts with attacks ↓ to≤1 ≥50% ↓ HAM-A CGI of 1-2	82% paroxetine vs. 50% placebo had ≥50% ↓ in # of panic attacks. 36% paroxetine vs. 16% placebo had 0-1 attacks at 12 weeks. Paroxetine> placebo in all other outcomes 77% paroxetine and 55% placebo patients had AE
Ballenger[34] RDB, multicenter **Paroxetine vs. placebo** N=278 Intention-to-treat 10 weeks	Panic disorder± agoraphobia (DSM-III-R) ≥ 2 full attacks during 2 week screening period	2 week placebo run-in paroxetine 10mg/20mg/40mg final dose for the 20mg and 40mg groups were reached at 8 and 15 days respectively	%free of panic attacks change from baseline in # of full attacks CGI-severity of illness %pts with ≥ 50% ↓ in # of full attacks	Paroxetine 40mg > placebo for % pts free of attacks, for change from baseline in # of full attacks and CGI-severity of illness Dry mouth, diarrhea, tremor and sexual dysfunction more common with ↑'ing paroxetine dose
Lecrubier[35] RDB, multicenter **Paroxetine vs. clomipramine(clomip) vs. placebo** N=367 Intention-to-treat 12 weeks	Panic disorder ± agoraphobia (DSM-III-R) ≥3 full attacks during 3 weeks prior to entry **and** ≥3 full attacks during placebo run-in	3 week placebo run-in week 1, paroxetine 10mg and clomipramine 25mg week 2, paroxetine 20mg and clomipramine 50mg max dose paroxetine 60mg and clomipramine 150mg	≥50% ↓ in # of full attacks (patient diary) % patients with full attacks ↓ to 0. Mean change in # of full attacks. HAM-A CGI-severity PGE Sheehan disability scale and phobic scale	76.1% paroxetine vs. 64.5% clomip vs. 60% placebo had ≥50% ↓ in # attacks. 50.1% paroxetine vs. 36.7% clomip vs. 31.6% placebo had attacks ↓ to 0. Paroxetine>clomip=placebo in mean change of attack #. Paroxetine=clomip>placebo in all other variables. Clomip>parox=placebo (AE)
DenBoer[36] RDB **vs. ritanserin vs. placebo** N=59 8 weeks	Panic disorder + agoraphobia (DSM-III-R) for ≥1 year HAM-D<15	No placebo run-in Week 1, 75mg and ritanserin 10mg Week 2, 150mg and ritanserin 20mg	State Anxiety Inventory Fear Questionnaire FQ-agoraphobia subscore Ultrecht Panic Attack Inventory HAM-A	Response rate 75% vs 10% ritanserin vs. 5% placebo based on ≥50% ↓ in HAM-A >ritanserin, placebo in all other measurements
Black[37] RDB **vs. cognitive therapy(CT) vs. placebo** N=75 Intention-to-treat 8 weeks	Panic disorder ± depression ± agoraphobia (DSM-III-R) weekly panic attack score of 25 ≥1 panic attacks during last week of placebo run-in	3 week placebo run-in 50mg x 3 days, 100mg x 5 days then 150mg x 6 days. Goal -200mg daily, maximum 300mg	# full panic attacks(patient diary) panic attack severity score Clinical Anxiety Scale CGI severity and improvement Sheehan Disability Scale	90% vs. 50% CT vs. 39% placebo patients responded based on ≥ moderate improvement in CGI >CT>placebo in all outcomes except Sheehan Disabil (all groups were =)
Nair[38] RDB,multicenter **(fluvox) vs. imipramine(imip) vs. placebo** N=132 Intention-to-treat 8 weeks	Panic disorder ± agoraphobia (DSM-III-R) ≥4 panic attacks 4 weeks prior to initial assess. or ≥1 panic attack with at least 1 month of persistent fear of having another. ≥1 attack during run-in	1-2 week placebo run-in fluvox/imip 50mg at week 1 fluvox/imip 100mg at week 2 fluvox/imip 150mg at week 3 unless pt. had an AE. Dose can be further ↑ to max of 300mg for fluvox or imip	% of patients free of panic attacks # of full and # of limited panic attacks (patient diaries) Clinical Anxiety Scale MADRS CGI-improvement, efficacy, severity scales.	Imipramine>= placebo in all efficacy measures. Drop-out rates =placebo> imipramine. Incidence of AEs similar in all groups
Sharp[39] RDB **vs. CT vs. placebo** N=190 12 weeks	Panic disorder±agoraphobia (DSM-III-R)≥3mos. HAM-A≥15	1 week placebo run-in week 1, 50mg week 2 100mg week 3 150mg(range 100-150mg). Compared to CT alone, placebo alone and placebo or + CT	HAM-A Symptom Rating Test MADRS Fear Questionnaire # of full and limited panic attacks (patient diaries)	All treatment groups>placebo for all rating scales. No significant difference between treatments. % free of major attacks-+CT 82.7%, Placebo+CT 75.7%, CT 70% 68.9%, Placebo 60.7%.

