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Review article

Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review

Meera Vaswani*, Farzana Kadar Linda, Subramanyam Ramesh

Department of Psychiatry, All India Institute of Medical Sciences, New Delhi 110029, India

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Abstract

The selective serotonin reuptake inhibitors (SSRIs) have emerged as a major therapeutic advance in psychopharmacology. As a result, the discovery of these agents marks a milestone in neuropsychopharmacology and rational drug design, and has launched a new era in psychotropic drug development. Prior to the SSRIs, all psychotropic medications were the result of chance observation. In an attempt to develop a SSRI, researchers discovered a number of nontricyclic agents with amine-uptake inhibitory properties, acting on both noradrenergic and serotonergic neurons with considerable differences in potency. A given drug may affect one or more sites over its clinically relevant dosing range and may produce multiple and different clinical effects. The enhanced safety profile includes a reduced likelihood of pharmacodynamically mediated adverse drug–drug interactions by avoiding affects on sites that are not essential to the intended outcome. SSRIs were developed for inhibition of the neuronal uptake pump for serotonin (5-HT), a property shared with the TCAs, but without affecting the other various neuroreceptors or fast sodium channels. The therapeutic mechanism of action of SSRIs involves alteration in the 5-HT system. The plethora of biological substrates, receptors and pathways for 5-HT are candidates to mediate not only the therapeutic actions of SSRIs, but also their side effects. A hypothesis to explain these immediate side effects is that 5-HT is increased at specific 5-HT receptor subtypes in discrete regions of the body where the relevant physiologic processes are regulated. Marked differences exist between the SSRIs with regard to effects on specific cytochrome *P*450 (CYP) enzymes, and thus the likelihood of clinically important pharmacokinetic drug–drug interactions. Although no clear relationship exists between the clinical efficacy, plasma concentration of SSRIs, nor any threshold that defines toxic concentrations, but therapeutic drug monitoring (TDM) may be useful in special populations, such as in elderly patients, poor metabolizers (PM) of sparteine (CYP2D6) or mephenytoin (CYP2C19), and patients with liver and kidney impairment. Several meta-analyses have reviewed the comparative efficacy of TCAs and SSRIs, and concluded that both TCAs and SSRIs have similar efficacy in the treatment of depression. SSRIs have demonstrated better efficacy and tolerability in the treatment of obsessive compulsive disorder (OCD). They have also been found to be effective in the treatment for social anxiety disorder both in reducing total levels of social anxiety and in improving overall clinical condition. The benefit of SSRIs in anorexia nervosa (AN) is apparently short-term unless medication is given in the context of nutritional or behavioral therapy. No single antidepressant can ever be recommended for every patient, but in a vast majority of patients, SSRIs should be considered as one of the first-line drugs in the treatment of depression.

Keywords: Anxiety disorders; Citalopram; Depression; Eating disorders; Fluovoxamine; Fluoxetine; Obsessive compulsive disorder; Paroxetine; Pharmacokinetics; Pharmacology; Serotonin; Sertraline; SSRIs

1. Introduction

The selective serotonin reuptake inhibitors (SSRIs) have emerged as a major therapeutic advance in psychopharmacology. They have established a pathophysiological role of serotonin (5-HT) in affective disorders and the spectrum of anxiety disorders. They are also the first to confirm the inhibition of neurotransmitter reuptake as an important therapeutic principle. As a result, the discovery of these agents marks a milestone in neuropsychopharmacology and rational drug design.

Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; DUAG, Danish University Antidepressant Group; MAOIs, monoamine oxidase inhibitors; OCD, obsessive compulsive disorder; RTD, rapid tryptophan depletion; SSRIs, selective serotonin reuptake inhibitors; 5-HT, serotonin; TCAs, tricyclic antidepressants; TDM, therapeutic drug monitoring.

* Corresponding author. Tel.: +91-11-6164288, +91-11-6593244; fax: +91-11-6862663, +91-11-6521041.

E-mail address: meeravaswani@hotmail.com (M. Vaswani).

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Prior to the SSRIs, all psychotropic medications were the result of chance observation. The phenothiazines came from a search for better pre-anaesthetic agents. The TCAs were the result of an unsuccessful attempt to improve the antipsychotic effectiveness of phenothiazines (Kuhn, 1958). The monoamine oxidase inhibitors (MAOIs) came from a failed attempt to develop effective antitubercular medications (Crane, 1957). The first studies of benzodiazepines were unsuccessful attempts to treat patients with schizophrenia. SSRIs are rationally designed class of psychotropic medications, and hence have launched a new era in psychotropic drug development (Carlsson, 1999). They are currently among the most frequently prescribed therapeutic agents in medicine.

Earlier, Carlsson and Lindqvist (1969) reported that the reuptake of 5-HT by central serotonergic neurons was blocked by imipramine. Their subsequent work found that the secondary amines were generally more potent than tertiary amines in terms of inhibiting noradrenaline uptake, whereas the reverse was true for inhibition of 5-HT uptake. In an attempt to develop a SSRI, they discovered a number of nontricyclic agents with amine-uptake inhibitory properties, acting on both noradrenergic and serotonergic neurons with considerable differences in potency. This led to the discovery of zimeldine, which was marketed by Astra. Zimeldine was approved as an antidepressant agent in early 1980s and was extensively used. The drug was withdrawn from the market in all countries due to the report of Guillain–Barre syndrome in few patients (Fagius et al., 1985; Carlsson, 1999; Edwards and Anderson, 1999). However, because of its outstanding therapeutic properties, zimeldine continued to be used ‘on license’ in Sweden for several years.

The development of subsequent SSRIs occurred over a relatively short period and the five SSRIs were eventually launched successfully in many countries around the world. Each was developed by a different company: citalopram by Lundbeck, fluvoxamine by Solvay, fluoxetine by Lilly, paroxetine by SmithKline-Beecham and sertraline by Pfizer. The fact that five different companies produced the five SSRIs is a testimony to the shift from a discovery process dependent on chance observation to a process of rational drug development.

2. Rational development of SSRIs

A drug must act on a site of action that is physiologically relevant to the effect. The drug recognizes and binds to that site, which may be an uptake pump, an enzyme or a receptor. The activation or inhibition of a specific site is termed the drugs mechanism of action. For example, a drug may be an agonist or antagonist at a specific 5-HT receptor. A given drug may affect one or more sites over its clinically relevant dosing range and may produce multiple and different clinical effects. Such drugs are more characteristic of chance discovery, whereas the goal of rational drug development is to produce drugs with a more limited range of effects. The goal in such development is to produce agents that are more efficacious, safer and better tolerated than older medications (Stahl, 1992; Preskorn, 1993). This enhanced safety profile includes a reduced likelihood of pharmacodynamically mediated adverse drug–drug interactions by avoiding effects on sites that are not essential to the intended outcome (Preskorn, 1994).

The SSRIs were all developed to have a similar mechanism of action: the potentiation of 5-HT by the inhibition of its neuronal uptake pump. As such, all SSRIs have common 5-HT agonistic that appears to mediate both their desired and undesired effects. As a class, SSRIs are considerably more selective in comparison to TCAs in terms of their central nervous system mechanisms, but differ in other clinically relevant aspects.

The reason to choose 5-HT uptake inhibition as the mechanism is based on the understanding of the role of 5-HT in the brain as well as on the pharmacology of TCAs and MAOIs. From a phylogenetic standpoint, 5-HT is one of the oldest neurotransmitters (Sjoerdsma and Palfregman, 1990). It is found in such relatively simple organisms as jellyfish. In the human brain, 5-HT-containing neurons are highly localized in specific clusters in the brainstem and spinal cord (Tork, 1990). From these sites, the cells send out axons that end in 5-HT-containing terminals innervating the diverse areas throughout the brain. Given these distributions, dysfunction of 5-HT neurons has been implicated in a wide variety of diseases, including major depression (Dubovsky and Thomas, 1995; Graeff, 1997). For the same reason, 5-HT-active drugs can have many different clinical effects. This anatomy explains why SSRIs can produce so many diverse clinical effects as well as being useful in several disorders such as major depression, anxiety disorders, pain disorders and premature ejaculation. SSRIs are selective in terms of affecting the neuronal uptake pump for 5-HT. This action effects a multitude of specific postsynaptic 5-HT receptors (e.g., 5-HT1A, 5-HT1D, 5-HT2A, 5-HT2C and 5-HT3), which, in turn, effects a multitude of neural systems (Hoyer et al., 1994; Roth, 1994).

