SSRIS- A Recent Review

S SULEMAN* H R CHAUDHRY** Z EHSAN*** U A BARULA***
M R CHAUDHRY***

**Department of Psychiatry, Sir Ganga Ram Hospital, Lahore.*
*** Department of Psychiatry, Postgraduate Medical Institute, Lahore*
****Fountain House, Lahore*
Correspondence to Dr. Haroon Rashid Chaudhry

This paper reviews the pharmacokinetics, clinical uses and side effects of SSRIs. Clinical profile of SSRIs has been compared with other antidepressants. Furthermore differences between currently available SSRIs have also been reviewed. Special emphasis is given to their use in high-risk patients and in patients with coexisting medical problems.

Key Words: SSRIS, Antidepressants

Perhaps no other area of drug therapy has experienced the revolution in development that has occurred in Psychopharmacology over the last four decades. This progress is particularly notable in the pharmacological treatment of depression.

Major advances in the antidepressant drug therapy that were the result of chance discovery include Lithium in 1949, Monoamino-oxidase Inhibitors (MAOIs) in 1952 and Tricyclic Antidepresents (TCAs) in 1955 (Table I). Since the introduction of imipramine[1] as the first tricyclic antidepressant in the pharmacotherapy of endogenous depression almost 45 years ago, several first generation tricyclic antidepressants were marketed. The later generated tricyclic antidepressants in their clinical efficacy were not found to be superior to imipramine[2-6]. The enthusiasm about the unique opportunity of treating depressed patients by pharmacological compounds without the drawback of early MAOIs diminished by clinical finding that one third of the treated patients did not respond[5] and also that each class has limitations. This had sustained interest in the development of new antidepressant drugs[7].

Search for antidepressants with lesser side effect profile led to the introduction of second generation antidepressants. Agents like maprotiline, mianserin and trazodone are less or almost as effective as the tricyclic antidepressants in the treatment of endogenous depression but do not show the same side effect profile especially anticolinergic side effects[8-11].

It took sometime until the role of serotonin in depression was pointed out at the end of sixties[12] and since then pharmacological agents with serotoninegic properties were generated. This development climaxed and led to the generation of antidepressants known to be Selective Serotonin Reuptake Inhibitors (SSRIs) in 1987. These drugs targeted at a specific site of activity, the serotonin reuptake carrier. One of the earliest SSRIs to be studied worldwide was Zimelidine but was withdrawn subsequently due to its toxicity. The pharmacological properties of other SSRIs have been subjected to extensive clinical investigations and broad range of its potential clinical uses have been reported. This article is focused on the pharmacokinetics, therapeutic uses and side effects of currently available SSRIs (Fluoxetine, Paroxetine, Fluvoxamine, Citalopram and Sertraline). It also addresses the differences between different SSRIs.

Table-1:Milestones in the development of antidepressant drugs.

Year	Drugs
1949	Lithium
1952	MAOIs
1955	TCAs
1987	SSRIs

Pharmacokinetics & drug interactions of SSRIs

After oral administration SSRIs are well absorbed and has bioavailability of about 60%.

Fluoxetine reaches peak plasma concentrations after 6 to 8 hours, food slows but does not reduce its absorption. Fluoxetine is aprox. 94% bound to plasma proteins and its half life is 1 to 3 days. Its major metabolite, norfluoxetine, is also serotonin specific and has an exceptionally long half life of 7-15 days.

Fluvoxamine reaches peak plasma levels within 2 to 8 hours. Food does not significantly effect its absorption[13] and drug is aprox. 77% bound to plasma proteins[14]. Plasma half life of fluvoxamine is about 15 hours and aprox. 94% is recovered in urine[15]. Studies suggest that it possesses no active metabolite[16].

Paroxetine reaches peak plasma levels 2 to 8 hours following an oral dose. Plasma half life is 20 hours aprox[17] allowing once daily dosage. It is aprox. 95% bound to plasma proteins[18]. Food and antacids do not significantly inhibit its absorption[19].

Sertraline is relatively slowly absorbed from the gastrointestinal tract, peak plasma levels reaches 6 to 8 hours after an oral dose[20]. Sertraline is very highly (99%) bound to plasma protein and the average half life is 25 hours. The primary metabolite, desmethyl sertraline, is also selective serotonin reuptake inhibitor, but is 5-10 times less potent than the parent compound[21-22]. Plasma half life of desmethylsertraline is aprox. 66 hours.

Citalopram has half life of about 36 hours and undergoes minimal first pass metabolism in man. The

mono-and di-methylated metabolites of citalopram has the same specificity for serotonin as citalopram, but are less potent by factors of aprox. 4 and 13 respectively. Metabolities enter the train less readily and are present in lower concentration. Hence the therapeutic effect of citalopram is essentially due to parent compound itself.