Lecrubier[40] RDB, multicenter **Paroxetine vs. clomipramine(clomip) vs. placebo** N=176 Intention-to-treat 36 weeks	Patients completing the 12 week trial who wanted to participate in long-term trial	Pts. continued on same medication and dose as at completion of 12 week trial.	# of full panic attacks (patient diary) HAM-A CGI PGE Sheehan Phobic and Disability Scales MADRS	# of full attacks continued to ↓ with paroxetine and clomip. Placebo group showed fluctuation. 84.6% paroxetine vs. 72.4% clomip vs. 59.1% placebo were free of attacks. Paroxetine=clomip>placebo in all other measures. Clomip>paroxetine>placebo (AE)

[a]RDB=randomized double-blind, HAM-D=Hamilton Rating Scale for Depression, HAM-A=Hamilton Rating Scale for Anxiety, CGI=Clinical Global Impression, AE=adverse event, PGE=Patient Global Evaluation, MADRS=Montgomery-Ashberg Depression Scale, CT=cognitive behavioral therapy

V. ADVERSE EFFECTS [74-75]

The SSRIs have an improved adverse effect profile when compared to tricyclic antidepressants(TCA) and monoamine oxidase inhibitors(MAOI). Side effects reported during clinical trials and compiled by the manufacturer are presented in **Table 8.**

Table 8. Incidence of Side Effects (%) Reported During Placebo-controlled Trials

SIDE EFFECT	FLUOXETINE[a,b] 2444/1331 (N/N)		SERTRALINE[a,c] 1824/1501		PAROXETINE[a,c] 1432/1010		[a,d] 892/778	
NERVOUS SYSTEM	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Headache	21.0	20.0	26	23	18.0	17.0	22	20
Agitation	(NR)[e]	(NR)	6.0	4.0	5.0	4.0	2	1
Nervousness	13.0	9.0	6.0	4.0	5.0	3.0	12	5
Anxiety	13.0	8.0	4.0	3.0	3.0	2.5	5	3
Tremors	10.0	3.0	9.0	2.0	9.4	1.4	5	1
Insomnia	20.0	11.0	22.0	11.0	18.8	9.0	21	10
Drowsiness	13.0	6.0	14.0	7.0	22.0	9.0	22	8
Dizziness	10.0	7.0	13.0	8.0	13.0	4.3	11	6
Blurred vision	3.0	1.0	4.0	2.0	2.7	<1.0	3	2
CARDIOVASCULAR								
Palpitation	2.0	1.0	(NR)	(NR)	1.6	<1.0	3	2
GASTROINTESTINAL								
Nausea	23.0	10.0	28.0	13.0	22.8	8.0	40	14
Vomiting	3.0	2.0	4.0	2.0	(NR)	(NR)	5	2
Dyspepsia	8.0	5.0	8.0	4.0	2.0	1.0	10	5
Diarrhea	12.0	8.0	20.0	9.0	11.0	8.0	11	7
Constipation	(NR)	(NR)	7.0	5.0	12.8	7.0	10	8
Anorexia	11.0	3.0	6.0	2.0	7.4	2.5	6	2
SEXUAL DYSFUNCTION								
Abnormal ejaculation	1.1[f]	<1.0	14.0	1.0	13/23/21[g]	0-1	8	1
Impotence	1.8[f]	<1.0	(NR)	(NR)	10/8/5[g]	0-1	2	1
Decreased libido	4.2	<1.0	5.0	1.0	(NR)	(NR)	2	1
AUTONOMIC								
Dry mouth	10.0	7.0	15.0	9.0	18.0	10.8	14	10
Sweating	8.0	3.0	7.0	2.0	11.2	3.4	7	3
SKIN								
Rash	4.0	3.0	3.0	2.0	1.7	<1.0	(NR)	