SSRIs were developed for inhibition of the neuronal uptake pump for 5-HT, a property shared with the TCAs, but without affecting the various other neuroreceptors (i.e., histamine, acetylcholine and adrenergic receptors) or fast sodium channels, effected by the TCAs. Actions on these latter sites are responsible for many of the safety and tolerability problems of the TCAs (Preskorn and Fast, 1991; Preskorn and Burke, 1992). The fact that SSRIs were designed to avoid affecting these other sites explains many of the pharmacological differences between the SSRIs and the TCAs, and explains the similarities between the SSRIs. However, there is nothing to suggest that any one SSRI is more effective than another, but not all patients respond to the same agent. Published reports indicate that 42–71% of patients who are switched to a second SSRI after an initial failure will respond to the new SSRI (Sussman and Stahl, 1996).

Fluoxetine is a highly active 5-HT reuptake blocker in vitro and in vivo. The development of fluoxetine was based on the fact that it has a chemical structure closely related to diphenhydramine, which has 5-HT, and noradrenaline-reuptake inhibitory properties (Carlsson, 1999). This was analogous to the development of zimeldine, which closely resembles in structure to pheniramine. Its selectivity for the 5-HT transporter, lack of affinity for neurotransmitter receptors and retention of selectivity following metabolism to norfluoxetine make fluoxetine a useful tool to explore pharmacologically induced increases in 5-HT neurotransmission (Fuller et al., 1991). The evolutionary process of fluoxetine along with its effects in various in vitro assays and in animal studies including receptor downregulation, neurochemical and behavioral models has been described by Wong et al. (1995).

Zimeldine and fluoxetine were later followed by several others SSRIs. Citalopram, a potent inhibitor of 5-HT reuptake, had no significant effect on noradrenaline reuptake (Pollock, 2001). Paroxetine, a phenylpiperidine derivative, is the most potent inhibitor of the reuptake of 5-HT and is a very weak inhibitor of norepinephrine uptake but it is still more potent at this site than the other SSRIs (Bourin et al., 2001; Rasmussen and Brosen, 2000). Fluvoxamine is a potent SSRI that has little or no effect on other monoamine reuptake mechanisms. It is generally well tolerated and is associated with a low risk of suicidal behavior, sexual dysfunction and withdrawal syndrome. Fewer anticholinergic or cardiovascular events are associated with fluvoxamine than tricyclic antidepressants (TCAs) (Figgitt and McClellan, 2000). Sertraline, a naphthylamine derivative, is a widely used SSRI that has been shown to have both antidepressant and antianxiety effects (MacQueen et al., 2001). All these drugs are selective not only in regard to inhibition of 5-HT reuptake as compared to that of catecholamines but also that unlike TCAs, they lack affinity for a number of receptors and have no membrane stabilizing action leading to cardiotoxicity and lowered seizure thresholds. Therefore, the goals of rational drug design with regard to SSRIs were fulfilled, as they were equipotent to existing antidepressant drugs but with an increased therapeutic index. Their side effects are such that they are better tolerated by a vast majority of patients.

3. Mechanism of action of SSRIs

The therapeutic mechanism of action of SSRIs involves alteration in the 5-HT system. However, the drugs are not effective after acute administration, which suggests that the primary mechanism of action is not antagonism of 5-HT reuptake. The plethora of biological substrates, receptors and pathways for 5-HT are candidates to mediate not only the therapeutic actions of SSRIs, but also their side effects. Specifically, the immediate actions of SSRIs are mostly side effects and may be mediated by initiating the actions of SSRIs, namely negative allosteric modulation of the 5-HT transporter. A hypothesis to explain the immediate side effects are that 5-HT is increased at specific 5-HT receptor subtypes in discrete regions of the body where the relevant physiologic processes are regulated. Desensitization of postsynaptic receptors in these brain regions may explain the development of tolerance to side effects. The explanation for therapeutic effects characteristic of SSRIs may be found in delayed neurochemical adaptations. A leading hypothesis for this action is desensitization of somatodendritic 5-HT1A autoreceptors in the midbrain raphe nucleus. This explains that somatodendritic 5HT1A autoreceptor desensitization increases 5-HT in critical brain regions and at key 5-HT receptor subtype(s), which may mediate the pathophysiologies of the various disorders (Fuller, 1986; Gonzalez-Heydrich and Peroutka, 1990; Goodwin, 1996; Stahl, 1998). It has also been postulated that 5-HT is a modulator, which modulates a homeostasis between dopamine, noradrenaline and GABA, which mediate thought process, anxiety and mood, respectively. When this homeostasis gets disturbed, depression sets in. Serotonergic drugs merely reinstate the homeostasis (Davis et al., 1999).

Meyer et al. (2001) in a recent study on the effects of SSRI treatment on 5-HT2A receptors in the cortex of drug-free depressed patients concluded that in young depressed subjects, paroxetine downregulates 5-HT2A receptors. This downregulation attenuates with age, which suggests that increased 5-HT agonism occurs on 5-HT2A receptors over 6 weeks of treatment. In addition, the 5-HT reuptake inhibition-induced remission from depression is dependent upon the integrity of 5-HT neuronal system. Studies using tryptophan depletion have shown that depleting 5-HT leads to recurrence of the disorder (Delgado et al., 1989; Charney et al., 1990). Moore et al. (2000) reviewed the rapid tryptophan depletion (RTD) methodology and its controversial association with depressive relapse. RTD has been used over the past decade to deplete 5-HT and to probe the role of the central 5-HT system in a variety of psychiatric conditions. Its current popularity has been stimulated by reports that RTD reversed the antidepressant effects of SSRIs and MAOIs in remitted patients with a history of depression but not in patients treated with antidepressants, which promote catecholaminergic rather than serotonergic neurotransmission. Similar results have been found for anxiety disorders. This suggests that increased levels of 5-HT are necessary in the synapse for the SSRI to be effective in the treatment of depression and panic disorder. In obsessive compulsive disorder (OCD), depletion of 5-HT in patients does not cause relapse probably due to receptor adaptation.

4. Pharmacology of SSRIs

Marked differences exist between the SSRIs with regard to their effects on specific CYP enzymes, and thus the likelihood of clinically important pharmacokinetic drug–

drug interactions. Cytochrome *P*450 (CYP) describes a class of heme-containing proteins that represent the major enzymes responsible for the oxidation and reduction of numerous endogenous substrates and drugs (Lin and Lu, 1998). The *P*450 enzymes have been classified based on their amino acid homology. CYP1A, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A enzymes account for approximately 70% of human liver CYP. Genetic polymorphisms have been clearly identified in two CYP isoenzymes, CYP2C19 and CYP2D6. This genetic polymorphism divides the population in two subpopulations, i.e., one group of individuals with a normal catalytic function, so-called extensive metabolizers (EM), and a group of individuals with a severely impaired catalytic capacity, so-called poor metabolizers (PM) (Smith et al., 1998). The CYP2D6 PM phenotype occurs at a frequency of approximately 5–10% in the Caucasian population. In other populations, however, the PM phenotype is considerably less frequent, only 2% in Black Americans and $<1\%$ in Orientals. The frequency of the CYP2C19 PM phenotype in Caucasians is 2–5%. In Orientals, a greater frequency of about 20% is observed (Smith et al., 1998). Patients who are unable to metabolize substrates of these enzymes have a higher risk of adverse effects when treated with such drugs (Brosen, 1996). CYP2D6 is inhibited by SSRIs, in order of decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram and fluvoxamine (Baumann, 1996a). Briefly, Fluvoxamine potently inhibits CYP1A2 and CYP2C19, and has mild to moderate inhibitory effect on CYP2C9, CYP2D6 and CYP3A4. Both fluoxetine and paroxetine potently inhibit CYP2D6 and the first also exerts a moderate effect on CYP3A4 activity. Sertraline has a modest effect on CYP2D6. The current knowledge on citalopram suggests little interaction potential with coadministered drugs.