Table 2. Pharmacokinetic parameters of fluoxetine, fluvoxamine, paroxetine and sertraline in healthy subjects.

Parameter	Fluoxetine	Fluvo-xamine	Parox-etine	Sertra-line
Time to peak plasma concen-tration from initial dose-hrs	4-8	2-8	3-8	6-10
Elimination half life (hours)	84 (26-220)	15 (13-19)	21 (4-65)	26
Protein binding(%)	95	77	95	97
Time to steady-state plasma concentration (daus)	14-28	10	4-14	-
Volume of distr-ibution (1/kg)	25 (12-42)	>5	13 (3-28)	25*
Plasma clearance (1/kg/h)	0.29 (0.09-0.53)	-	0.76 (0.21-1.31)	=
Active metabolites	Norfluox-etine	None	None	Desmthyl sertraline

(Leonard, Drugs 1992; 43 (Suppl 2): 3-10) —*Values from rat and dog

The metabolism of the SSRIs is predominently by oxidation in the liver, catalysed by cytochrome P450 (CYTP450). Several isozymes of CYP450 have been identified (IA2, 2C, 2D6) of which CYT450 2D6 appears to be of primary importance. Each CYTP450 isozyme catalyses specific groups of drugs and knowledge of isozyme- specific oxidation of a drug provides the rationale basis for the production of difference in pharmacokinetics and for predicting drug-drug interactions. CYT P450 2D6 catalyses the oxidation of TCAs, some neuroleptics (e.g. thioridazine), beta-blockers and antiarrhythmics.

Paroxetine and Fluoxetine are potent inhibitors of 2D6 and hence may cause interaction with TCAs, some neuroleptics and some antiarrhythmics. Citalopram, fluvoxamine and sertraline do not cause such interactions as they do not inhibit this isozyme. However, fluvoxamine does inhibit the 1A2 isozyme and thereby reduces the metabolism of some TCAs and theophylline. Such observation suggest care must be taken in combining SSRIs with TCAs in the treatment of drug resistant depression and in administering an SSRI to patients on beta blockers or antiarrhythmic drugs. Clearly theophylline should not be given to a patient being treated with fluvoxamine.

Table 3 Substrates and inhibitors of isoenzymes of Cytochrome P450

Isoenzymes	Polymorphism	Substrate	Inhibitor
1A2	?	Phenacetin; caffeine; theophylline; desmethylation pathway of TCAs; warfarin; propranolol	Fluvoxamine
2C	2-3% Caucasians 15-25% Orientals	Diazepam; desmethylation pathway of TCAs; warfarin; tolbutamide; phenytion	Fluvoxamine Fluoxetine Sertraline
2D6	5-8% Caucasians; low in other racial types	Haloperidol; thioridazine; perphenazine; clozapine; risperidone; nortriptyline; desipramine; fluoxetine*; beta-blockers-timolol, metoprolol, propranolol; type IC antiarrhythmics e.g. encainide, flecainide	Fluoxetine Paroxetine Sertraline
3A4	?	Desmethylation pathway of TCAs; triazolam	

- Values from rat and dog.

Clinical applications of SSRIs

Use in depression

The primary issue for any antidepressant is its efficacy compared with placebo and standard agents in the acute treatment of depressive illness. There is little doubt that SSRIs are superior to placebo and table 4-8 summarizes the results of placebo controlled studies of the different SSRIs. Studies have also shown they are almost as effective as the tricyclic antidepressants in the treatment of depression (table-9). A wealth of clinical literature suggests that currently available SSRIs are clinically equipotent in the management of patients with major depression. Fluvoxamine however, have demonstrated superior efficacy in a number of subgroups including patients with severe depression, suicidal thoughts or depression associated with anxiety.

Table - 4: Placebo-controlled studies of fluoxetine

Study	N	Result
Placebo	336	FLX20mg>PLC
Wernicke et al[22]	FLX40mg>PLC	FLX60mg=PLC
Wernicke et al[23]	354	FLX5mg>PLC
	FLX20mg>PLC	FLX40mg=PLC
Fabre and Crimson[24]	37	FLX>PLC
Rickets et al[25]	38	FLX>PLC
Fluoxetine + Impiramine	589	FLX=IMI>PLC
Stark and Hardison[26]		
Heiligenstein et al[27]	52	FLX>PLC
Placebo + Mainserin	70	FLX>PLC+MIA
Muijen et al[28]		

FLX. Fluoxetine, PLC placebo, IMI, imipramine, MIA, Mianserin

Table 5: Placebo-controlled studies of fluvoxamine

Study	N	Result
Placebo		
Conti et al [29].	45	FLV > PLC
Placebo + imipramine		
Amin et al [30].	481	FLV = IMI > PLC
Itil et al [31].	69	FLV < IMI > PLC
Lydiard et al [32].	52	FLV = IMI = PLC
Feighner et al [33].	86	FLV > IMI = PLC
March et al [34].	40	FLV > IMI = IMI
Placebo + desipramine		
Roth et al [35].	90	FLV = DMI > PLC

FLV, fluvoxamine; PCL, Placebo; IMI, imipramine; DMI, desipramine.