[a]N/N=number of patients active drug/placebo
[b] combines data from major depression, OCD and bulimia nervosa studies
[c] combines data from major depression, OCD and panic disorder studies
[d] combines data from major depression and OCD studies
[e](NR)not reported
[f]incidence may be under reported; data collected before SSRI effects on sexual dysfunction appreciated
[g] incidence for depression, OCD and panic disorder reported separately

A discontinuation syndrome has been described when SSRIs are stopped (either abruptly or during taper) or following dosage reduction.[76-77] Some of the symptoms described include disequilibrium, nausea/vomiting, flu-like symptoms, sensory disturbances, sleep disturbances, anxiety, agitation and irritability. Symptoms usually begin 1-3 days after drug discontinuation or dosage decrease and may last for 2 weeks. Reinstitution of the agent or similar agent results in resolution of symptoms within 24 hours. The order of frequency of this syndrome based on reports are, paroxetine>>sertraline>fluoxetine. It is theorized that drugs with shorter half-lives such as paroxetine and are more likely to cause this syndrome, however the true incidence is unknown because of probable under reporting. Prospective studies specifically addressing this issue are needed to better define incidence and severity; 2 such studies are underway. Patients receiving an SSRI(except fluoxetine) for at least 2 months should be gradually tapered from the drug when discontinuing therapy.

VI. DRUG INTERACTIONS [78-82]

The SSRIs interact with several of the cytochrome P450 isoenzymes. The major ones involved in metabolic reactions such as hydroxylation, demethylation, dealkylation are CYP2D6, CYP3A3/4, CYP1A2, CYP2C9 and CYP2C19. Drugs can act as substrates, inducers or inhibitors of these enzymes. The degree to which a drug can effect the enzyme depends on drug characteristics such as the affinity a drug has to the enzyme and the concentration of drug at the enzyme site. Two of the enzymes, CYP2D6 and CYP2C19 have a polymorphic distribution which genetically predisposes individuals to being slow or fast metabolizers of drugs that are substrates. The inhibitory effect of the SSRIs on the P450 isoenzymes are summarized below. Knowing the SSRIs inhibitory profile helps in predicting potential drug interactions with other drugs metabolized by these enzymes.

Table 10. Relative inhibition of SSRIs on CYP450 isoenzymes

CYP 2D6	Fluoxetine (substantial) > paroxetine (substantial) > sertraline (mild) > (unlikely)
CYP 3A3/4	(moderate) > fluoxetine (mild) > sertraline and paroxetine (unlikely)
CYP 1A2	
CYP 2C9	Fluoxetine (unclear)
CYP 2C19	(substantial) > fluoxetine (moderate) > sertraline (insignificant) > paroxetine?

Table 11. Drug interactions[a]

SSRI	INTERACTING DRUG	RESULT
All	MAOIs	May precipitate serotonin syndrome
Fluoxetine,paroxetine, sertraline --- Fluoxetine, paroxetine,	Desipramine --- Imipramine, amitriptyline	↑ plasma concentration of TCA
Fluoxetine	Phenytoin	↑ plasma concentration of phenytoin
Fluoxetine,	Carbamazepine	Some studies have found ↑plasma concentration of carbamazepine whereas other have not found an interaction
Fluoxetine, paroxetine,	Warfarin	Small studies and case reports show potential for ↑ PT/INR or bleeding.
	Theophylline	↑ theophylline concentration and clinical reports of toxicity
Paroxetine, sertraline	Cimetidine	↑ plasma concentration of SSRI
Fluoxetine,	Lithium	Results of both ↑/↓ conc of lithium and case reports of adverse neurologic effects. Lithium is used to augment response in treatment resistant depression.
	Clozapine	↑ plasma concentration of clozapine
Fluoxetine,	Propranolol/metoprolol	Case reports of heart block and bradycardia
All	Selegiline	Case reports of mania and hypertension with fluoxetine. Selegiline manufacturer recommends avoiding use with all SSRIs
Fluoxetine,	Diazepam, alprazolam, triazolam	↑ plasma concentration of BZD
	Terfenadine, astemizole	Co-administration contraindicated by manufacturer due to risk of interaction resulting in ↑ terfenadine/astemizole
	Cisapride	Co-administration contraindicated by MFR due to risk of interaction resulting in ↑ cisapride