SSRIs also present some interindividual differences with regard to their affinity for adrenergic, muscarinic, histaminergic and serotonergic receptors, as well as for 5-HT and noradrenaline transporters (Stanford, 1996; de Jonghe and Swinkels, 1997). The most extensive in vitro and in vivo research has been done with fluoxetine, fluvoxamine and sertraline, while less research has been done with paroxetine and citalopram (Preskorn, 1997).

Studies have shown neither clear relationship between the clinical efficacy and plasma concentration of SSRIs nor any threshold that defines toxic concentrations (Gupta and Dziurdzy, 1994; DeVane, 1994; Amsterdam et al., 1997). Therapeutic drug monitoring (TDM) is limited to indications such as lack of compliance, nonresponse despite adequate doses or the response in special populations such as the elderly (Rasmussen and Brosen, 2000). Therapeutically, effective blood concentrations of SSRIs, however, still need to be established. The statement that dose titration guided by TDM is necessary for TCAs, but not for SSRIs, has neither been verified nor falsified in the literature. The suggested lack of data on a "therapeutic window" for SSRIs, therefore, cannot be considered as an advantage of SSRIs over TCAs, as long as valid studies on therapeutic serum concentrations are missing for SSRIs (Hiemke and Hartter, 2000).

Lower doses of citalopram, fluoxetine and sertraline have been suggested for patients with liver diseases (Baumann, 1998). With paroxetine, a drug eliminated mainly by kidneys, the dose should be carefully titrated in patients with renal disease. Although controlled studies of elderly patients are lacking with regard to doses, it is advisable to decrease the recommended doses of citalopram, paroxetine and sertraline. Hence, in special populations, such as in elderly patients, PM of sparteine (CYP2D6) or mephenytoin (CYP2C19), and patients with liver impairment, the measurement of plasma concentrations may be useful (Rasmussen and Brosen, 2000).

The following sections discuss the individual pharmacokinetics of the five clinically used SSRIs.

4.1. Fluoxetine

After oral administration, fluoxetine is almost completely absorbed. Due to hepatic first-pass metabolism, the oral bioavailability is $<90\%$. The volume of distribution of fluoxetine is by far the highest among all SSRIs. The accumulation is highest in lungs, an organ enriched with lysosomes. Fluoxetine undergoes extensive metabolic conversion leading to the active metabolite norfluoxetine. Fluoxetine has a half-life of 1–4 days, whereas the half-life of norfluoxetine ranges between 7 and 15 days. The long $t_{1/2}$ of fluoxetine may be both advantageous and disadvantageous. It is advantageous for a patient with poor compliance, since drug concentrations decrease only slightly when the patient omits a dose. On the other hand, at least 4 weeks of constant medication are necessary to reach steady state levels of fluoxetine. Moreover, in the case of fluoxetine nonresponse, long washout periods are necessary before switching the patient to a TCA or a MAO inhibitor to avoid drug interactions or the development of a 5-HT syndrome. Fluoxetine exhibits nonlinear kinetics indicated by a disproportionate increase in its blood concentration after dose escalation. Abnormalities in the elimination of fluoxetine have not been noted for patients with renal disease, whereas liver cirrhosis significantly reduces the plasma clearance of fluoxetine (Benfield et al., 1986). After oral administration, fluoxetine is mainly excreted in urine with $<10\%$ excreted unchanged or as fluoxetine *N*-glucoronide.

So far, few studies had investigated the CYP isoenzymes responsible for the metabolism of fluoxetine but the results have been inconclusive. Fluoxetine, its metabolite norfluoxetine, are potent inhibitors of CYP2D6 activity, whereas norfluoxetine has a moderate inhibitory effect on CYP3A4. Hamelin et al. (1996) reported a meaningful contribution of CYP2D6 in the *N*-demethylation of fluoxetine in healthy volunteers. Recently, it has been shown that the clearance of *R*- and *S*-fluoxetine and *S*-norfluoxetine strongly depends on

the CYP2D6 activity (Fjordside et al., 1999). An in vitro study suggested that CYP2C9 plays a pivotal role in the *N*-demethylation of fluoxetine with a possible contribution of the CYP2C19 and a CYP3A isoform, whereas the contribution of CYP2D6 was found to be negligible (von Moltke et al., 1997). Hemeryck and Belpaire (2002) reported that fluoxetine has weak capacity to inhibit CYP1A2 and moderate to weak effect on CYP2C19 and CYP2C9 activity in vitro. Although there are no formal in vivo studies on the effect of fluoxetine on CYP1A2 activity, this SSRI is expected to produce only a minimal inhibitory effect towards this isoform, based on their low in vitro potency.

The relationship between blood concentration of racemic fluoxetine and norfluoxetine and clinical outcome or adverse effects was studied recently. These studies could not find a relationship between clinical outcome and plasma concentration of either fluoxetine or norfluoxetine or both (Amsterdam et al., 1997; Koran et al., 1996; Beasley et al., 1990). Fluoxetine and its main metabolite norfluoxetine have low affinity to neurotransmitter receptors, e.g., serotonin 5-HT2A receptors, muscarinic acetylcholine receptors, dopamine D_2-receptor or β-adreno-receptor (Stanford, 1996). However, some of the rare adverse effects might be attributed to effects on receptor sites under conditions when high blood concentrations of fluoxetine or norfluoxetine are achieved. This may be relevant for patients with CYP2D6 deficiency, since the clearance of both fluoxetine enantiomers and of *S*-norfluoxetine depends on the activity of CYP2D6 (Fjordside et al., 1999). The extra-pyramidal symptoms occasionally described in patients treated with fluoxetine, therefore, might be due to metabolic deficiency, which leads to high fluoxetine and norfluoxetine blood levels (Leo, 1996).

One of the most prominent features of all SSRIs is their potential for pharmacokinetic drug interactions with other class of drugs. Fluoxetine was the first SSRI for which drug interactions have been reported. Clinically relevant interactions have been observed for TCAs and neuroleptics (Spina et al., 1998). The mechanism of these interactions could be ascribed to inhibitory effects of fluoxetine and norfluoxetine on the isoenzyme CYP2D6. The extent of inhibition correlated with plasma concentration of fluoxetine and norfluoxetine respectively. This suggests that fluoxetine and norfluoxetine can compete with other drugs for metabolism by CYP2D6. Recently, a moderate inhibitory effect has been reported for norfluoxetine on CYP3A4 (Hemeryck and Belpaire, 2002; Greenblatt et al., 1996).

4.2. Citalopram

Citalopram is a selective 5-HT reuptake inhibitor that has demonstrated antidepressant efficacy in numerous controlled clinical trials (Pollock, 2001). It has by far the highest selectivity for inhibiting 5-HT reuptake over noradrenaline reuptake (Baumann, 1996b). It is marketed as a racemate, but its pharmacological effects are almost exclusively ascribed to the *S*(+)-enantiomer. The main metabolite of citalopram measurable in plasma is *N*-desmethylcitalopram, which is also an SSRI showing the same enantiomeric differential as its parent drug. However, the pharmacologic activity of the metabolite is weak as compared to the parent drug (Bauman and Larsen, 1995). In addition to its ability to inhibit 5-HT uptake, citalopram has some affinity to α-1-adreno-receptors and slight histamine H_1 receptor blocking potency (Owens et al., 1997).

As for other lipophilic drugs, the absorption of citalopram from the gastrointestinal tract is almost complete. In contrast to other SSRIs, the first pass effect of citalopram seems to be of minor importance, which is in line with absolute bioavailability of about 80%. A linear relationship between citalopram dosage and plasma concentration has been reported under steady state conditions, but the interindividual variability increases with dose, which might be due to saturation of an elimination pathway (Bauman and Larsen, 1995). Although the half-life of *N*-demethylated metabolite is ~2–3 times longer than the main drug, it does not exceed the plasma concentration of its parent drug (Baumann, 1996b). This indicates the relatively poor contribution of metabolites to the overall clearance of citalopram.

Protein binding of citalopram amounts only to about 80%, which makes interaction at specific protein binding sites quite unlikely. There have been few studies of blood concentration and therapeutic effect for citalopram.