Table-6: Placebo-controlled studies of citalopram

Study	N	Result
Mendels et al[36]	142	CIT>PLC
Montgomwery et al[37]	199	CIT40mg>PLC
		CIT 20mg>PLC

CIT, citalopram, PLC, placebo.

Table-7: Placebo-controlled studies of paroxetine

Study	N	Result
Placebo [38]		
Cohn	50	PAR = PLC
Rickels	111	PAR > PLC
Claghorn	72	PAR > PLC
Smith	77	PAR = PLC
Kiev	81	PAR > PLC
Naylor	47	PAR = PLC
Placebo+Imipramine [39]		
Feighner	120	PAR > PLC
Cohn	120	PAR > PLC
Mendels	125	PAR = PLC
Shrivastava	120	PAR > PLC
Fieve	121	PAR > PLC
Fabre	120	PAR > PLC

PAR, paroxetine; PLC, placebo.

Table-8: Placebo-controlled studies of sertraline

Study	N	Result
Placebo		
Febre[40]	369	SER>PLC
Placebo + Amitriptyline		
Reimherr et al	448	SER=AMI>PLC

SER, sertraline, PLC, placebo.

Use in anxiety disorders

The relative efficacy of the SSRIs in the psychopharmacological treatment of anxiety disorders is difficult to estimate as direct comparisons are scarce, however, quantitative methods have been used to compare the efficacy of SSRIs between studies.

The effect of fluoxetine in OCD have been studied in a number of single blind and open trials and the result indicate that fluoxetine is effective in reducing the symptoms of OCD in adults and adolescents. These results also appear to be independent of the drug's antidepressant effect [41-46]. The literature suggests that the therapeutic effects are maintained during chronic treatment. Two meta-analysis have showed that clomipramine was found to be associated with the largest effect size followed by fluoxetine and fluvoxamine (all d>1.0) Sertraline was the least effective of the SSRIs studied (d=0.5)[47].

Table- Table 9. Comparative studies of selective serotonin re-uptake inhibitors in major depression. (Feighner et al., 1991).

SSRI	Efficacy vs comparative drug
Fluoxetine	>Impiramine
	=Impiriamine. Amitriptyline, Traxodone, Doxepine
	Mapotiline
Fluvaxamine	>Impiramine
	=Impiramine, Amitriptyline, Clomipramine
Paroxetine	>Impiramine
	=Imipramine, Amitriptyline, Clomipramine, Doxepine
Sertraline	>Amitriptyline
	=Amitryptyline

Efficacy endpoints were HAMD and CGI scales.

Fluvoxamine is the best-studied SSRI for panic disorder followed by Citalopram, aprox. 60% of patients became panic free with treatment[47].

Little is known about the treatment effects of SSRIs in anxious depressed patients, however, two double blind studies performed with fluvoxamine indicate that this SSRI is more effective than placebo, and equally as effective as benzodiazepines, in reducing anxiety and depression.

Use in schizophrenic depressed patients

Depression is a common complication of schizophrenia and is associated with increased morbidity and mortality. Contrary to traditional clinical wisdom, depressive symptoms occur during all phases of schizophrenia and are not restricted to the postpsychotic period[48]. Taking into consideration the hypothetical role of the serotoninergic system in the genesis of schizophrenia, use of fluoxetine as co-treatment with neuroleptics is found beneficial in various studies [49].

Use in drug dependence

Fluoxetine has also been found to be effective in detoxified opiate dependants, providing an antidepressant effect as well as reducing the risk of early relapse [50].

Use in high risk patients

Perhaps the greatest advantage of SSRIs over tricyclic antidepressants and other older antidepressants is its safety in high risk patients and its lesser side effects.