[a]Table not intended to be inclusive of all drug interactions

VII. DOSING AND ADMINISTRATION [74]

Table 12. Dosing and Dosage Forms

DRUG	INITIAL DOSE	DOSING RANGE	DOSAGE FORMS	DOSAGE ADJUSTMENT
Fluoxetine	20mg q am Dosage may be increased after several weeks if indicated	20-80mg Doses >20mg may be given BID (am and noon)	10mg,20mg capsules 20mg/5ml liquid- 120ml	Elderly/hepatic dysfunction-↓ dose or administer less frequently Renal dysfunc. -use care
Sertraline	50mg q am or q hs (depression and OCD), 25mg q am (panic disorder) Dosage may be increased at weekly intervals	50-200mg	25mg, 50mg, 100mg (all strengths scored), film-coated tablets	Hepatic dysfunction-↓ dose or administer less frequently. Renal dysfunc-use care
Paroxetine	20mg q am (depression and OCD), 10mg q am (panic disorder) Dosage may be increased by 10mg at weekly intervals	20-50mg (depression) 20-60mg (OCD) 10mg-60mg (panic disorder)	10mg, 20mg (scored), 30mg,40mg film-coated tablets	Hepatic/renal dysfunction, elderly- starting dose 10mg
	50mg q hs Dosage may be increased by 50mg increments every 4-7 days as tolerated	100-300mg Doses >100mg should be divided (am and hs)	25mg, 50mg (scored), 100mg (scored) film-coated tablets	Elderly/hepatic dysfunction- titrate dose slowly

VIII. CONVERSION STUDIES

There are 3 published articles looking at patients who are stabilized on one SSRI and switching them over to another SSRI. Kreider et al[83], in a randomized double-blind trial, studied 242 patients in a 4 week trial evaluating a switch from fluoxetine to paroxetine. Patients were randomized to either a group where the switch was immediate, or to a 2 week placebo-washout followed by 2 weeks of paroxetine. The majority of patients were on 20-40mg of fluoxetine daily, and were switched to 20mg of paroxetine. Ten patients in each group dropped out. Overall, adverse events were equal in both groups, but occurred earlier in the immediate switch group. Patients showed a small improvement in depressive and anxiety symptoms as measured by the HAM-D and Covi Anxiety Scores. The authors concluded that patients can be safely switched from fluoxetine to paroxetine.

In a 3 month single blind study by Haider et al[84], 70 patients were randomized to one of three groups, looking at a switch from fluoxetine to sertraline. Group 1 received 50mg of sertraline for every 20mg of fluoxetine (F20:S50). Group 2 received 75mg for every 20mg of fluoxetine (F20:S75) and group 3 continued to receive their current dose of fluoxetine. The HAM-D, Beck Depression Inventory and CGI-change scales were used to measure improvement or worsening. The number of drop-outs were the same in each group. In the F20:S50 group, 47% versus 13% in the F20:S75 versus 15% in the fluoxetine group were considered to have clinically worsened. The authors concluded that switching from fluoxetine to sertraline is safe and that F20:S75 was the better conversion factor, although further study is needed.

Stock[85] et al retrospectively compared 3 groups in a fluoxetine to sertraline switch. Group 1 had 50mg of sertraline for every 20mg of fluoxetine (n=54). Group 2 continued on fluoxetine (n=31) and group 3 was only treated with sertraline (n=41). 20 patients in group 1 did not tolerate the switch. Data was available for 12 of the 20 failures; 10 were because of adverse events and 2 due to lack of efficacy. In the sertraline only group, 5 patients discontinued treatment. No information was provided on the fluoxetine group.

IX. PHARMACOECONOMICS

Acquisition cost is not the only factor considered when selecting an SSRI for formulary status. Other costs, such as need for concomitant therapy, dosage titration, physician visits, hospitalizations, discontinuation of treatment and switching therapy all contribute to the overall cost of therapy.[86] Several studies have shown that although drug acquisition costs of the SSRIs when compared to the TCAs are high, they have an economic advantage when all costs are considered. Studies comparing the cost advantage of one SSRI to another through retrieval of computerized claims data, have evaluated the other costs.

A study by Navarro[87] et al, looked at concomitant anxiolytic/hypnotic usage for fluoxetine, sertraline and paroxetine in 2 different settings, an independent practice association (IPA) and a staff model HMO. For the IPA, rates of concomitant therapy were the same among the SSRIs but the costs/day were greater for sertraline>fluoxetine>paroxetine. For the HMO, 40% of paroxetine, 23% of fluoxetine and 38.5% of sertraline patients used concomitant agents, however the daily costs were the same. Rascati[88], in a drug utilization review in Medicaid patients, found that 41.7% of paroxetine, 35.8% sertraline and 33.1% fluoxetine patients used concomitant anxiolytic/hypnotic. Gregor[89] et al found anxiolytic use was 11.4% for paroxetine, 9.5% for sertraline and 9.5% for fluoxetine for patients participating in the PCS Health Systems.