It has been shown that CYP2C19 and CYP2D6, both polymorphically expressed isoenzymes, play a role in the biotransformation of citalopram. In vitro formation of *N*-desmethylcitalopram from citalopram is dependent on both CYP2C19 and CYP3A, with a possible contribution of CYP2D6 (Rochat et al., 1997; Kobayashi et al., 1997; Hemeryck and Belpaire, 2002). Only citalopram and desmethylcitalopram have been evaluated for their inhibitory effect on CYP2E1 activity in vitro and were found to be weak inhibitors of this isoform (Olesen and Linnet, 1999). In vivo data shows that further demethylation of *N*-desmethylcitalopram is mainly catalyzed by CYP2D6 (Sindrup et al., 1993). The contribution of CYP3A4 to the clearance of citalopram is also indicated by accelerated metabolism of citalopram under concomitant treatment with carbamazepine (Leinonen et al., 1996). Chronic treatment with citalopram slightly reduces the activity of CYP2D6, which is probably due to inhibitory properties of *N*-desmethylcitalopram (Bauman and Larsen, 1995). With other psychotropic drugs, including TCAs, neuroleptics, tranquilizers, relevant pharmacokinetic drug interactions are rather unlikely. Therefore, citalopram is the safest SSRI with respect to pharmacokinetic drug interaction. It is the only SSRI available for intravenous treatment.

4.3. Sertraline

The naphthylamine derivative sertraline is the second most potent inhibitor of 5-HT reuptake and the second most

selective blocker of 5-HT over noradrenaline uptake. It is the only SSRI that binds to dopamine transporter (Richelson, 1994). With exception of an α-adreno-receptor blocking potential, the affinity of sertraline for neurotransmitter receptors is low (Owens et al., 1997). Linear pharmacokinetics is suggested for sertraline (Preskorn, 1993). In young men, half-life is 30% shorter (22.4 h) than in females or aged patients (32.1–36.7 h) (Ronfeld et al., 1997). This suggests sex- and age-dependent differences either in the tissue distribution or in the metabolism of sertraline. Similar age and sex differences have been shown for the *N*-demethylated metabolite (Ronfeld et al., 1997).

Although the hepatic metabolism is the most important elimination pathway, with only 0.2% of an oral dose being excreted unchanged in the urine, information on the metabolism of sertraline is rather limited (Murdoch and McTavish, 1992). *N*-Demethylation is the main metabolic step in the biotransformation of sertraline. The *N*-demethylated metabolite is more slowly eliminated due to its longer half-life than the parent drug. Hence, the plasma concentration of *N*-desmethylsertraline is one to three times that of sertraline (Rudorfer and Potter, 1997). The *N*-desmethylation correlates with the activity of CYP3A4, suggesting that this enzyme is involved (Preskorn, 1997). Sertraline has a modest effect on CYP2D6 and moderate to weak effect on CYP2C19 (Kobayashi et al., 1995). Only one study by Crew et al. (1992) reported that sertraline is a potent inhibitor of CYP2D6. Conclusive data on enzymes responsible for the metabolism of sertraline however are still lacking. Sertraline is a substrate of a CYP3A and suggests its potential for drug interactions at these isoenzymes (Rapeport et al., 1996). Therefore, its metabolism in the gut may be important.

To date, there have been few reports on studies on a blood concentration and clinical effect relationships for sertraline. There are, however, indications that low concentration might be advantageous. Sertraline is administered orally and its usually effective antidepressant dose is 50 mg/day (Burke and Preskorn, 1999). It is at least as effective as higher dosages, which was mainly ascribed to a reduced side effect burden (Preskorn and Lane, 1995; Stock and Kofoed, 1994). Surveys indicate that almost two thirds of patients are satisfactorily controlled on 50 mg/day (Mendels, 1995).

4.4. Fluvoxamine

Fluvoxamine facilitates serotonergic transmission by potent and selective inhibition of 5-HT reuptake into presynaptic neurons. The selectivity for blocking 5-HT uptake is markedly higher than for noradrenaline or dopamine (Richelson, 1994). The plasma protein binding of fluvoxamine is low (77%), which makes protein binding interaction with other protein bound drugs (e.g., valproic acid) unlikely to occur (Van Harten, 1995). The plasma half-life ranged between 8 and 28 h (mean 15 h) after administration of a single oral dose of 25–100 mg fluvoxamine maleate. This relatively short half-life indicates that steady state concentration should be attained within 1 week. Fluvoxamine, however, exhibits nonlinear kinetics, which becomes most prominent after multiple dosing. After increasing dosages up to 200 mg/day, the half-life was found to be 32 ± 11 h, an almost 100% increase. Therefore, sometimes steady state conditions may not reach before 10 days of continuous treatment with fluvoxamine (DeVries et al., 1992, 1993; Hartter et al., 1993; Spigset et al., 1997b, 1998). Similar to other SSRIs, fluvoxamine's main route of elimination is through hepatic metabolism. After ingestion of fluvoxamine, 11 metabolites have been detected in urine, all of which are unlikely to possess pharmacological activity (Claassen, 1983). As for other drugs with a first pass metabolism, fluvoxamine concentrations in blood are difficult to predict from any given dose. A relationship between blood concentrations and clinical effects or a therapeutic window has not been established (Kasper et al., 1993; Walczak et al., 1996). However, side effects were suggested to correlate more directly with serum concentrations of fluvoxamine (Kasper et al., 1993) supporting the notion that there is a U-shaped relationship between drug concentrations and therapeutic response. TDM might be helpful to improve therapy with fluvoxamine.

Recent reports have tried to identify CYP isoenzymes involved in the hepatic biotransformation of fluvoxamine (Carrillo et al., 1996; Spigset et al., 1995, 1997a, 1998). All these investigations were performed in healthy volunteers and in vitro studies are still lacking. The metabolism of fluvoxamine was found to be associated with CYP2C19, CYP1A2 and polymorphic CYP2D6 activity (Carrillo et al., 1996; Spigset et al., 1995). The studies, however, did not reflect clinical conditions as they used a low single dose of 50 mg in young healthy volunteers instead of a mixed-patient population. Moreover, some results are inconsistent, perhaps because of the use of different phenotyping approaches. The use of de-brisoquine to phenotype CYP2D6 pointed to a meaningful contribution of CYP2D6 (Carrillo et al., 1996), whereas another study that used dextromethorphan as a probe indicated a moderate role of CYP2D6 (Spigset et al., 1997a). Fluvoxamine is the only SSRI that potently interacts with an isoenzyme different from CYP2D6, namely CYP1A2 and CYP2C19 (Brosen et al., 1993; von Moltke et al., 1996). In short, fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor (Xu et al., 1996) and a moderate CYP2C9, CYP2D6 and CYP3A4 inhibitor (Fleishaker and Hulst, 1994; Schmider et al., 1997). The widespread inhibitory effects of fluvoxamine point to a common inhibitory mechanism, perhaps by interaction of fluvoxamine or one of its metabolites with the heme moiety of the cytochromes, as has been shown for cimitidine (Levine and Bellward, 1995). On the other hand, it should be emphasized that the concomitant use of fluvoxamine gives the opportunity to improve therapeutic effects of

psychotropic drugs (Szegedi et al., 1995; Silver and Shmugliakov, 1998). The observed improved response may be due to reduced rate of formation of toxic metabolites that decreases the occurrence of side effects or prolongation of half-life, resulting in persistent optimal blood concentrations of the drug and thus reducing the difference between minimal and maximal drug concentrations (Bender and Eap, 1998).

4.5. Paroxetine

Paroxetine is a chiral SSRI but is marketed as its active (*S*)-enantiomer. It is a secondary amine and is the most potent 5-HT reuptake blocker. However, it has lower selectivity for the 5-HT reuptake site than either fluvoxamine or sertraline. In addition, it blocks muscarinic acetylcholine receptors to almost the same degree as the TCAs such as imipramine or doxepin, and even more effectively than desipramine or maprotiline (Owens et al., 1997). In spite of this property, anticholinergic side effects are likely to be restricted to toxic doses of paroxetine that are much higher than those required for therapeutic actions. Paroxetine is administered orally and its usual effective antidepressant dose is 20 mg/day (Burke and Preskorn, 1999). Paroxetine is efficiently absorbed from the gastrointestinal tract, but is readily metabolized during its first pass through the liver (Kaye et al., 1989). The half-life is variable, depending on both dose and duration of administration (Van Harten, 1993). After 15 days of oral administration of 30 mg of paroxetine/day, the half-life is increased by more than 100% (Kaye et al., 1989).