SSRIs are both safe and effective in elderly depressed patients. The result of most studies including those of fluoxetine[51-52], fluvoxamine[53-55], paroxetine[56] and sertraline[57] make it clear that the SSRIs are of comparable efficacy to the TCAs and other comparators such as mianserin, are superior to placebo, and have significant advantages over the TCAs in producing fewer side effects, particularly fewer anticolinergic side effects, which often cause treatment termination in the elderly because of

causation of confusional states. A number of other studies have raised the possibility of the efficacy of the SSRIs in dementia of Alzheimer's and other types independent of changes in mood, although the mechanism of action remains unclear[58-62]. One double blind multicenter study [58] treated 98 patients who were comorbid for dementia and depression with 10 to 30 mg/day of citalopram or placebo. The citalopram treated group showed significant improvement in emotional blunting, confusion, irritability, anxiety, fear/panic, depressed mood and restlessness. In another open study[59]. 10 patients aged 71 to 88 with senile dementia were treated for 3 weeks with fluvoxamine, 4 of these subjects showed improvement as indicated by scores on a Dementia Rating Scale, the Wisconson Card Sorting Test and Wechsler Adult Intelligence Scale (WAIS).

SSRIs are probably safer than TCAs in cardiac compromised patients and seems to be free of the quinidine like side effects of TCAs. Evidence of the safety may be inferred from studies of cardiac effects of the drugs on normal volunteers and on depressed patients. In studies[63-64] no conduction abnormalities were observed with SSRIs except there were a small decrease in heart rate. However, situation with citalopram is less clear. Early preclinical studies in cats showed TCA-like effect on heart rate at high doses [65] which was eventually attributed to a species-specific metabolite not found in humans [66].

Between 19% and 31% of epileptics may present for treatment of concurrent depression [67], although some mood changes are present in 60% of epileptics. Most first and second generation antidepressants lower the seizure threshold and thus raises the risk of seizures [68]. Since the withdrawal of Nomifensine it has been difficult to choose with confidence an antidepressant for epileptics. The incidence of epileptic adverse events with older MAOIs is negligible[69] but surprisingly, they have not been more popular for this indication. Current literature suggests that the SSRIs have a low potential for producing seizures. This is supported by animal models [70], normal volunteer research [71] and limited research in epileptic patients. A review of methodology in assessment of epileptogenic potential in antidepressants [69] quotes pre-marketing and post-marketing surveillance figures for new antidepressants including SSRIs and cautiously concludes that the incidences are broadly in line with, or fewer than, those reported for the TCAs.

Hepatic impairment and depression may frequently be found to co-exist in patients with a history of alcohol abuse. Attention to the effect of varying degree of hepatic impairment will thus often be required, when prescribing antidepressants. Consideration of safety is particularly with the SSRIs which are likely to be given to depressive patients with a history of alcohol abuse because of both a lack of interaction with alcohol and the suggested anti-craving effect of this group of drugs. An increased susceptibility to the sedative effects of psychotropic drugs has been described in cirrhotic patients [72]. Particularly in those patients with subclinical encephalopathy. For this reason non sedating SSRIs would seem preferable to the sedating tricyclic antidepressants for depressed patients with a history of alcohol abuse. In a study of 15 patients with chronic liver disease and hepatic encephalopathy [73], 50 or 100 mg of fluvoxamine given over a 2 weeks period had no effect on liver function, total or free plasma tryptophan or renal function nor deterioration in psychometric measures.

As regard the dose of SSRIs in cirrhotic patients, a study has suggested a 50%, reduction in fluoxetine[74] because of the longer half lives and reduced plasma clearance of both fluoxetine and norfluoxetine. For paroxetine and sertraline lower end of therapeutic range are suggested for hepatically impaired patients.

Use in pregnancy

Although no antidepressant is safe in pregnancy and caution should be taken to give any anti-depressant especially in the first three months of pregnancy. In a study of 10 severely depressed females who refused to accept ECT, fluoxetine given from first month of pregnancy through 3 months after delivery, produced no adverse effects in mother and newborns [75].

Psychomotor performance and SSRIs

Perhaps the greatest difference between TCAs and SSRIs is a low behavioral toxicity of the later group of drugs. TCAs are predominantly anticholinergic and these properties ensure that a patient's cognitive skills (memory, mental ability, problem solving) will be impaired and the psychomotor speed and integrity will also be disturbed. As regards SSRIs, it has repeatedly been demonstrated that at normal clinical doses, these have no more effect on psychomotor performance than does placebo; some SSRIs even show performance benefits over placebo in some situations on some subtests [76].

Moreover, despite the lack of sedative effect of SSRI, careful analysis of sleep changes with treatment have shown rapid improvement with the SSRIs, demonstrating the dissociation of sleep from sedation[77].