Navarro[87], in the same study mentioned earlier, evaluated treatment discontinuation. In the IPA model, 46% of paroxetine, 37.4% fluoxetine and 54% sertraline patients had discontinued treatment by day 60, with the original SSRI prescribed. Likewise, in the HMO group, 54% of paroxetine, 36.8% fluoxetine and 57% sertraline patients had discontinued treatment by day 60. However, by day 180, the rates were more similar between groups. For the IPA group, 66.8% paroxetine, 56% fluoxetine and 69% sertraline patients had discontinued treatment and in the HMO group, 63% paroxetine, 71.7% fluoxetine and 63% sertraline had discontinued treatment.

Gregor[90] et al, looked at dosage titration of fluoxetine and sertraline (paroxetine was omitted because of too few prescriptions). Over a period of 9 prescription refills, the mean dose of fluoxetine went from 21mg $\pm$6 to 25mg$\pm$11, and for sertraline, the mean dose went from 59mg$\pm$28 to 117mg$\pm$66. By refill #9, 24% of patients were still taking fluoxetine versus 8.2% of sertraline. Donoghue tracked percentage of prescriptions written for the various strengths of SSRIs. He found 6% of fluoxetine prescriptions were for >20mg, 17% of paroxetine were >20mg, 52% of sertraline were>50mg and 17% of were >100mg. Navarro[87], in the earlier mentioned study, found that the mean daily starting dose for fluoxetine was 25mg and that by day 180, it had increased to a mean of 28mg. The mean daily starting dose for sertraline was 47mg and by day 180 it was increased to a mean of 73mg.

Sclar[92] et al compared direct health service expenditures (physician, psychiatrist, laboratory and hospitalization) for fluoxetine, sertraline and paroxetine. Using multivariate regression, patients receiving fluoxetine used $284.68/year less than those receiving paroxetine and $315.96/year less than those receiving sertraline ($p \leq 0.05$). Comparison between sertraline and paroxetine did not show any significant difference in expenditures.

Singletary[93] et al looked at drug acquisition cost savings in a VA population. Sertraline was selected as the 1st line SSRI for all new patients, with fluoxetine reserved for sertraline failures or intolerance. By making sertraline a 1st line agent, the medical center saved over $300,000 annually. Other health service expenditures were not considered.

The above studies were conducted in a naturalistic setting. However, controlled trials can also provide valuable information. Montgomery[94], in a meta-analysis of double-blind placebo-controlled studies on SSRIs looked at discontinuation rates due to adverse effects. Fluoxetine at daily doses of 20mg, 40mg and 60mg had discontinuation rates of 8%, 12% and 30% respectively. Sertraline at 50mg, 100mg and 200mg had discontinuation rates of 11%, 16% and 36% respectively. Paroxetine at 20mg, 30mg and 40mg had discontinuation rates of 26%, 33% and 26% respectively. Also summarized in **Table 13,** are the discontinuation rates, use of concomitant medications and dosage titration data from the major depression studies presented earlier.