Plasma concentrations at steady state and the elimination half-life are generally prolonged in elderly subjects (Lundmark et al., 1989). Like other lipophilic psychotropic drugs, paroxetine undergoes extensive metabolism in the liver to form more hydrophilic excretable compounds. None of the metabolite is assumed to contribute to the pharmacologic effects of paroxetine (Kaye et al., 1989). Paroxetine is a potent inhibitor of CYP2D6 (Lane, 1996). The isoenzyme CYP2D6 is likely to be involved in the metabolism of paroxetine, as paroxetine's clearance cosegregates with the CYP2D6 phenotype in vivo, a finding supported by in vitro data. CYP3A4 could also be involved in the oxidative degradation of paroxetine because cotreatment with carbamazepine, a potent CYP3A4 inducer, lowered paroxetine plasma concentrations in patients. Recent data indicates that paroxetine potently inhibits CYP2D6, exerts a moderate effect on CYP3A4, moderate to weak effect on CYP2C19 activity and has weak effect on CYP1A2 activity (Hemeryck and Belpaire, 2002).

Similar to the findings for other SSRIs, studies to date on paroxetine do not give evidence of the existence of a relationship between blood concentration and clinical effects (DUAG, 1990; Kuhs et al., 1992). However, the magnitude of CYP2D6 inhibition correlates with the plasma concentration of paroxetine (Jeppesen et al., 1996).

5. SSRI's in psychiatric disorders

The indications of SSRIs are many. The focus of the review is mainly on the role of SSRIs in the following psychiatric disorders:

Depression
Anxiety disorders
Eating disorders

A passing mention is also being made of other psychiatric indications such as premenstrual dysphoric disorder (PMDD), impulse control disorder and suicide.

5.1. Depression

Over the past decade, tremendous strides have been made in the treatment of major depression due to the ability to rationally develop psychiatric medications (Preskorn, 1995). The introduction of the SSRIs in the late 1980s has radically changed the treatment of depressive disorder worldwide and they have emerged as the first line of treatment for depressive disorders. The five SSRIs currently marketed were found to be superior to placebo and, at least, for most clinical populations, of equal efficacy when compared to the older generations of TCAs (Newman and Nierenberg, 1999).

The common features of SSRIs with regard to treatment of depression are, flat dose–antidepressant response curve, equal efficacy at usual therapeutic dose (i.e., 40 mg/day of citalopram = 20 mg/day fluoxetine = 20 mg/day paroxetine = 50 mg/day sertraline), and similar efficacy when used on maintenance basis. The usual effective minimum dose of each SSRI causes 60–80% inhibition of 5-HT receptors and benign side effect profile. Although SSRIs have a flat dose response curve, an increase in dosage is warranted in cases of partial response to a lower dose. Most flexible dosing strategies in head to head comparison of SSRIs with placebo show superiority of higher doses in the treatment of major depressive disorder. Thus, 40–60 mg/day of citalopram is superior to lower doses (Kelsey and Nemeroff, 2000). However, differences in the onset of action and adverse effects have been a subject of debate but most clinicians believe that the timing of clinical effects is the same for each of the SSRIs (Newman and Nierenberg, 1999). The following sections explore the clinically relevant data among the five SSRIs for the treatment of depression.

5.2. Comparison with TCAs

Certain findings are relevant and worth noting for the use of the SSRIs by clinicians. The influential studies of the Danish University Antidepressants Group (DUAG, 1986, 1990) had earlier sparked debate about the relative efficacy of the SSRIs and TCAs. Their studies suggested that clomipramine is superior to citalopram and paroxetine in severely depressed in-patients (Nirenberg, 1994; Perry,

1996; Newman and Nierenberg, 1999). Later, Anderson (2000) found that SSRIs are not proven to be as effective as TCAs in in-patients and against amitriptyline. George and Lydiard (1991) reviewed 11 double-blind, placebo-controlled trials specifically looking for differences in speed of onset of action between fluoxetine and TCAs but found no differences.

Several meta-analyses have reviewed the comparative efficacy of TCAs and SSRIs and concluded that both TCAs and SSRIs have similar efficacy (Song et al., 1993; Montgomery et al., 1994; Anderson, 2000). There was no significant difference in the compliance rates. No significant differences were found in patients who dropped out due to lack of efficacy, but significantly fewer patients discontinued studies due to side effects from the SSRIs compared to the TCAs (Song et al., 1993; Montgomery et al., 1994; Peretti et al., 2000). The higher discontinuation rate with tricyclics, however, may be due to a subtle bias with TCAs being started at higher doses rather than using tolerable dose escalations (Newman and Nierenberg, 1999; Peretti et al., 2000). A recent meta-analysis by Geddes et al. (2000) showed that, clinically, there was no significant difference in effectiveness among the SSRIs and TCAs, and that the treatment decision needs to be based on considerations of patient acceptability, tolerability and cost.

In terms of tolerability and toxicity, SSRIs appear to be more acceptable to both patients and their physicians than older antidepressants as they are equally efficacious compared to the TCAs (Song et al., 1993; Montgomery et al., 1994; Newman and Nierenberg, 1999; Anderson, 2000). They differ from the TCAs with regard to their safety of administration, acute therapeutic index, long-term safety, minimal alcohol potentiation activity, better tolerability (no cardiotoxicity, sedation, weight gain, anticholinergic side effects), overall response rate, speed of onset of action, use in maintenance and prophylaxis (Peretti et al., 2000). The use of the SSRIs are also cost-effective, simple, easy to administer and devoid of the need for laboratory monitoring. In summary, comparison between TCAs and SSRIs indicate equal efficacy and onset of action but slightly different side effects.

5.3. Comparison with newer antidepressants

Unlike the wealth of data comparing SSRIs and TCAs, there is a paucity of data comparing most of the atypical antidepressants to the SSRIs, with the exception of trazodone. The literature suggests that SSRIs and trazodone are equally effective in treating depression. However, these studies compared trazodone to fluoxetine and not with any other SSRIs. The results also indicated that trazodone has more sedating side effects, while fluoxetine has more activating side effects leading to a trend for favoring fluoxetine for completers of the study (Debus et al., 1988; Perry et al., 1989; Beasley et al., 1991; Hellerstein et al., 1994; Haria et al., 1994).

A meta-analysis by Workman and Short (1993) found no difference in effect size between imipramine, bupropion and fluoxetine. Preskorn (1995) reported that bupropion had a higher rate of tremors than fluoxetine, sertraline or paroxetine using placebo-adjusted rates. Only two studies have compared nefazodone with a SSRI in major depression, and both the medications demonstrated equal efficacy and tolerability except that sertraline had negative effects on sexual function (Feiger et al., 1996; Baldwin et al., 1996). In a review looking into the comparative tolerability of newer antidepressants, Preskorn (1995) reported that nefazodone had fewer cumulative adverse effects (dizziness, confusion and visual disturbance) than fluoxetine.

Comparison of venlafaxine with fluoxetine found that fluoxetine at 20 mg/day was equally effective as compared to venlafaxine 75 mg/day, whereas venlafaxine at 200 mg/day was found superior to fluoxetine at 40 mg/day (Dierick et al., 1996; Clerc et al., 1994). However, Preskorn (1995) found that venlafaxine had the highest incidence of nausea and anorexia while using placebo-adjusted incidence rates when compared with fluoxetine, paroxetine and sertraline. Wheatley et al. (1998), while comparing the effects of mirtazapine and fluoxetine in depressed patients, concluded that mirtazapine was as well tolerated as fluoxetine and was found to be significantly more effective after 3–4 weeks of therapy.

5.4. Comparison with monoamine inhibitors

Three studies have compared the use of MAOIs with fluoxetine in the treatment of depression. Pande et al. (1996) reported equal response to both medications, but adverse effects were more with phenelzine. Williams et al. (1993) also found equal efficacy with fluoxetine and the reversible MAOI, moclobemide. Fluoxetine-treated patients reported more sedation, nausea and vomiting, while moclobemide-treated patients complained more of insomnia. However, the differences in these side effects were not statistically significant. The third study comparing moclobemide and fluoxetine showed a nonsignificant difference in reduction of standardized ratings of depression (Lonnqvist et al., 1994).