Table-10:A summary of the comparative behavioural toxicity of the SSRIs

	Psychomotor Speed	Cognitive processing	Arousal	Interaction with alcohol
Fluoxetine	0	?	0	⇓
Fluvoxamine	0	0	0	0
Paroxetine	0	0	⇑	?
Sertraline	0	0	⇑	?

0=No difference from placebo, ⇓=Decrease, ⇑= Increase

?: no/ambiguous data available

Side effects of SSRIs

Side effect profile is perhaps the most important area in which the SSRIs differ from earlier antidepressants.

A major difference is that SSRIs are less cardiotoxic than TCAs and are much safer in overdose. SSRIs also lack anticolinergic and antihistaminergic effects and are

therefore, non-sedating. Broadly side effects can be grouped in three categories shown in table.

Table 11 Oxford textbook of psychiatry third edition,1996

Gestrointestinal	Common	Nausea, anorexia, diarrhoea, constipation, dry mouth, dyspepsia
	Uncommon	Vomiting, weight loss
CNS	Common	Headache, insomnia, dizziness, somnolence, anxiety, fatigue tremor
	Uncommon	Extrapyramidal (parkinsonism, akathesia) agitation, irritability, restlessness, seizures mania
Other	Common	Sweating, delayed orgasm, anorgasmia, sexual dysfunction
	Uncommon	Rash, pharyngitis, dyspnea, serum sickness, hyponatremia alopecia

Another rare but serious side effect of SSRIs called 5-HT toxicity syndrome has been reported which occurs after simultaneous administration of SSRIs and MAOIs and cause hyperpyrexia, rigidity, myoclonus, comma and death.

Table. Table 11 Summary of adverse event profiles of fluvoxamine, fluoxetine, sertraline, and paroxetine-data submitted to the US FDA and published as product prescribing information

Adverse events	Fluvoxamine	Fluoxetine	Paroxetine	Sertraline
Nausea	26.0	11.0	14.3	16.4
Diarrhoea	4.0	5.3	8.4	4.0
Headache	2.0	4.8	1.3	0.3
Abnormal ejaculation	7.0	1.9	13.3	12.9
Insomnia	11.0	6.7	7.6	7.1
Somnolence	14.0	5.9	7.5	14.3
Anxiety	2.0	3.9	1.3	2.1
Nervousness	7.0	6.4	1.5	2.6
Anorexia	4.0	7.2	1.2	4.5
Dry mouth	4.0	3.5	7.0	6.0

Value given as the difference between the percentage of patients reporting adverse events with drug and the percentage reporting adverse events with placebo (Devane, 1995).

Note: Data for paroxetine and sertraline from patients with depression; data for fluoxetine and fluvoxamine from patients with depression or obsessive-compulsive disease.

Conclusion

In conclusion SSRIs have widened the scope for pharmacological treatment of depression. They are almost as effective as TCAs for the treatment of depression and have considerable advantage for providing relief without anticholinergic, antihistaminergic and cardiovascular side effects. Perhaps the greatest advantage is low behavioural toxicity. SSRIs are also very useful in high risk patients and elderly. The benefit of safety in overdose is equally applicable in all ages and in all groups of patients. The user friendly side effect profile will increase apparent efficacy by increasing compliance and this will be more evident in long term treatment. Continued use and experience with SSRIs has enhanced our understanding of the central serotonergic system and has led to the development of more selective drugs.

Table-12: Summary of differentiation in adverse effects of the SSRIs-data submitted to the US FDA and published as product prescribing information.

Adverse Event	Conclusion/Comment
Nausea	Common with all SSRIs; dose-related; dissipates with use to equal incidence
Diarrhoea	Higher incidence with sertraline
Dry mouth	Paroxetine and sertraline > fluoxetine and fluvoxamine
Anorexia	More likely with fluoxetine
Headache	Common with all SSRIs; highest with fluoxitine
Somnolence	Paroxetine-fluvoxamine > sertraline and fluoxetine
Anxiety/nervousness	More common with fluoxetine
EPS	Low overall incidence; more reports with fluoxetine; lowest incidence likely with fluvoxamine
Sexual dysfunction	Occurs with all SSRIs; sertraline > fluvoxamine

EPS: Extrapyramidal side effects (De Vane, 1995).

Note: data for paroxetine and sertratine from patients with depression, data for fluoxetine and fluvoxamine from patients with depression or obsessive-compulsive disease.

However, another important point which need to be kept in mind during practice and especially in developing countries is the cost of SSRIs which varies in different countries but is definitely higher than TCAs. In addition TCAs are time tested and extensively studied antidepressants as against SSRIs which are in use for 12 years only. So it will be worthwhile to conduct long term studies using large no of patients in local settings also.

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