Table 13. Discontinuation Rates of SSRIs

Study	Concomitant therapy	Dosage titration	Discontinuation(d/c)
Tignol[4]	Chloral hydrate allowed but no data on usage	Fixed dose of fluoxetine or paroxetine	Same in both groups
Schone[5]	Benzodiazepines allowed but no data on usage	81% of paroxetine patients were on 20-30mg and 64% of fluoxetine patients were on 20-40mg	11.1% paroxetine and 13.5% fluoxetine d/c treatment due to adverse events
Gagiano[6]	Benzodiazepines allowed but no data on usage	Paroxetine-87% on 30mg Fluoxetine- 80% on 40mg	14% drop-out with paroxetine and 18% with fluoxetine
De Wilde[7]	Benzodiazepines allowed but no data on usage	Paroxetine- 71% were on 30mg and 22% on 40mg fluoxetine- 76% on 40mg and 22% on 60mg	5.4% paroxetine and 9.7% fluoxetine d/c due to adverse events. Overall discontinuation, 16.2% for paroxetine and 21.9% fluoxetine.
Ontiveros[8]	None	Fixed dose of paroxetine or fluoxetine	11.7% drop-out with paroxetine and 14.8% with fluoxetine due to AE ± lack of efficacy
Aguglia[9]	40% of sertraline and 60% of fluoxetine patients used benzodiazepines as allowed by protocol.	Mean dose for sertraline, 71.88mg. Mean dose for fluoxetine, 28mg	15% fluoxetine and 7% sertraline d/c treatment due to adverse events. 19.6% fluoxetine and 9.6% sertraline d/c due to treatment failure
Bennie[10]	Chloral hydrate or temazepam allowed but no data on usage	Sertraline- 76% were on 50mg and 24% were on 100mg Fluoxetine- 76% were on 20mg and 24% were on 40mg	3% in both groups d/c due to treatment failure. 14% sert and 13% fluox d/c due to adverse events
Van Moffaert[11]	63% sertraline and 62% fluoxetine patients used chloral hydrate or short-acting benzodiazepine	Sertraline- 64% were on 50mg and 36% were increased to 100mg Fluoxetine- 63% were on 20mg and 37% were increased to 40mg	17% of sertraline and 19.5% of fluoxetine patients d/c treatment. Reasons not given for acute phase (given as combined data for acute and continuation phase)
Zanardi[12]	Lithium for those previously taking. Flurazepam allowed but no data on usage	Dosage increase per protocol for sertraline or paroxetine	41% of parox and none of sert d/c due to adverse events. High drop-out probably related to fast titration.
Ansseau[13]	Benzodiazepines and chloral hydrate but no data on usage	Paroxetine- 46% used 20mg and 54% used 30mg - 8% used 50mg, 30% used 100mg and 58% used 200mg	5.4% paroxetine and 17.2% d/c due to AE. 3.6% paroxetine and 4.7% d/c due to lack of efficacy
Rapaport[14]	12% of and 9% of fluoxetine patients used chloral hydrate	- mean 110mg at end of week 4 and 102mg by week 7. Fluoxetine- mean 28mg at end of week 4 and 34mg by week 7. 15% and 25% fluoxetine patients needed a dosage ↑ by week 4.	2 pts. in each group d/c due to adverse events.
Kiev[15]	Antacids, laxatives, acetaminophen, nonsteroidals, aspirin and chloral hydrate allowed but no data on usage.	Mean dose of fluvox 102mg and parox 36mg. 53% of fluvox titrated to max of 150mg and 33% of parox titrated to max of 50mg	6.9% of fluvox and 13.8% of parox d/c due to adverse events. 3.5% fluvox and 10.3% parox d/c due to lack of efficacy.

X. CONCLUSIONS

A. Efficacy/outcomes:

The SSRIs all have similar efficacy in treating major depression and obsessive-compulsive disorder.

B. Safety:

The SSRIs have a better safety profile than the TCAs and the MAOIs. Adverse effects associated with the SSRIs as a class include nausea (transient effect), headache, sexual dysfunction, sleep disorder and tremor. Certain side effects may have a higher incidence with a specific agent. For example, fluoxetine is associated with a higher incidence of jitteriness, anxiety or nervousness. Sertraline has a higher incidence of diarrhea, paroxetine with sedation, constipation and dry mouth and fluvoxamine with insomnia.

C. Pharmacokinetics/drug interactions:

Pharmacokinetically, fluoxetine differs from the other SSRIs in that it has an active metabolite and the longest half-life. is mainly bound to albumin (77%) whereas the others are bound to alpha-1-acid glycoprotein. Drugs bound to alpha-1-acid glycoprotein are less likely to undergo protein displacement drug interactions than are ones bound to albumin.

The potential for drug interactions varies among the agents because of their ability to inhibit the cytochrome P450 isoenzymes differently. Fluoxetine and paroxetine have a significant inhibitory effect on CYP 2D6. has the greatest inhibitory effect on CYP 3A3/4 and CYP 1A2 and both and fluoxetine on CYP 2C19.

D. Compliance:

The SSRIs are administered as a single daily dose. However, for fluoxetine, doses exceeding 20mg may be divided. should be given twice daily if the dose exceeds 100mg.

XI. RECOMMENDATIONS

The agents fluoxetine, paroxetine, and sertraline will be added to the VA National Formulary with equal status. Blanket Purchase Agreements for lower prices will be pursued for each agent.

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