6. Anxiety disorders

6.1. Obsessive compulsive disorder

OCD is a chronic illness associated with substantial morbidity, which often requires long-term medication. The best-studied therapeutic agent in the treatment of this disorder is the TCA clomipramine, and it was the first agent approved for use in OCD. However, clomipramine has serious adverse effects and the SSRIs offer significant advantages. Consequently, SSRIs have been the focus of several large-scale, placebo-controlled studies of OCD.

Pigott and Seay (1999) reviewed the efficacy of SSRIs in the treatment of OCD and reported that the SSRIs have demonstrated efficacy and tolerability in separate multicentric trials. In contrast, clomipramine, though efficacious, is often associated with substantial adverse events, particularly anticholinergic side effects.

Fluoxetine was the first SSRI approved for the treatment of OCD in the USA. In a recent review, fluoxetine was found to be effective in OCD within the dose range of 40–60 mg/day and the efficacy was maintained over 3 years. A comparison of fluoxetine and clomipramine showed comparable efficacy and a superior safety profile of fluoxetine both in terms of anticholinergic side effects and cardiotoxicity or overdose (Montgomery et al., 1993; Etain and Bonnet-Perrin, 2001). The relapse rate was similar with both drugs. Fluoxetine was found to have a good safety profile and the adverse effects rarely led to discontinuation of the treatment. A long history of the disorder, severity of the symptoms, obsession of collection, washing compulsions, obsessional slowness and comorbidity with a schizotypic personality or vocal or motor tics were associated with a poorer response with fluoxetine. Fluoxetine also alleviates depressive symptoms by significantly reducing suicidal ideation and impulsiveness in OCD patients. Therefore, fluoxetine is effective and well tolerated in OCD placing it among the first line of treatment. The rate of therapeutic response to fluoxetine and other SSRIs is slower in OCD as compared to depression. Relatively higher doses and longer duration of treatment may be necessary to effect a response in OCD (Kelsey and Nemeroff, 2000).

Uncontrolled clinical trials have found no difference between fluvoxamine and clomipramine for the treatment of OCD. However, a meta-analysis of four controlled trials showed clomipramine to be superior (Figgitt and McClellan, 2000; Kelsey and Nemeroff, 2000). Koponen et al. (1997) reported that the dosage of 40–60 mg/day of citalopram were effective in 75% of the OCD subjects. Hence, SSRIs have emerged as the first-line agents in the treatment of OCD. Numerous clinical trials have confirmed their efficacy and established their superior risk–benefit ratio in comparison with clomipramine, a non-SSRI (Hughes et al., 1999; Vythilingum et al., 2000; Etain and Bonnet-Perrin, 2001).

6.2. Social phobia

Social phobia either individually or as a comorbid condition effects 10–15% of the population (Kessler et al., 1994). It is a chronic condition, which leads to significant disability in professional life of patients. It often coexists with depression, alcoholism, and substance abuse. Due to its early age of onset it effects crucially, the ability to form interpersonal relationships and thus impedes the growth of a person. Two forms of social phobia are recognized, viz. a generalized form in which the person fears a multitude of social and performance situations and a second milder specific form in which less than three situations are feared. A variety of drugs have been used to treat social phobia. The nonselective MAO inhibitor phenelazine is highly effective but has serious side effects profile. Alprazolam and clonazepam are effective but being benzodiazepines, increases risks of drug dependency in the long term. SSRIs are highly effective in social phobia. Fluvoxamine was the first SSRI demonstrated to be superior to placebo in patients meeting DSM-III-R criteria of social phobia (van Vliet et al., 1994). A statistically significant effect was seen on measures of social anxiety and anticipatory anxiety in patients treated with fluvoxamine. The level of phobic avoidance also decreases. Considerable data exists for the use of paroxetine in this condition and it is the only SSRI indicated for the treatment of social anxiety (Wagstaff et al., 2002). Baldwin (2000) reported that paroxetine was effective in reducing the symptoms of anxiety, disability and impairment. There are no head-to-head trials of paroxetine with other SSRIs in social phobia. Ballenger et al. (1998) reported that though clinical improvements in social phobia occur in about 8 weeks of initiating treatment with an SSRI, but the treatment needs to be continued for at least 1 year. Van der Linden et al. (2000) concluded with a high degree of confidence that SSRI treatment for social anxiety disorder is effective, both in reducing total levels of social anxiety and in improving patient's overall clinical condition. The efficacy of SSRIs for social anxiety is so encouraging that it has been called the gold standard for the pharmacological treatment of this order (Van Amerigen et al., 1999).

6.3. Generalized anxiety disorders

Patients with generalized anxiety disorders (GAD) experience chronic excessive uncontrollable worry combined with irritability, sleep disturbance and muscle tension. The intensity of symptoms fluctuate and when severe, causes substantial impairment in socio-occupational functioning. GAD is an early onset disorder, which usually has duration of more than 5 years by the time it is diagnosed. As a condition it needs chronic medication, which make such patients poor candidates for benzodiazepine treatment alone. The azaspirone, buspirone has been used for prolonged therapy as it does not produce physical dependence. Emerging evidence suggests that SSRIs are effective in the treatment of GAD. Evidence is robust for paroxetine, which has been evaluated in almost 2000 patients in placebo controlled short and long-term trials. The effect of paroxetine has been mainly on psychic symptoms of GAD, which is reflected by a marked decrease in harm avoidance and an increase in self-directedness (Zohar and Westenberg, 2000). Also, it must be remembered that GAD often exists comorbidly with other psychiatric disorders such as panic disorder and social phobia, for which SSRIs have been shown to be effective.

6.4. Panic disorder

Panic disorder is characterized by discrete periods of intense fear and physical discomfort. Typically, symptoms include shortness of breath, palpitations, dizziness, sweating and signs and symptoms of dysphoric arousal. Invariably, panic disorder is associated with significant distress and marked socio-occupational dysfunction. Coexistent anxiety, agoraphobia and depression are common. Pharmacological treatment of panic disorder includes use of both benzodiazepines and antidepressants. However, prescribing benzodiazepines is associated with a high incidence of rebound anxiety and withdrawal symptoms on rapid drug taper. The presence of sedation, decreased alertness, impaired cognition, risk for dependence and drug abuse are all disadvantages of benzodiazepine use. The antidepressant effect in addition to anxiolysis is probably responsible for the efficacy of these drugs. Among the antidepressant drugs, SSRIs are at least as effective as TCAs for panic disorder, with fewer and less troublesome side effects. Controlled trials with fluvoxamine, paroxetine, citalopram, sertraline and fluoxetine have all demonstrated efficacy in the treatment of panic disorder. Black et al. (1993) reported faster and better response with fluvoxamine vis-a-vis cognitive therapy for panic disorder. Figgit and McClellan (2000) reported that fluvoxamine $\leq$300 mg/day for 6–8 weeks was as effective as imipramine in patients with panic disorder and significantly more effective than placebo. Similar response has been reported with paroxetine, but at a higher dose as required for treating depression. A meta-analysis by Boyer (1995), comparing SSRIs and imipramine and alprazolam for the alleviation of panic attacks, found that, while all the three drugs were superior to placebo, the SSRIs were superior to imipramine and alprazolam. Of all SSRIs, fluvoxamine is commonly reported to have a better tolerability profile. On the basis of current treatment guidelines, fluvoxamine, like other SSRIs, is recommended as first-line treatment for a number of anxiety disorders. It appears to offer some pharmacokinetic advantages and a different drug interaction profile to the other SSRIs with similar spectrum of adverse effects. Large trials comparing the efficacy of fluvoxamine and other SSRIs in patients with anxiety disorders are warranted.

6.5. Posttraumatic stress disorder (PTSD)

PTSD is an anxiety disorder, currently defined by the coexistence of three clusters of symptoms (namely reexperiencing, avoidance, hyper arousal) persisting for at least a month, in survivors of traumatic event. The diagnosis of PTSD involves both an observation of current symptoms and attribution of such symptoms to specific traumatic event. It is felt that PTSD is the final pathological outcome of all types of traumatic events, from the most horrifying to the most frequent ones (Shalev, 2000). Several open studies have investigated the role of SSRIs in the treatment of PTSD. De Boer et al. (1992) studied fluvoxamine in 24 Dutch resistance fighters with chronic (DSM-III-R) PTSD or partial PTSD. Modest improvement was reported on a PTSD self-rating scale with 5 of the 11 completers reporting substantial improvement. Davidson et al. (1998) reported similar response with fluvoxamine in civilian population. A recent study reported that paroxetine in doses of up to 60 mg over 12 weeks was effective in noncombat-related PTSD. The study showed that improvement in hyper arousal and avoidance occurred over first 8 weeks, while reexperience of symptoms improved more gradually over 12 weeks (Marshall et al., 1998). van der Kolk et al. (1994) reported significant response to fluoxetine in doses up to 60 mg/day over 5 weeks, while Davidson et al. (1997) did not find any benefit with fluoxetine at lower doses. Recent work with sertraline also suggests that this drug is both safe and effective in PTSD (Rothbaum and Farfel, 1999). Finally, a meta-analysis of six controlled trials of PTSD showed a correlation between greater serotonergic activity and better treatment response (Penava et al., 1996–1997). Overall, the efficacy of SSRIs in PTSD appears to be moderate.

6.6. Eating disorders

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in attitudes toward weight and perception of body shape. Emerging data supports the possibility of substantial biologic and genetic vulnerabilities contributing to the pathogenesis of these disorders. Multiple state-related neuroendocrine and neurotransmitter abnormalities have been documented in AN and BN, which tend to normalize after symptom remission and weight restoration. However, elevated concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid after recovery suggest that altered 5-HT activity in AN and BN is a trait-related characteristic. Elevated 5-HT activity is consistent with behaviors found after recovery from AN and BN, such as obsessions with symmetry and exactness, harm avoidance, perfectionism and behavior over-control (Kaye et al., 1998). In BN, serotonergic modulating antidepressant medications suppress symptoms independently of their antidepressant effects.

Despite the expectations, clinical investigations in the use of SSRIs in eating disorders have yielded mixed results (Mayer and Walsh, 1998). The data on AN are limited and suggest a lack of efficacy for SSRIs in patients with AN who are malnourished and under-weight (Ferguson et al., 1999; Kaye et al., 1998). The nonresponse to SSRIs could be a consequence of inadequate supply of nutrients, which are essential for normal 5-HT synthesis and function. However, when given after weight restoration, fluoxetine may significantly reduce the extremely high rate of relapse seen in AN. This benefit is apparently short-term unless medication is given in the context of nutritional or behav-

ioral therapy (Jimerson et al., 1993; Bowers and Andersen, 1994; Agras, 1997; Strober et al., 1997). The data on BN are clearer and suggest that antidepressant therapy, fluoxetine being the drug most widely studied, is superior to treatment with placebo but less effective than cognitive behavior therapy (CBT) alone, with one such study suggesting that the combination may provide optimal treatment (Mitchell et al., 2001). Recently, Frank et al. (2001) reported five cases of underweight women with binge eating/purging-type eating disorders who gained weight and had reduced core eating disorder behaviors in response to sertraline.

6.7. Premenstrual syndrome (PMDD)

PMDD affects 3–8% of women in the reproductive age group (Steiner et al., 1995). A number of studies involving fluoxetine, sertraline, paroxetine and citalopram have found that PMDD responds to treatment with SSRIs. A multicenteric trial indicated that lower dose of fluoxetine (20 mg/day) was effective, while higher dose (60 mg/day) leads to drop outs due to side effects (Steiner et al., 1995). While most studies seem to indicate the need for treatment through out the menstrual cycle (Elks, 1993), recently, some studies have also supported intermittent dosing during the luteal phase (Wikander et al., 1998).

6.8. SSRIs and impulse control disorder

A number of studies have suggested that aggression in primates and possibly in humans may be related to decreased central serotonergic activity as seen by a decrease in CSF levels of 5-HIAA (Mehlman et al., 1994). Some of the studies have also reported a significant decrease in aggression in patients with personality disorder and in depressed patients with aggression on treatment with fluoxetine (Fava et al., 1993).

6.9. SSRIs and suicide

Early literature reported an intensification of suicidal ideation on fluoxetine use (Teicher et al., 1990). A subsequent meta-analysis found that emergence of suicidal thoughts was lower with fluoxetine than with placebo or TCAs (Beasley et al., 1991). In fact, suicide victims have lower imipramine binding sites in the frontal cortex and lower levels of 5-HIAA in the CSF. Thus, it is possible that SSRIs may actually decrease suicidal ideation faster than other antidepressants (Montgomery et al., 1995).

7. SSRIs in special populations

7.1. Children and adolescents

Since their introduction, SSRIs have been increasingly used in psychiatric disorders in childhood and adolescents. However, data supporting the efficacy is still limited (Ziervogel, 2000; Kastelic et al., 2000). The most robust data is in the treatment of childhood OCD and depression. A review of the available data from pediatric SSRI trials, including 10 double-blind, placebo-controlled trials and two abstracts of open-label continuation studies of SSRIs associated with large pediatric efficacy studies reported significant superiority of SSRIs over other drugs in OCD.

Anxiety disorders are the most prevalent psychiatric disorders in children and adolescents. Research into the use of SSRIs for childhood anxiety disorders is increasing. A review on the effectiveness and tolerability of SSRIs in the pediatric population showed that these drugs are safe and promising for the treatment of children and adolescents with panic disorder, and are increasingly being recognized as first-line therapy (Murphy et al., 2000). However, randomized controlled trials evaluating the effects of SSRIs and other interventions (e.g., cognitive therapy) for treating panic disorder in children and adolescents are warranted.

7.2. Elderly

Like most drugs, SSRIs have not been widely tested in clinical trials that approximate geriatric situations. However, studies completed to date provide valuable information about the efficacy, safety and tolerability of this class of antidepressants among elderly patients with depression, including those with depression secondary to stroke or dementia and those with other comorbid physical disorders (Emslie and Judge, 2000; Cole et al., 2001). SSRIs are frequently recommended as a first-line treatment for depression in elderly patients. The evidence for this recommendation appears to be weak, because studies examining the comparative efficacy, safety, tolerability and effectiveness of SSRIs and TCAs suggest that there are few advantages for one over another (Emslie and Judge, 2000; Solai et al., 2001). Furthermore, there are a number of potential adverse effects of SSRIs that pose risks to the elderly, namely frequent falls, hyponatremia, weight loss, sexual dysfunction and drug interactions (Mort, 1999; Herrmann, 2000; Kirby and Ames, 2001; Arfken et al., 2001). These potential risks, however, are equally balanced by advantages such as fewer anticholinergic effects, a benign cardiovascular profile, ease of use and safety in overdose with SSRIs. Hence, clinicians must maintain expertise in prescribing TCAs/SSRIs for elderly patients.

Existing data do not support claims such as one SSRI is more efficacious or better tolerated by elderly patients than another. Other factors such as significant drug–drug interactions may influence the choice of agent. Such interactions are seen more with fluoxetine, fluvoxamine and paroxetine than with citalopram or sertraline. In contrast to other SSRIs, fluoxetine has a longer half-life, which can be advantageous in weaning off therapy as it may reduce the

incidence of discontinuation symptoms. However, a significant disadvantage is that the patient may not tolerate the drug or experience an adverse drug–drug interaction (Solai et al., 2001).

7.3. Pregnancy and lactation

A multicentric case control study (Kulin et al., 1998) reported data on 267 pregnant women who took SSRIs at least during the first trimester. In this study, the use of fluvoxamine, fluoxetine and sertraline showed no increase of birth defects in the developing fetus. While the use of SSRIs have not shown any increase in the rate of major structural anomalies or of spontaneous abortions, a two-fold increase in the incidence of three or more minor structural anomalies in neonates exposed to fluoxetine during pregnancy has been reported (Chambers et al., 1996). They also found a higher incidence of premature deliveries, lower birth weights and shorter birth lengths. Jitteriness in particular has been reported to those infants exposed to SSRIs in the last trimester of pregnancy. The decision to use SSRIs in pregnancy should be made on a case-to-case basis with active involvement of the patient in the informed consent process during which the risks and benefits are discussed and documented (Stewart, 1998). Gupta et al. (1998) reviewed the current literature for the safety profile of SSRIs in pregnancy and lactation. SSRIs are excreted in breast milk and their long-term effects on the newborn are unknown at present.

In conclusion, it can be summarized that SSRIs should be first-line treatment in children and adolescents as TCAs have questionable efficacy and definite safety issues. Although TCAs and SSRIs show equivalent efficacy in elderly patients, the safety profile of the SSRIs makes them a more prudent choice in this population. In pregnancy, there is no definitive data that contraindicates the use of a particular antidepressant. However, the bulk of reassuring pregnancy outcome data exists for the SSRIs specifically for fluoxetine. No single antidepressant can ever be recommended for every patient, but in special patient populations, SSRIs should be considered the first line of choice in the treatment of depression (Emslie and Judge, 2000).

8. Side effects of SSRI's

The SSRIs lack affinity for α-1 adrenergic, muscarinic and histaminergic receptors, and thus do not cause very many anticholinergic, cardiac or sedative effects (Cusack et al., 1994). The most important advantage of the SSRIs is the absence of severe adverse effects and death from over dose. The adverse effect profile of SSRIs and TCAs is generally different, with those related to the former being most consistent with 5-HT agonism. The common side effects include the following.

8.1. Gastrointestinal side effects

8.1.1. Nausea

It is relatively common with SSRIs (15–35%), and is usually transient and dose-related. In a recent study, the incidence rate of nausea with fluvoxamine was found to be 29% (Ueda et al., 2001). It often improves with dose reduction, taking after food and use of drugs, which block the 5-HT3 receptors such as cisapride. However, it may be noted that drugs like fluvoxamine, a potent inhibitor of CYP3A3/4, may inhibit the metabolism of cisapride leading to serious side effects such as cardiac arrhythmias, which occur due to high levels of cisapride (Gram, 1994).

8.1.2. Anorexia and weight loss

SSRIs are known to induce anorexia and weight loss which is more pronounced in over weight patients and patients with carbohydrate craving. In the long run, there may be a tendency to gain back the lost weight (Marcus and Bradley, 1990). In a recent study, acute therapy with fluoxetine was associated with weight loss. After remission of depressive symptoms, weight gain for patients taking fluoxetine for longer periods was not different from those patients taking placebo and was most likely related to recovery from depression (Michelson et al., 1999). Other side effects include loose stools and constipation.

8.2. Neurological side effects

8.2.1. Anxiety, nervousness and headache

In some patients, SSRIs may precipitate or exacerbate restlessness, agitation and sleep disturbances. These side effects often attenuate with time or dose reduction. Insomnia may be effectively treated by the addition of trazodone up to 100 mg at bedtime or concomitant treatment with benzodiazepines (Karasu et al., 2000). SSRIs may also cause tremors on drug initiation, which responds to dose reduction, treatment with β-blockers or benzodiazepines.

8.2.2. Movement disorders

A variety of movement disorders have been reported with SSRI use. These include akathesia, dystonia, dyskinesia, tardive dyskinesia, parkinsonism and bruxism. These movement disorders could either be a direct result of the drug use or exacerbation of an underlying condition. Predisposing factors may include use of antipsychotics, existing neurological diagnosis, old age or preexisting movement disorders (Gerber and Lynd, 1998; Masand and Gupta, 1999).

8.3. Sexual dysfunction

SSRIs can cause a variety of sexual dysfunctions including delayed ejaculation, anorgasmia and decreased libido. The sexual side effects of SSRIs were grossly under estimated during the early clinical trials, which

relied on spontaneous reporting by patients. Further, these adverse effects may appear after several weeks of treatment. Overall, about 30–40% of patients on adequate doses of SSRIs develop sexual dysfunction. SSRIs decrease libido. Jacobsen (1992) reported a decrease of libido in 21% of patients on fluoxetine treatment. While precise mechanism of effect on libido is not known, it is believed that decreased dopaminergic function secondary to increased serotonergic activity may be responsible for the same. Similarly, errectile dysfunction and inhibition of orgasm have also been reported (Patterson, 1993). Anorgasmia is probably related to increased neurotransmission at the postsynaptic 5-HT2C-receptor level. Treatment with cyproheptidine, which has high affinity to 5-HT2C receptors, is effective in treating SSRI-induced sexual dysfunction at the risk of precipitating relapse of depressive symptoms. Dopaminergics such as amantidine and other stimulants such as dextroamphitamine may also be effective. In a study, 94% of patients with orgasmic dysfunctions and 81% of patients with other sexual dysfunctions improved on an 8-week trial with Bupropion (Walker et al., 1993).

8.4. 5-HT syndrome

This rare but often lethal syndrome often occurs as a result of the interaction of two or more drugs acting via different mechanisms to potentiate the central effects of 5-HT at 5HT1A receptors in the brain stem and spinal cord. The most frequent clinical features are changes in mental state, restlessness, myoclonus, hyper-reflexia, diaphoresis, shivering and tremors (Sternbach, 1991). Although 5-HT syndrome can occur with the use of SSRIs alone, it is usually associated with the simultaneous use of multiple serotonergic agents such as SSRIs together with MAO inhibitors, fenfluramine or dexfenfluramine. Literature also suggests that the optimum treatment approach is to discontinue the suspected medication and provides supportive measures. In case, these measures are not effective; methysergide and propranolol can be considered as treatment adjuncts (Sternbach, 1991).

8.5. Others

8.5.1. Dyselectrolytemia, bleeding and bruising

Dyselectrolytemia has been reported as a rare side effect of SSRI use. Fluoxetine and the other SSRIs have been associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), especially in the elderly. The resultant hyponatremia may present as nervousness, agitation or even worsening of depression and if unrecognised may be fatal. SSRIs as a class, inhibit platelet aggregation, which may be responsible for bruising or bleeding (Kelsey and Nemeroff, 2000).

In conclusion, it is apparent that SSRIs have a different side effect profile vis-a-vis TCAs. However, the most important advantage is the relative absence of serious cardiac side effects, seizures or death from overdose. SSRIs have a relatively flat dose response curve, meaning that, on an average, there is less likelihood of increased response with higher doses. Realizing this fact can help minimize many dose-related adverse effects by resisting the temptation to increase the dose within the first 2–4 weeks of treatment.

9. SSRIs withdrawal syndrome

Abrupt withdrawal of SSRIs is often followed by withdrawal syndrome. The relative risk of withdrawal symptoms is most with paroxetine and fluvoxamine but less with fluoxetine (Price et al., 1996). The common withdrawal symptoms are a sense of disequilibrium, gastrointestinal symptoms, flu like symptoms, sensory and sleep disturbances, extra-pyramidal symptoms, anxiety, crying spells, irritability, confusion and aggression.

The mechanism responsible for withdrawal symptoms could be:

(I) Cholinergic rebound: paroxetine has some anticholinergic property and sudden cessation of the drug could lead to cholinergic rebound.
(II) Abrupt discontinuation of SSRIs could lead to relative deficiency of 5-HT at the synapse.
(III) Drug pharmacokinetics: drugs with faster elimination such as paroxetine bring about relatively acute state of cholinergic and serotonergic dysregulation, which in turn could precipitate withdrawal symptoms.

Patients with panic disorder are particularly susceptible to SSRIs withdrawal symptoms. The best way to prevent the emergence of the withdrawal symptoms is to gradually taper off the SSRIs dosage. The principles are similar to those recommended for benzodiazepine withdrawal (Ashton, 1994).

10. Conclusion

Looking to the future, as more information accumulates, we will be able to take on a more rigorous comparison of the SSRIs with the next generation of antidepressants. In fact, it is interesting to note that, whereas the emphasis with the SSRIs has been on their selectivity, recent developments have tended to move towards less selective agents, such as 5-HT noradrenaline reuptake inhibitors (SNRIs, Venlafaxine) or single molecule polypharmacy such as the noradrenergic and specific serotonergic antidepressants (NaSSAs, Mirtazapine). In doing so, drugs have emerged with interesting combinations of monoamine reuptake inhibition and receptor interaction. Time will tell whether this leads to a significant leap forward for pharmacotherapy. Till then,

SSRIs will remain one of the favored alternative agents for the treatment of various psychiatric disorders.

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